IEO
European Institute of Oncology

Scientific Report 2013
Ongoing Research 2014

IEO
Istituto Europeo di Oncologia

Scientific Report 2013
Ongoing Research 2014

Colophon

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We thank all the authors for their contribution to this report

Carlo BUORA
Chairman

Chairman's message

The European Institute of Oncology prepares to celebrate its twenty years of activity within a framework of financial stability and significant growth in treatment and research. At the same time the scientific publications have shown a further increase in impact factor with respect to an already record-breaking 2012. Our innovative capacity and appeal on the national stage thus appear to be gaining in strength.

The IEO model has demonstrated its sound validity over time, as the first private not-for-profit hospital in Italy, where scientific expertise and managerial skills have been combined, along with the principles of both public and private healthcare. Our statute provides for the reinvestment of any profits into research and development, and thanks to this, the IEO has always been able to rely on its founding members who have constantly invested in, and supported, the outstanding ideas and commitment of the doctors, researchers, and staff. This is exemplified by the technology we employ in diagnostic imaging, robotics, radiotherapy, as well as our being at the forefront in Europe for DNA sequencing methods. All this enables us to provide our patients with the most advanced treatment that science has to offer.

We have therefore been able to maintain high quality standards even at a time of national and international economic crisis.

All the above gives us encouragement and hope for the future, and from this perspective we have already drawn up and launched a new and ambitious avenue of development for the next twenty years.

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Mauro MELIS
Chief Executive Officer

Chief Executive Officer's Message

For the European Institute of Oncology, 2013 has been a year marked by strong growth, which confirmed both its clinical and scientific reputation and the economic viability of its hospital. The value of production grew as well as the net income, which is a driving force of our activities. These results are even more significant when considered in the national context, which still offers no concrete signs of overcoming one of the most serious economic and financial crises of recent times, and which, inevitably, has also greatly affected the health sector.

We have challenged the economic downturn with the optimization of our available resources, which led to the re-structuring of the entire clinical organization in a series of programs, each dedicated to a single pathology. This process is already showing results: increased efficiency and, above all, greater focus on the patient by a multidisciplinary team of medical specialists and experts in the different aspects of their illness.

We have also expanded our international activities preparing to receive the increased flows of patients from European regions and emerging countries. Our international outlook is taking a central role in our development strategy.

We have identified shared objectives that indicate a clear path towards a personalized medicine, targeted to a person's unique disease and therapeutic response. We will work on the establishment of an integrated care pathway (prevention, diagnosis, treatment and follow-up) and on the development of clinical and translational research, so that every patient can be offered the best available diagnostic and therapeutic options, using the most advanced experimental therapies.

We are thus facing 2014, the year of our twentieth anniversary, with renewed confidence in our future and a sense of belonging and pride in our past. I would like to thank all our staff, who have made possible this new beginning.

Umberto VERONESI, MD
Scientific Director

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"None of what I have achieved professionally can be attributed exclusively to me as an individual.
Every piece of research, every project, every programme, has involved a team, and thanks to the contribution of each of its members we have achieved many victories.
The IEO was born twenty years ago, with the philosophy of taking care of the quality of life of the person during and after treatment.
Over the years we have developed many methods that have improved clinical practice, opening new research frontiers. Over the next twenty years the institute will continue to strive to carry out its mission: to be an ever-present European landmark for innovation in the fight against cancer".

Umberto Veronesi

Scientific Director's Report

The Scientific Directorate is responsible for strategic choices for the future. The foundations of our strategies are: the centrality of the patient, the main importance of prevention, quick transfer of research results from laboratory to clinical research, increasingly earlier diagnoses, and increasingly conservative therapies with a focus on the quality of life.
We hold to ten principal values for our patients and these are: the right to scientifically proven treatments, the right to prompt treatment, the right to a second opinion, the right to privacy, the right to know the truth, the right to be informed about treatment, the right to refuse a proposed treatment, the right to the living will, the right not to suffer, and the right to the respect of personal dignity. From this perspective, during 2013, in agreement with the University of Milan, was created the Applied Research Unit for Cognitive and Psychological Science directed by Gabriella Pravettoni.
The fundamental concept of this unit consists of multiple research disciplines, including psychology, philosophy, neuroscience, linguistics, and anthropology. It therefore embraces many levels of analysis.
This year our scientific activity has yielded many excellent results. We have produced 421 scientific papers with a total impact factor of 2458,53 and an average impact factor of 7,02. Three hundred fifty of these papers were published in scientific journals with an impact factor, whilst forty were published in non-impact factor journals. In addition, thirty-one documents fell into the category of books, chapters, conference papers or other items.
IEO devotes much attention to Fundamental Research and its translation into cancer prevention and better cures for our patients.
Our fundamental-research activities are located at the IFOM-IEO Campus, a new area that also hosts the IFOM research institute (the FIRC Institute for Molecular Oncology) and an outstation of the Italian Institute of Technology (IIT). The Campus represents one of the largest European centres for cancer research, with 24,000/m2 and 450 researchers. Our research is mainly focused on molecular (genomic instability; epigenetic changes) and biological (tumor cell-heterogeneity, microenvironment) mechanisms of transformation.

European Institute of Oncology Staff

MD and PhD	381
Post Doctoral Fellows	217
Nurses	454
Technicians	158
Administratives	390
Total	1600

Emphasis is given to generation of tumor models, applications of high-throughput screening-technologies (proteomics, (epi) genomics, and structural biology) and development of dedicated computational tools and approaches.
To accelerate translational research and innovation in prevention, diagnosis and treatment, IEO has launched a dedicated Molecular Medicine Program, whose laboratory activities are located within the IEO hospital building, and a series of multidisciplinary programs, which put together our Doctors, Clinical-, Translational- and Fundamental-Scientists. The IEO Multidisciplinary Programs are focused on homogenous clinical-scientific areas, such as Tumour-Types or Treatment-Modalities, and aim at building an integrated care pathway (prevention, diagnosis, cure and follow-up), ensuring the "best-available diagnostic/treatment-options" and providing each patient with the most advanced innovative therapies (new drugs or treatment modalities, and patient stratification for treatment through the use of genomic screens).
These new initiatives stem from our front line activities in cancer prevention, early diagnosis (for example our programs on cervical, breast and lung cancer) and novel treatment modalities (targeted peptide- or antibody-guided radionuclide therapy).

Our institute also devotes much attention to technology updates and to the development of new technologies. Since these activities demand ample investments and critical mass, IEO has decided to join efforts with IFOM and together they created a Consortium dedicated to the development of new technologies (Cogentech), including most-updated DNA sequencing technologies.

In addition to intense research activity, we have established four PhD programs at the European School of Molecular Medicine Foundation (SEMM), in collaboration with IFOM and the University of Milan and Naples. These are the Molecular Medicine Programme, the Medical Nanotechnology Programme, the Computational Biology Programme and the Foundations and Ethics of the Life Sciences Programme. The school enrols over 150 PhD students from around the world.
In 2009 we launched a program of Drug Discovery. Traditionally, basic research into diseases and disease-mechanisms has been conducted in academic institutions, while its application to drug discovery has been the responsibility of the pharmaceutical industry. In recent years, a strong need has emerged for molecularly-targeted drugs that are based on knowledge of disease mechanisms. This need has exposed the limitations of conducting basic and applied research separately and has created the basis for new interactions between academia and the pharmaceutical industry. To address this problem, IEO launched a new Drug Discovery Program, which is fully intertwined with ongoing basic research at the IFOM-IEO Campus. One important aim of the program is to establish collaborations with private and public institutions whose mission is to cure disease.
There seems to be little doubt that the agenda for cancer biology in the next decade will be mainly focused on the understanding of how simple individual molecular functions are integrated into complex pathways and systems, how multiple systems are integrated to govern multifaceted cellular behaviours, and how subversion of these molecular machineries leads to cancer. With this complex picture in mind our scientific efforts are concentrated on three major objectives:

1. Understanding the complex systems controlling cell proliferation. Two major lines of research are being developed aimed at the understanding of exogenously-originated signals (which follow the engagement of surface receptors) and endogenously - originated signals (which follow DNA damage). This is supported by high throughput technologies, including high definition genomic technologies and proteomics, and by a vast array of genetic tools in mammals, fish, nematode and yeast.

2. Understanding complex circuitries in the "actual" picture of naturally-occurring cancers. This is being pursued through expression profiling and genetic analysis of cancers with respect to questions of clinical relevance, such as prognostic evaluation, disease classification and patient stratification for therapeutic purposes. These programs are organized within a transversal approach across several 'task forces' established around "disease-oriented programs". Presently, we have programs on breast, lung, ovary, leukemias and melanoma. These programs are centred on first-class clinical resources and supported by high throughput technologies and a vast repertoire of bioinformatics and biostatistics expertise, which provides support to the disease programs in addition to developing its own lines of research.

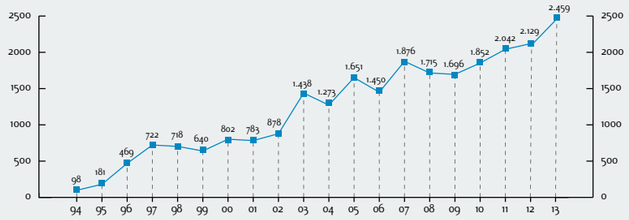
3. Integrating complex circuitries in higher order cellular programs or at the organism level. Several lines of investigation are being pursued here. First, we are analyzing the impact of stem cells on cancer phenotypes. Efforts are concentrated on leukaemia, breast, melanoma and lung cancer stem cells, with the perspective of integrating these lines of research in the disease-oriented programs. Second, we are intensively investigating mechanisms of immune-surveillance of tumor growth and strategy to activate immune-mediated clearance of tumor cells. Finally, efforts are being directed at the generation of reliable models of mammalian carcinogenesis, by engineering in model systems mutations that mimic those naturally occurring in human cancers (leukaemia, breast cancer, ovary cancer and melanomas).

The Basic Research and Molecular Medicine Programs will not detract from our mission of improving prevention, early detection, effective treatments and quality of life of our patients, using the best of all the available knowledge. On the contrary, we firmly believe that the best way to cure cancer is by speedy application of the knowledge acquired from research activity to the patient ward.
The number of patients enrolled in clinical trials was 3466 and we have now 37308 patients in follow- up. Many new clinical projects were initiated during the year, after approval of our Ethics Committee. The number of visitors and residents from all parts of the world has been considerable.
Training of young scientists and physicians is a critical component of our mission. Many members of our staff are actively involved in teaching at the University of Milan and at numerous meetings and courses throughout the country.
Furthermore, our researchers have continued to make up a relevant part of the teaching staff of the European School of Molecular Medicine.
As in previous years, numerous scientific and teaching meetings were directly organized by IEO, both for external and internal attendance.
Another source of pride for IEO is the Center for Advanced Radiotherapy (ARC), which is among the top ten centers in the world for treatment, research and technology. It provides radio therapeutic treatment of the latest generation for the treatment of tumors and is able to identify with precision the target tumor, spare the surrounding healthy tissue, preserve the organs and their functions, and significantly reduce the duration of the treatments. The ARC utilizes the most modern equipment in the world. We may mention: 1) the True System, which is a linear accelerator capable of performing so-called "tumor tracking": the beam of radiation follows the movement of the organs of the patient and synchronizes with extreme accuracy on the latter. Within minutes, the machine can act on more outbreaks. It is used to treat cancers of the prostate, lung and liver 2) the Cyberknife System, which is a sort of virtual scalpel capable of providing, at any part of the body, radiation to ablate the tumor. In the IEO is used for the treatment of brain tumors, primary and secondary, spine, liver, pancreas and lung and for the treatment of relapses 3) the Tomo Therapy System, which is able to adjust the intensity of radiation depending on the organ to be treated. It can intervene in all the anatomical sites and allows treatments to be performed on the whole body. In the IEO it is used for patients operated on for cancer of the breast, even if already treated with intraoperative radiation therapy, to completion of the cure, with mini irradiation global breast 4) Trilogy™

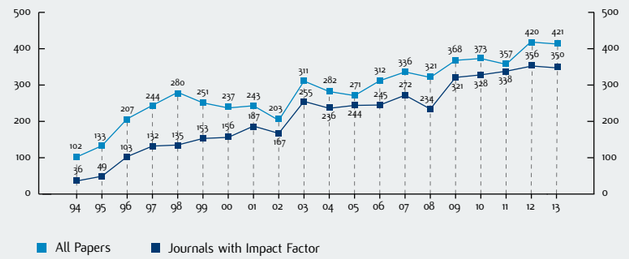
Publications 2000 - 2013

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Full Papers *Journals with Impact Factor*	156	187	167	255	234	245	245	272	234	285	276	312	358	350
Total Impact Factor (*)	801,62	782,82	877,81	1.438,12	1.273,42	1.651,96	1.441,55	1.874,70	1.716,79	1.693,28	1.849,55	2.040,59	2129,47	2458,53
Average Impact Factor	5,14	4,19	5,26	5,64	5,44	6,74	5,88	6,89	7,33	5,94	6,70	6,54	5,94	7,02
Full Papers *Journals without Impact Factor*	9	13	2	17	16	15	26	39	48	49	52	24	42	40
Total Full Papers	165	200	169	272	250	260	271	311	282	334	328	336	400	390
Books, chapters, and others	72	43	34	40	33	37	39	25	38	31	44	18	26	31
Total publications	237	243	203	312	283	297	310	336	320	365	372	354	426	421

(*) *For each year the IF was calculated using the values published in the Journal Citation Reports of the previous year.*



Impact Factor 1994-2013



IEO - Research Activity Figures - Publications

System Integrates, which allows one to irradiate the tumor and visualize the anatomy of the patient immediately before administering the fraction of the dose. It then detects the movement of respiration, allowing the irradiation of the tumor only when it is in the correct position. In the IEO it is used to treat cancers of the head-neck tract where, thanks to its extreme precision, allows the functionality of the parotid gland to be preserved. It is also used in gynecological cancers.
IEO continued its scientific collaboration at the international level. Specific efforts have been devoted to establish new relations with Mediterranean countries, and with India, Madagascar, and Africa. In addition to this, the result of the experience of western countries where mortality for breast cancer is now declining with respect to eastern countries, drove us to create an agreement with China. Our goal is to involve other eastern countries to disseminate our surgical techniques and our medical knowledge in the field of oncology.
Thanks to a close cooperation and an intensive sharing of knowledge and expertise, and frequent contacts between the IEO and international centers, our successful experience in clinical research, prevention and therapy is becoming a model for the creation of new cancer approaches in many countries. In particular, we have focused on the fight against feminine tumors (breast and cervix) through specific models from training and education through to the projects for new comprehensive cancer centers.
As in previous years, we have been very successful in securing funds to support our research activities both at the national and international level. Success in fundraising has been crucial for the steady expansion experienced by IEO during the past several years. The hiring of new research directors has been made possible by competitive start-up packages, including provisions to fund students and postdoctoral fellows and the availability of many state-of-the-art core facilities.
Out of a total of million Euro, came from the European Community, from the ISS (the Italian National Institute of Health), from the Ministry of Health, from AIRC from 5x1000 Fiscal Contribution and from other sources, including the Lombardy Regional Authorities, the Umberto Veronesi Foundation (FUV), MIUR (Ministry of Education, Universities and Research), the American Institute for Cancer research, CNR, FIRC, FIEO, Vollaro Foundation, Human Frontier Science Program, and the Lega Italiana per la Lotta Contro i Tumori (LILT). We are very grateful to all the funding agencies, which recognized the validity of our projects.
In conclusion, I would like to extend our appreciation and gratitude to the President, the CEO, the Board of Directors, and all clinical, scientific, technical and administrative staff of IEO, for their continuous efforts. I wish to thank Pier Giuseppe Pelicci, Roberta Carbone, Eva Bruschini and the various Writing Committees for their valuable collaboration in this annual report.

Press Office

The Scientific Press Office follows scientific and medical content, falling within the area of the Scientific Directorate, in close cooperation with the Central Directorate of Marketing and Communication. Scientific and medical output provided for the general population or published in scientific newspapers or mutually exchanged with international centers are under the supervision of the Scientific Directorate, through the Scientific Press Office.
IEO communication organizes marketing issues and continuous and detailed information for the population and media: the Scientific Press Office works within the global network of institutional communication under the coordinated direction of the Scientific Director, the CEO and the Central Director of Marketing and Communication.

Grants Office

The Grants Office acts as a liaison between researchers and sponsoring agencies and is a central source of information on major national and international agencies, foundations, and institutions that support research and scholarship, and assists researchers in identifying appropriate research funding opportunities. It provides assistance to researchers in the preparation of applications, developing proposal narratives and budgets, completing the application forms and interpreting the regulations of the funding agencies, assuring compliance with the sponsor policies and requirements. It negotiates the terms and conditions of awards of successful proposals and provides support for the administration of research grants, including funding allocation and producing financial statements.
It manages research contracts, preparing, whenever necessary, subcontracts or consortium agreements with collaborating institutions, acts as administrative contact point on multicenter research projects, and provides administrative support for IEO research activities.

Collaboration with the University of Milan

Since its launch, IEO has established a very close collaborative relationship with the University of Milan, as regards teaching, research and care activities.
In fact, while many university professors lead IEO clinical and research Divisions and Units, IEO hosts PhD students and junior residents specializing in various disciplines, as well as many post-doctoral activities.
Significant is the collaboration between IEO and the University of Milan within the SEMM, a school dedicated to the training in Molecular Medicine (see page 220).
This partnership is progressively growing, slowing becoming a sharing of strategic objectives between the two institutions.

Ethics Committee

In the first 6 months of 2013, 72 new clinical trial applications were evaluated in 5 plenary sessions of the Ethics Committee as well as 160 applications for substantial amendments on ongoing trials.
Due to major changes to the clinical trial regulation in the mainframe of a general revision of the legislation, in order to improve national competitiveness in the field of drug development, the ethics committee national system was reviewed. As a result, after 16 years the Ethics Committee of the European Institute of Oncology concluded its activity on September 2013.
With reference to the Research Hospitals and Treatment Centres, a network of twelve ethics committees were selected by the Lombardy Region Health Authority and as part of this network a unique Ethics Committee was appointed for the European Institute of Oncology and the Monzino Cardiology Center.
The components of the new committee were selected in order to continue to provide high level of pharmacological and clinical expertise in the two different therapeutic areas and in compliance with the ex-novo professional skills required by the national and regional decrees. The lack of any conflict of interest was also a major concern.
On September 25th the Ethics Committee of the Research Hospitals and Treatment Centres – Istituto Europeo di Oncologia e Centro Cardiologico Monzino has been accredited by the Lombardy Region and the National Medicinal Agency.
By December 2013, 33 research proposals as well as 84 amendments on ongoing trials were evaluated in 3 plenary sessions. The therapeutic use of drugs still under investigation in clinical trials, for advanced cancer patients, was approved for 11 patients.

Ethics Committee

As from May 2014

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SECRETARIAT	Daniela TAMAGNI
OBSERVER	Mauro MELIS

Clinical Trial Office

Main objectives of the Clinical Trial Office (CTO) are to improve the management of the Clinical Trials conducted at the European Institute of Oncology and promote clinical research, according to Good Clinical Practices.
The CTO includes the "Data Management" and "Clinical Trials and Regulation" Offices.
The CTO supports IEO clinical research through several activities:

Sponsored & Academic Trial Activation: scientific/ administrative assistance and support during the preparation of clinical trials and grant application, as well as in the management of contacts between IEO and the Sponsor(s) of the studies.

Trial Management: study management support, from design to data-analysis and publishing. Support in the administrative set up, management and reporting of clinical trial results. Reporting activities. Drafting of clinical trial documentation. Patients' screening/registration and randomization in clinical trials.

Probity and scientific evaluation of clinical trials: support in the evaluation of clinical trial during their selection, assuring compliance with IEO policies and international probity requirements.

Clinical research website implementation: creation of web pages specifically designed to describe IEO clinical research to patients and their General Practitioners.

Clinical research international network implementation: support in the development of an international network promoting clinical research and IEO participation in highly innovative clinical trials.

Clinical research training: on site and online training in clinical research for both IEO and non-IEO personnel.

CTO uses Standard Operating Procedures validated and approved by the IEO Quality Service.

Data Management

The Data Management (DM) Office supports clinical research from trial design to publication of final results.
It is responsible for high quality collection and processing of clinical research data, offers support for their analysis and publishing, and gives an important contribute to the administrative set up, management and reporting of clinical trial results. It deals with the 1) screening and overseeing of data accrual, 2) supervision of the scheduling of study procedures and controls, 3) supervision of data collection and processing, 4) compliance with relevant Institutional or governmental regulatory guidelines in the conduct of clinical research, 5) assistance in the interactions with research staff both at the Institute and at other collaborating institutions, 6) coordination of protocol production and submission of regulatory documents to the Ethics Committee and regulatory bodies, 7) monitoring of patients and test result reporting, and 8) assistance in the preparation of research reports and manuscripts for publication and presentations. The main goal is to ensure individualised care to all the patients participating in the trials.

DM activities are concentrated in three main areas with different responsibilities.

Trial Activation & Reporting

- Protocol review and feasibility evaluation
- Preparation and submission of regulatory documentation
- Cost evaluation and budgeting
- Management of a dedicated area in the institutional e-network
- Status report on trial documentation
- Support for site qualification visits and audit activities
- Staff training and activity analysis and coordination
- IEO investigators' meetings
- Check of study site closeout with Sponsor

Trial Management

- Support for site qualification visits
- Integration and verification that all required research tools are present during the initiation visit or sponsor monitoring visit
- Monitoring and auditing activities
- Supervision of Case Report Forms (CRFs) and database management
- Updating of trial documents and reports
- Quality control
- Patient recruitment and management
- Contacts with trial sponsors
- Adverse Event and Serious Adverse Event registration
- End of study visits
- Secure storage of study files

Clinical Trial support

- Patient screening/recruitment/enrolment
- Control of correct scheduling for patient visits
- Source documentation/data collection
- Ongoing monitoring
- Biological samples management
- Randomization and treatment assignment
- Drug accountability
- Filing of safety reports
- Handling of clinical duplicates

Several procedures ensure the correct execution of these activities. They include internal Standard Operating Procedures such as the use of CRFs and Database Management, Data Entry process, Patients Registration, Data Manager training.

The DM Office is composed of 20 data managers, 5 fellowship data managers and 5 data entry clerks. During 2013 the DM Office has supported the activation of 81 new clinical trials (27% observational studies and others; 73% phase I, II, III, IV) and the conduction of 336 on-going clinical trials.

Furthermore, the DM Office has introduced and developed the "Collaboration project": an important element to promote the collaboration between data managers, clinical staff and all the people involved in clinical trials. This is a key factor to improve the quality of trial management. A specific tool allows direct access to the clinical trials on the IEO Intranet website, and to the relevant documentation. Through this tool, all the members of a research team can find out which clinical trials are on-going in the different Clinical Units/Divisions and how to access them.

The DM office actively contributes to clinical research training and professional development of the IEO personnel, ensuring excellence in care and research, and also offers courses in basic and advanced research, using modern on-line technologies, for non-IEO personnel. The DM has also realized an on-line course supported by the IEO-Education Office: "The Management of Clinical Trials: scientific and ethical basis for the correct experimentation"; this course, available in Italian and English, aims to provide an overview of clinical research as a methodological process, offering practical and theoretical knowledge on study types, regulations governing clinical trials, tools to enable and conduct clinical research.

Library

The Library strives to serve and support the biomedical, nursing and research literature needs of the staff throughout the Divisions and Units of the IEO.
To this end it offers a wealth of high-quality, evidence-based electronic information tools coupled with a quiet space in the Mirror Tower conducive to the study and consultation of the literature both online and in print.
The Library catalogue is the key to a valuable resource through which IEO staff have access to e-journals and e-books.
The Library does not exist in isolation, and has access to interlibrary document delivery services when resources are not available electronically or on-site. A network of 59 IRCCS libraries, known as BiblioSan, working within the Network for Inter-Library Document Exchange (NILDE) ensures that IEO staff can readily access journals and databases from outside the institute.
The Italian National Collective Catalogue of Periodicals (ACNP) links to over 110,000 journals and 2500 Libraries throughout Italy. The Biomedical Library System of Lombardy (SBBL) consortium links to the regional health libraries.
The Library is also a member of GIDIF-RBM, a consortium of key biomedical and pharmaceutical libraries in Italy, and of DOCLINE (via the Italian National Institute of Health and the National Library of Medicine in the USA).
Via these consortium agreements, 8000-plus journals are accessible 24 hours a day, 7 days a week. Through SBBL over 1000 e-books are available via Springer Publishers.
All can be accessed via the Library "AtoZ catalogue". In 2013 this catalogue had a total of 5584 accesses. The average session time was 3 minutes, and a total of 18,356 pages were viewed.
IEO staff have a comprehensive range of resources for health-related literature searches. Naturally there is access to Medline, the prestigious and most widely-used medical literature database (via the user-friendly Ovid interface). In addition we have the more pharmaceutically-focused Embase, and also the prestigious nursing resource CINAHL – the Cumulative Index to Nursing and Allied Health Literature. Furthermore, there are quality bibliographic full-text databases specialising in psychology, health administration, science and technology, and food science. Last but not least, is the key resource for systematic reviews - the Cochrane Library.
Data on "impact factors" (whereby a numerical value represents the yearly "impact" of a journal) and the h-index (a measure of quantifying a person's scientific research output and impact) is provided by the Journal Citation Reports and the ISI Web of Science respectively.
IEO staff can store bibliographies in a personalised reference handling software package called RefWorks. This generates lists of reference citations in keeping with the different formats required by publishers of the major international scientific journals.
The Librarian provides personalised assistance in searching the literature on a desired research or clinical topic and in making efficient and effective use of the considerable number of quality biomedical information sources available.

The IEO activities in Spain and in Latin America

Since the opening in 1994 (and from 2005 with the creation of the *Iberian-Latin American Office* by Prof. Veronesi and Dott. Ciani) the IEO developed an intensive CME program in Spain and Latin America, consisting of more than 100 courses, with a global participation of more than 20.000 medical doctors, following the Veronesi's philosophy of diffusing the science without frontiers. 35 IEO speakers participated at the Teaching Division and some of them many times throughout the years. On the other hand, more than 1.500 medical doctors from these countries visited the IEO in Milan, participating at educational programs developed in one week, one month or one year. The most important courses was organized in Madrid, Barcelona, La Coruna, Alicante and Lleida, all these in Spain; and in Mexico DF, Caracas, Cartajena, Bogotà, Cancum, Bahia, Rio de Janeiro, Sao Paulo, Porto Alegre, Montevideo, Buenos Aires, Cordoba, Rosario and Santiago in Latin America. This educational program was organized with the financial contribution of the peripheral countries and, in practice, without any cost for the IEO. In conclusions, more than 20.000 medical doctors treat their patients in Spain and Latin America following the IEO guidelines for cancer treatment, in surgery, radiotherapy, medical oncology, nuclear medicine, radiology and Anatomy Pathology. These educational activities were coordinated since 1994 by Gabriel Farante, MD, from the IEO Division of Senology and the Scientific Direction.

ecancermedicalscience

ecancer,the leading oncology channel continues to provide a free service to oncologists in the form of an open access journal, expert videos, news, and education modules. Each month over 0.5 million people visit the ecancer website to read and watch the latest content. ecancermedicalscience, is fully indexed in PubMed and other leading databases guaranteeing over 10,000 views of articles a month. The introduction of the special issue programme has significantly stimulated article submission rates which in total are up by 50% compared to this time last year. A continued rejection rate of approximately 60% has resulted in an increase the publication rate of 140% over the same period in 2012.

ecancer will apply to Web of Science at the end of the year so are hoping for an Impact Factor to be announced in June 2015. It has been unofficially estimated at around 1.08 for 2013.

ecancermedicalscience is an approved member of COPE, the Committee on Publication Ethics.

ecancer continues to participate to the most important oncology conferences generating current, informative videos. ecancer.tv now features around 2800 videos of interviews with eminent oncologists, roundtables and press conferences, which have been watched over 2 million times. This is the only site of its kind with such a rich resource for oncology professionals.

ecancer is actively involved in the management of three European Commission funded FP7 projects in partnership with the IEO. P(ersonalized)Medicine is aimed at developing internet tools to assist clinical research, especially clinical trials in the era of genomic led therapies. IEO is responsible for the clinical trials work package while ecancer leads on Patient Empowerment and Education in collaboration with Prof Gabriella Pravettoni (University of Milan and IEO). EurocanPlatform is a project linking 23 leading cancer institutes; ecancer is responsible for communication and dissemination of results. EURECA (Enabling information re-Use by linking clinical Research and Care) is looking at semantic ontologies of health IT systems.

ecancer's Education platform continues to grow with several new elearning modules being released in the coming months. ecancer developed an elearning course in palliative care in partnership with the African Palliative Care Association, Cardiff University and the University of Cape Town. The course was launched in January 2014 and comprises of 20 modules covering all aspects of palliative care tailored to the specific needs of African healthcare professionals. Development of the course was funded by the International Atomic Energy Agency and the modules are available to do on ecancer.org as well as through the Virtual University of Cancer Control.

ecancer.org recently redesigned website has ensured an increased profile on search engines and is compatible for mobile devices; the new app for iPhone, Android and iPad was released last year.

The Spanish version of ecancermedicalscience "ecancer Latino America" was launched in June 2013. Two interlinked websites, one for the medical community and one for general public address all the oncology related health issues within Latin America and disseminate key oncology developments from the international community. A Portugeuse version has also recently been developed. All articles submitted in Spanish\Portugeuse are translated for free into English if they pass peer review. To date 14 Spanish and 2 Portugeuse articles have been published; these are available in English and in their original language.

ecancer continues to place the European Institute of Oncology at the forefront of multi-media communications, looking at innovative solutions to promote equal access to oncology research and learning. The Founding Editors are Professors Veronesi and McVie and Dr. Linda Cairns is the Science Editor.

ecancer is supported by the European Institute of Oncology, The Foundation of the IEO, The Umberto Veronesi Foundation, The European CanCer Organisation and Swiss Bridge.

The Directive Board

CEO acting as Chairman	Mauro Melis
Scientific Director	Umberto Veronesi
Scientific Co-Director	Roberto Orecchia
Scientific Co-Director	Pier Giuseppe Pelicci
Chief Communication, Marketing and Customer Service Officer	Barbara Cossetto
Chief Financial Officer	Mario Cesana
Chief HR Officer	Daniele Piacentini
Chief Information Technology Officer	Emanuele Balistreri
IEO-CCM Group Chief Medical Officer	Massimo Castoldi
Chief Medical Officer	Oliviero Rinaldi
Research Management Director	Domenico Triarico

The mission of IEO Management is to aim the everybody's efforts towards the strategic objectives of the Institute and to create the best conditions to allow the operators to put their expertise and knowledge to the patients' service.
There are many ways to play this role in a complex organization. However, we believe that our managers must necessarily own the following principles:

- a continuous thrust towards innovation and an international dimension; the best treatments can be found where research is performed. We believe that a research institute can only excel if it is based on mature and advanced management tools;
- a team culture to be searched for and promoted every day in the relationships with all those who operate inside the Institute;
- the awareness that, in such no-profit organizations as IEO, the management systems justify their existence insofar as they strongly contribute to create the conditions to reach and maintain excellence in the fight against cancer.

This is, in synthesis, the "philosophy" that guides the behavior of the areas that coordinate and support IEO's clinical and research activities. Our job, our active contribution to the fight against cancer, is to try and put into practice this "philosophy" every day.

Communication, Marketing and Customer Service

Barbara COSSETTO
Chief Communication, Marketing and Customer Service Officer

Customer Service Staff
Admissions Office: Francesco Bernasconi
Clinical Secretariat: Fabrizio Di Stefano (until December 2013)

Marketing & Communication Staff
Marketing: Marco Vianello
Communication and PR: Barbara Cossetto (ad interim)
Corporate Communication and Website: Emanuela Ottolina
New Media: Giovanna Gatti

Head of the Secretariat: Jolanta Orlikowska

Customer Service involves more than 180 resources. Services are delivered to Patients to support their clinical path and internally to physicians.

Marketing:
- Product Management
- Relation and Sales with Healthcare Insurances
- International Relationship

Customer Service:
- Booking Call Center
- Clinical Secretariat
- Admittance Front Lines

Communication and PR:
- Brand Image
- Website
- Corporate Events
- Public Relations
- New Media

Finance and Administration

Mario CESANA
Chief Financial Officer

STAFF Executive Assistant: Viviana Muggiana
Financial & Accounting Controller: Angelo Longoni
Legal Affairs: Renato Galasso
Purchasing Office: Marco Falso
Budget & Finance Controller: Antonio Di Filippo

Integration of the clinical, research and administrative areas represents the basic principle underlying the management model adopted by the Finance and Administration Management.

The main tasks of the Administrative Directorate are as follows:
- Economic - financial management of the Institute
- Administrative, legal and tax requirements
- Managing the accounting, procurement and stock

The Finance and Administration Management is reported to by the following services:
- Accounting & Financial
- Legal Affairs
- Purchasing Office
- Budgeting & Financial

Human Resources

Daniele PIACENTINI
Chief HR Officer

STAFF Recruitment and Performance Management: Anna Lauro
Training & Development: Elena Mazzoleni
HR Research Department: Annalisa Ariesi
Payroll & Labor Laws Department: Nicoletta Golin
Organization & Process Engineering Department: Silvio Pozzi
HR Controller: Marco Colombi
Head of Secretariat: Stefania Piacentini

The central role of the individual and top-quality assistance are the two principles that have always inspired the organizational and management work done by the HR Office in each of the above areas. In fact, we are convinced that the quality of health services is determined by the quality of those who provide them: this principle has enabled the Institute to achieve its main objective, that is to say the improvement of the quality of life of each patient, who must be considered not simply as a person who needs treatment but, above all, as a human being.

Main tasks of the HR Department are as follow:

- Recruitment and Selection
- Education and Training
- Performance Evaluations
- Staff Administration and Payroll
- Salary Packages and Incentive Policies
- Personnel Management, Planning and Costs
- Union Relations
- Organization

The HR Department reported the following services:

- Recruitment and Performance Management
- Training & Development
- HR Research Department
- Payroll & Labor Laws Department
- Organization & Process Engineering Department

The best example of this approach is the "Job Family Model", a model for managing human resources for professional families that has been extended to all roles of the Institute and aims to promote, develop and reward the skills and knowledge of our key employees. Through this model IEO wants to realize two fundamental goals for an health organization:

1. To ensure qualified and high skilled employees and constantly develop them
2. To ensure motivated employees who want to apply their knowledge in their everyday job

This took us years to get major awards, such as the Great Place to Work in 2003-2005-2006-2009, Joint Commission International certification for excellence in 2002 and the Prize Betershamal as one of the 6 best hospitals in the world, demonstration of the quality of work and all our employees. In 2011-2012-2013-2014 IEO awarded the Top Employers Italy as one of the Italian companies which proved excellent in management of its human resources.

Information Technology & Facility Management

Emanuele BALISTRERI
Chief Information and Technology Officer

STAFF Head of the Secretariat: Jolanta Orlikowska
IT Operations: Andrea Dupplicato
IT Integration & Transformation: Luigi Grilli
IT Business Applications: Paolo Zilioli
IT Architecture, Security & Innovation: Alessandro Della Vedova
Facility Management: Gianfranco Piantelli
Space & Logistics: Chiara Gallia

The Information Technology & Facility Management Service manages all the technical resources of the organisation, including IT, biomedical systems, plant and buildings. Its directorate is also responsible for security services and mobility.
The services are dedicated to the support of clinical/administrative activities and research activities.

Information Technology

- Hospital Information system
- IT infrastructure and security
- Telecommunications, network and telephony

Facility Management

- Plant and buildings operation and maintenance
- Clinical Engineering
- General Services

CEO's Office

Medical Office

Massimo CASTOLDI, MD
IEO-CCM Group Chief Medical Officer

Oliviero RINALDI, MD
Chief Medical Officer

STAFF Assistants: Giovanni Grieco, MD, Camilla Ranieri, MD
Legal and Insurance Medicine: Luigi Orlando Molendini, MD
Head of Secretariat: Stefania Piacentini
Executive Assistant: Evelina Guaragna
Service for Nursing, Technical and Rehabilitation Staff: Giorgio Magon
Quality & Accreditation and Customer Relations Office: Pier Luigi Deriu
Patient Safety & Risk Management: Massimo Monturano
Health Information Management & Medical Records: Daniele Dozzo, Andrea Chiesa
Pharmacy: Emanuela Omodeo Salè
Resources Planning Department: Alfonso Lorusso

Medical Office oversees all health areas and it not only handles activities related to the Institute's overall Clinical Governance but also provides its own specific services. Medical serves as a connection and interface for all clinical and health-related organizational and management processes that involve several divisions, operational units and services.

The main tasks of the Medical Office are as follows:

- Responsibility of all technical, organizational and hygienic aspects in the hospital.
- Participation in the process of strategic and operational planning of the Institute.
- Responsibility of Clinical Governance, with the identification and implementation of international guidelines and internal clinical care pathways.
- Responsibility of overall quality and technical efficiency - the production of operational performance ("vertical lines") and distribution services through the integration of individual products or services in assistance programs,
  geared to the individual and the community ("horizontal lines").
- Guarantor of integrated hospital health care, from the organization and management point of view.
- Responsibility of the proper organization and execution of welfare programs horizontal, the result of the integration of vertical lines responsible for the production of individual performance.
- Responsibility of Accreditation (both institutional and excellence) of both facilities and professionals working in the Institute. In particular responsibility of all requirements relating to safety.
- Responsibility of the Internal auditing program that aims at verifying the most critical processes of the Institute.

The Medical Office is also highly oriented towards developing new organizational and management procedures – working alongside Clinical and other IEO Divisions – in order to improve effectiveness, efficiency and appropriateness (i.e. quality) of services.

In order to develop plans and policies on Quality and Safety, the IEO Quality Committee (IQC) was created on September 17th 2001.

In order to continuously check the surveillance and control of hospital infections and the prevention of pharmacological errors in a perspective of collaborative work, two ad hoc Committees have been created: the Hospital Infections Committee and the Drugs and Medical Devices Committee.

Patient safety and quality have been one of the main objectives of Medical Office since the Institute opened. Since 2002 we have achieved Joint Commission International Accreditation; many processes have been Certified ISO 9001. In 2013 we received the OECI (Organization European Cancer Institutes) accreditation.

Hospital Activities

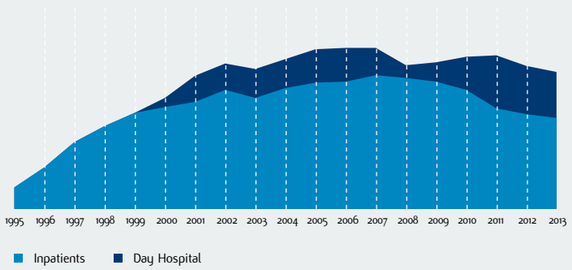
At the end of the year the clinical staff of the Institute numbered 390 physicians, 450 nurses, 106 health care assistants, 154 health technicians and 40 medical residents. 110 medical doctors coming from 18 countries spent a significant period (more than 30 days) of clinical training in one or more of our Clinical Divisions.

36.888 new patients were enrolled in 2013 adding up to a total patient census (as of 31 December 2013) of 615.529 patients since IEO opened in 1994.
Total hospital admissions decreased by 3.99% to 10.788 compared to the previous year, totalling 45.005 hospital days (47.950 in 2012) with an average length of stay of 4.17 (4.27 in 2012). The ratio between surgical admissions and total admissions ("surgical index") increased to 73% Case mix complexity, proxied by the Average Relative Weight, increased to 1.48.

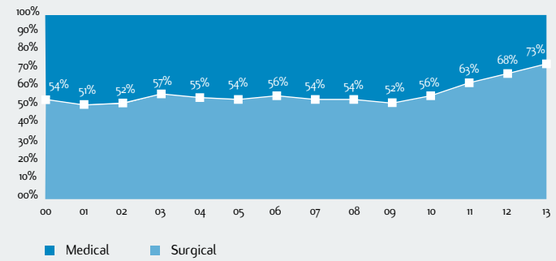
Hospital Activities

Day Surgery cases (surgical treatments which do not require an overnight stay) amounted to 4.553 (4.550 in 2012).

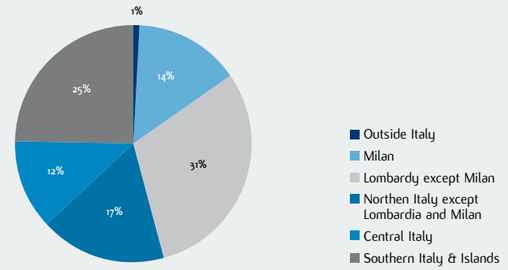
Day Hospital admissions, mainly for therapeutic pur poses (chemotherapy or radiation therapy) totalled 1.117 treatments (1.647 in 2012) and involved 898 patients (1169 in 2012).



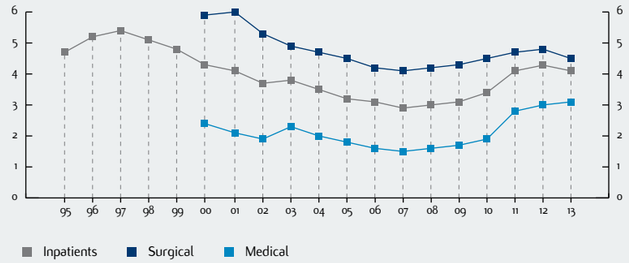
Key Case Mix Figures: Hospitalisations



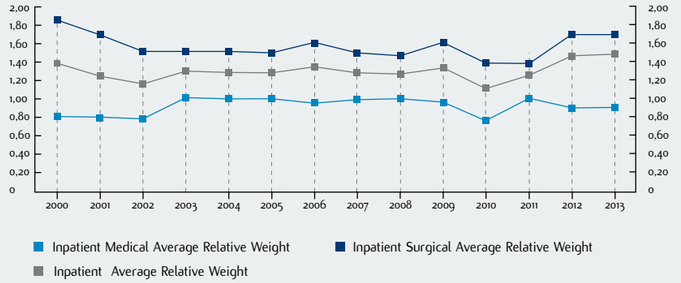
Key Case Mix Figures: Surgical Index



Key Case Mix Figures: Impatient Admissions by geographical area

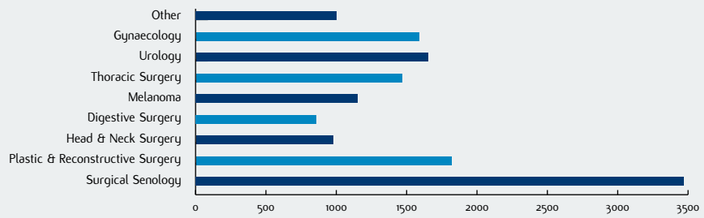


Key Case Mix Figures: Average Length of Stay (Alos)

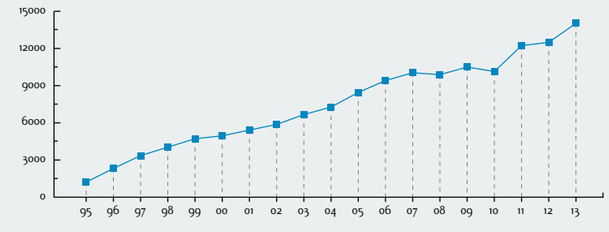


Key Case Mix Figures: DRG Average Relative Weight (ARW)

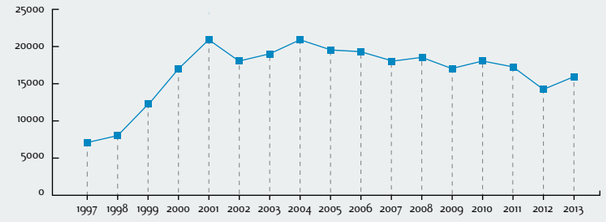
Key Case Mix Figures: Surgical Interventions



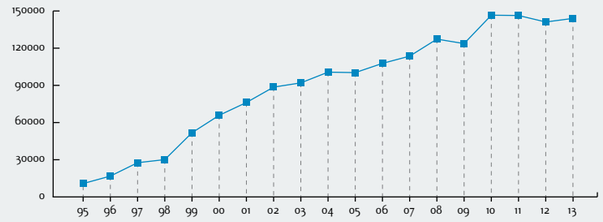
Key Case Mix Figures: Endoscopic Procedures



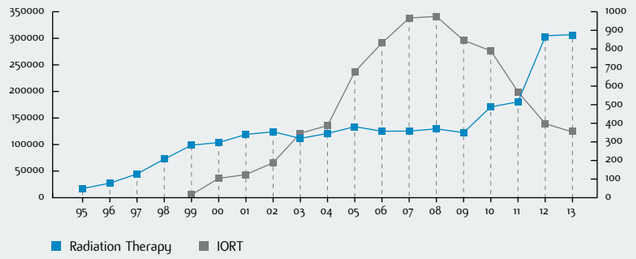
Key Case Mix Figures: Outpatient Admissions for Systemic Therapy



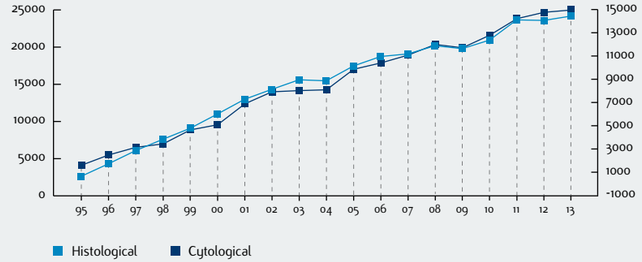
Key Case Mix Figures: Outpatient Visits



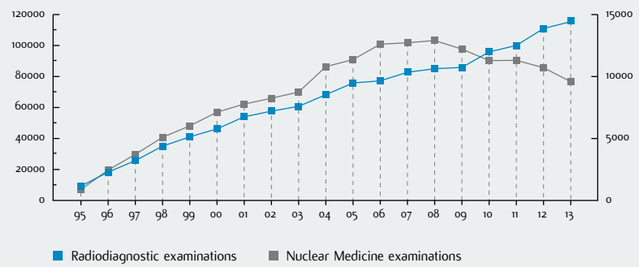
Key Case Mix Figures: Radiation Therapy & IORT



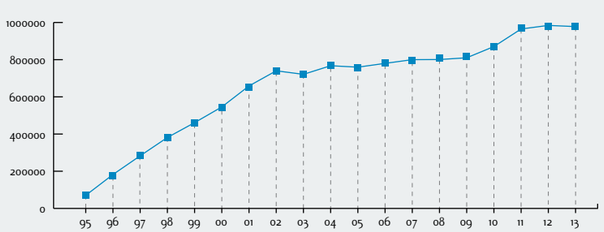
Key Case Mix Figures: Pathological Examinations



Key Case Mix Figures: Radiodiagnostic & Nuclear Medicine examinations



Key Case Mix Figures: Laboratory Tests



Research Operation

IEO is committed to build a knowledge-based environment for the rapid translation of scientific discoveries into patient benefits. Our goals are to promote and integrate Fundamental and Clinical Research, and to accelerate the access of our patients to innovation in oncology.

To this end, we have recently adopted a matrix-type organizational structure, in which patient management and clinical research are mainly entrusted to vertical lines (Multidisciplinary Programs), while horizontal ones (Clinical Departments and Clinical Services Platforms) are entrusted with the task of providing resources and services, as well as ensuring technological innovation and research in their respective fields of expertise. Fundamental-Research activities are hosted within the Department of Experimental Oncology.

The Clinical Departments are: I) the **Department of Medical Imaging and Radiation Sciences**, directed by Prof. Orecchia and II) the **Department of Pathology and Laboratory Medicine**, directed by Prof. Viale.

The Deparment of Experimental Oncology is directed by Prof. Pelicci.

The Clinical Service Platforms include Surgery Resources and Medical Resources.

The Multidisciplinary Programs include: the Breast Tumor Program, directed by Dr. Goldhirsch and Dr. Luini, the Gynecologic Tumor Program, directed by Prof. Colombo, the Lung Tumor Program, directed by Prof. Spaggiari and the Urogenital Tumor Program, directed by Prof. De Cobelli.

Other Multidisciplinary Programs are being structured, including the Immunotherapy Program, directed by Dr. Rescigno, the New Drugs Program, directed by Prof. Minucci and Dr. Curigliano and the Digestive and Hepato-Bilio-Pancreatic Program, directed by Dr. L. Capussotti.
The goals of our Multidisciplinary Programs includes building an integrated care pathway (prevention, diagnosis, cure and follow-up), ensuring the best-available diagnostic/treatment-options and the most advanced experimental therapies and promoting the integration of fundamental, translational and clinical research.

Centers of Excellence

Some of our activities have a long-standing experience of clinical-research integration and represent a consolidated reference for our patients, spanning all medical needs of cancer prevention, diagnosis, treatment and patient follow-up. They include the Advanced Radiotherapy Center (ARC; hosted by the Department of Medical Imaging and Radiation Sciences), the Cervical Cancer Center, the Ovarian Cancer Center (hosted by the Gynecologic Tumor Program), and the Cardioncology Center (hosted by the Medical Resources).

ARC: Advance Radiotherapy Center

ARC has the latest equipment available for the high-precision radiotherapy like Intensity Modulated Radiotherapy (IMRT, including dynamic arc IMRT using RapidArc technology), Image-Guided Radiotherapy (IGRT), respiratory gating, intraand extra-cranial stereotactic radiotherapy and 3-D conformal radiotherapy. There are 4 treatment planning systems (with image fusion modality), 2 computer tomography units and 6 linear accelerators for external beam radiotherapy including Trilogy and 3 accelerators installed at the beginning of 2012: Vero system, Tomotherapy and CyberKnife. Two mobile linear accelerators are installed in the operating theatres for the intraoperative electron beam radiotherapy (IORT with electrons, i.e. ELIOT). Molecular Imaging Unit and collaboration with Politecnico of Milan help in the definition of the optimal imaging, clinical and technological aspects of modern radiotherapy. Moreover, Brachytherapy Unit with low-, pulsedand high dose rate systems allows for the personalized approach in each patient. In 2013, 3366 new patients were treated in our Division: 2801, 352 and 213 with external beam radiotherapy, intraoperative irradiation (mainly for breast cancer) and brachytherapy, respectively. The highest proportion of patients has been treated for breast cancer (about 30%), metastastic disease (35%%) and prostate cancer (10%). Special selective RT techniques are employed in the majority of treatments: image guided intensity modulated RT (G-IMRT) was applied in 1186 patients whereas stereotactic radiotherapy in 457 patients. The patients treated with the last generation linacs include 381 patients treated with Trilogy, 429 treated with Tomotherapy, 585 with VERO system and 238 with CyberKnife. The choice of the treatment technique depends on the tumor position and extension as well on the patient characteristics (anatomy, concomitant diseases etc.). Based on the dosimetric and technological features of each linac the institutional rules has been established: VERO is dedicated mainly to prostate tumors and stereotactic body irradiation (thorax and abdomen), CyberKnife to stereotactic brain and spine radiotherapy, Tomotherapy to breast tumors and Trilogy to head and neck IMRT and pelvic IMRT (gynecological tumors, gastrointestinal malignancies, etc.)

CCC: Cervical Cancer Center

Opened in May 2011, the center is a unique facility that combines the latest prevention strategies with the most effective treatments of cervical cancer. Primary and secondary prevention, conservative surgery, imaging, pathology, robotic surgery, tailored chemo-radiation. Thanks to clinical studies and experience gained over the years, it has been possible to make a conservative path safe and reliable for young women with cervical cancer. All the sections of the center are top level and provide patients with the best available solutions from the interdisciplinary team. The Centre is involved in experimental clinical studies, national and international to evaluate new treatments for better health and fewer side effects. The center is also actively involved in a prevention program for the developing countries, and in particular for Madagascar.

OCC: Ovarian Cancer Center

Opened in September 2008, this center is a unique example of a multidisciplinary approach to patients with ovarian cancer. Specific aims of the Center are:

1. Patients' care
   a. Diagnosis: ultrasound and radiology specialists are dedicated to patients with ovarian cancer using the most modern diagnostic tools.
   b. Surgery: a strong collaboration between Gynecologic Surgeons, General Surgeons, Anesthesiologists, Pathologists grants the best surgical treatment to patients with ovarian cancer. Different approaches are performed, tailoring the most appropriate surgery for each patient: from minimally invasive fertility-sparing surgery for young patients with early disease, to the most aggressive surgical debulking for patients with advanced disease. More than 450 patients are treated surgically for primary/recurrent ovarian cancer.
   c. Chemotherapy: Gynecologic Oncologists offer the most innovative treatments, also allowing patients to participate in both National and International Trials. More than 2500 chemotherapies are administered yearly to patients with ovarian cancer.
   d. Supportive Therapy: psychological, nutritional support and palliative care are offered to all patients by dedicated Physicians and nurses.
2. Research: many collaborative trials and clinical/translational research are ongoing in order to improve the outcome of patients with ovarian cancer.
3. Education: ESGO fellowships for young Gynecologists and ESAGON School (European School of Abdominal/pelvic surgery) are part of the program of the OCC with the aim of training new generations of Gynecologic Oncologists and offering better care to patients with ovarian cancer.

Cardioncology Center

The International Cardioncology Society (ICOS, constituted the January 2009 by the Director of the Cardiology Division of the European Institute of Oncology, Dr Carlo Cipolla, Milan-Italy and the actual Director of Cardiovascular Research of the Vanderbilt University, Nashville-Tennessee, Dr Daniel Lenihan) promotes training and studies in the fields of: Cardiological and oncological comorbidities Cardiological implications of oncological treatments as:
- Chemotherapy, medical treatments (such as the use of monoclonal antibodies and target therapies)
- Radiotherapy
- Immunoradiotherapy
- Locoregional treatments
- High-dose chemotherapy
- Multiple, combined and sequential cancer treatments.
- It promotes basic biology research on anticancer drugs mechanisms of cardiotoxicity focusing on inflammatory and metabolic pathways involved in heart damage.

The clinical activities of the IEO Cardioncology Center relate to early diagnosis, prevention and treatment of chemotherapy induced cardiotoxicity.
In 2013 the out-patients clinic of the center has performed more than 1400 cardioncologic evaluations. An official internal clinical IEO protocol for cardiotoxicity early preclinical diagnosis and prevention is currently applied to all the IEO patients undergoing chemotherapy and newer target therapies. Moreover, in the Center are treated pericardial diseases, as neoplastic pericardial effusions by means of intrapericardial chemotherapy (with Thio-tepa) for pericardial effusion and, more in general, are treated all the potential relations between cancer and cardiovascular diseases.

Clinical Research

Breast Tumor Program

Aron GOLDHIRSCH, MD
Director

Alberto LUINI, MD
Co-Director

Components

- Division of Breast Cancer Surgery
- Division of Plastic and Reconstructive Surgery
- Division of Medical Senology
- Division of Breast Radiology
- Division of Cancer Prevention and Genetics
- Division of Early Drug Development for Innovative Therapies
- Division of Radiotherapy
- Applied Research Unit for Cognitive and Psychological Science
- Department of Pathology
- Department of Experimental Oncology
- Division of Epidemiology and Biostatistics
- Data Management

Vision and Mission

The mission of the Breast Program is to provide every woman with breast disease with the accurate personal attitude, through targeted diagnostics, therapeutics, appropriate education and support to strengthen (empower) the Patient's confidence and enhance the odds for early diagnosis and appropriate treatment, customized for each individual with breast disease.
The Breast Program is aimed at providing with a multidisciplinary method, excellence in diagnostics, clinical and surgical approaches, as well as clinically oriented research, to achieve the maximum effectiveness of the service to patients.
A vision that combines clinical research, basic research applied to the clinic and all the details of medical and surgical approaches may merely be obtained with a constant cooperation between various specialists. The expertise to each member of the multidisciplinary team is needed for continued progress in the field. In fact, this modality was the basis for the enormous progress made in the past at the IEO, being Breast Care a priority of our Institute. In particular, Breast Care is aimed at prevention, diagnosis, treatment, rehabilitation and psychological support of people affected or at risk for breast cancer.

The Breast Program is based upon a concrete personal approach to women with breast cancer. This is entirely centered upon a multidisciplinary methodology to the care of breast cancer, and innovation through clinical research. Particular attention is given to quality of life of patients and their families.
The IEO Breast Program creates, in an Italian and European environment, the ideal conditions for personalised approach to every patient with breast cancer: the personalization allows to get a treatment with the utmost probability of effectiveness and a positive and constructive relationship between patients and their care givers, conditions in which fear and doubt can be replaced by greater knowledge and regained hope.
The intensive interaction between various specialists at the IEO has always been a tradition which led to important progress in breast cancer care and research. Such approach led to customize technical excellence, fruit of collaboration between divisions and units at the Institute, as well as intense networking with several research institutions and cooperative groups around the world. Physicians at the IEO invented and proved valid the most widely used and effective techniques of surgical care with integration with radiation therapy and medical care adopted today worldwide. An important strength of the Breast Program are the distinct structured multidisciplinary discussions for each type of presentation of the disease, to allow the best diagnostic and therapeutic approach for each patient.
This includes specific discussions for preoperative systemic treatments, surgery, and postoperative local and systemic therapies. Furthermore, discussion about clinical research programs which might suit patients with advanced breast cancer is also taking regularly place.
The personalization of prevention and care is the basis for excellence, which benefits both the general population and the patients with breast disease. This obviously requires an educational program aimed at updating of the staff. Active participation in activities of in-house training, diagnosis, prevention and care, sharing experience and discussion of clinical research programs is an important component of the Breast Program. The discussion and recording of outcome of specific clinical conditions, participation in international conferences, contribution to various Italian and foreign research and academic institutions is an important part of the IEO Breast Program.
Starting 2013, within the program a number of objectives of innovation in the next future were identified:

- Maximize information on biological and prognostic features for all types of breast cancer before primary treatment (surgery, systemic therapy)
- In selected cases allow for a fast genetic counseling and testing for susceptibility genes for a proper surgical plan.

This early knowledge of the biological and genetic factors significantly helps to find the best choices of the therapeutic program.

Priority research projects

1. Research project to identify individuals with genetically defined high risk.
2. Research project to identify features predicting responsiveness to metronomic agents *in vivo* and *in vitro*.
3. Tumor banking for systematic evaluation of molecular variables in breast cancer to allow the selection of individuals in specific trials with specific molecular markers as selection criteria.

Other research projects

4. Cancer endocrinology
5. Biology of the stroma: reconstructive approaches
6. Lymphangitic breast cancer
7. Late recurrence
8. Psychosocial research projects

Division of Breast Cancer Surgery

Alberto LUINI, MD
Director

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Director, Unit of Integrate Senology: Paolo Veronesi
Director, Unit of Diagnosis and Therapy in Senology: Stefano Zurrida
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Auxiliary Personnel: Mercedes Monzo, Patrizia Frigatti, Rossana Vangelista, Rosa Soranno, Chiara Agratti
Case Managers: Caterina Cubeddu, Rocca Elena, Antonella Angeli
Clinial secretaries: Valeria Archinti, Simona Perri, Annamaria Corapi
Scientific secretary: Maria Grazia Villardita
Personal Assistant: Iliade Federica Lombardi

Activities 2013. The Division of Breast Surgery is the first in the World in terms of operations performed each year, performing 70% quadrantectomy or partial resection (the removal of the lesion with a certain amount of surrounding healthy tissue and a small portion of skin). In 30% of cases we perform mastectomy, the removal of the entire breast gland with immediate reconstruction with various techniques of reconstructive plastic surgery.
The Breast Surgery Division manages the follow-up of the majority of patients operated on for breast cancer or DIN and LIN, and — before any treatment — breast surgeons perform the clinical visit for diagnosis and indication of subsequent therapeutic approach. In the case of need of neoadjuvant chemotherapy, we immediately discuss the case with Breast Oncologists.
We cooperate daily with specialists of the Divisions that are part of the Breast Program, being the work in a multidisciplinary team the basis of excellence: this is evident from clinical studies conducted so far and still ongoing.
When the tumor is not palpable (microcalcifications or very small nodules), we use localization techniques to avoid errors and unnecessary removal of healthy tissue: the ROLL (Radioguided Occult Lesion Localization-localization of radio-guided occult lesions), invented at the IEO, is the most widely used around the world with the best results, but sometimes we can opt for skin mark.
Surgery for breast cancer is associated with sentinel node biopsy: the sentinel lymph node is the first lymph node that receives the lymph from the breast affected by cancer. Also in the case of the sentinel lymph node IEO was the first center in the World to validate the technique with a randomized trial. If the sentinel node analysis confirms the absence of tumor cells it is not necessary to proceed with the removal of the other axillary lymph nodes, but if the sentinel node contains cancer cells the surgery is completed with a lymph node dissection (all the lymph nodes are removed from the axilla for subsequent histological examination). A special case is the micrometastasis in the sentinel node, that is the presence of tumor cells up to 2 mm in diameter: in this situation we can avoid complete axillary dissection due to the results of an international multicenter study coordinated by IEO and recently concluded.
When the patient needs a mastectomy, in the majority of cases we guarantee the immediate reconstruction using techniques depending on the individual situation: breast surgeons cooperate with plastic-reconstructive surgeons to get the best cosmetic results. Breast conserving surgery and, rarely, mastectomy may be followed by radiation therapy.
The intraoperative radiotherapy is one of the symbols of the IEO clinical research in breast cancer. Thanks to the studies carried out in IEO, ELIOT (Electron Beam IntraOperative Radiotherapy) can be performed during quadrantectomy with a single dose of 21 Gy that completely replaces the course of external beam radiation therapy, or a dose of 12 Gy as a boost followed by a shorter course of external beam radiation therapy. The ELIOT is used in some cases of nipple-sparing mastectomy for irradiating the nipple-areola complex kept in place.
Nipple sparing mastectomy is a surgical technique developed by IEO more than ten years ago (dating back to 2002).
This technique allows the removal of the mammary gland preserving entirely the outer shell (skin and nipple) and the integrity of the female image. Breast reconstruction is done simultaneously with mastectomy, usually with implants (permanent prosthesis or expander). Over the years the technique constantly improved. The retroareolar tissue is removed completely and radically and thanks to the refinement of the surgical technique the risk of complications, in particular the necrosis of the nipple, is very low and in continuous reduction. We always perform an intraoperative histological examination of the tissue immediately below the nipple, to ensure the maximum oncological radicality. In case of positivity for tumor or DIN, the nipple-areola complex must be removed. Should reveals additional facts histologically, the multi-disciplinary consultation assesses the need for postoperative irradiation limited to the nipple-areola complex or extended to the entire breast area and / or regional lymph node.
The intraductal lesions are precancerous and do not have the potential to spread to other organs or to the axillary lymph nodes. For this reason, surgery is conservative and does not require the removal of axillary lymph nodes, even the sentinel lymph node. In the event that, given the extent of the tumor, more extensive surgery (mastectomy) is necessary, or in the case of multicentric DIN3, sentinel lymph node biopsy is indicated.
These guidelines come from the research of our Division.
In 2013 we performed 3466 surgical procedures: 1335 with traditional hospitalization and 1131 with day surgery. Globally, 2530 operations have been performed for breast carcinoma and 330 for in situ lesions: 1800 were conservative procedures and 1060 mastectomies with plastic reconstruction (451 nipple sparing). We performed also 1820 sentinel node biopsies and 321 ELIOT (Intraoperative Radiotherapy) treatments.
One of our main point of excellence is the multidisciplinary approach: every week we discuss all patients treated in our Division in the team of the Breast Program; during 2013 the mean time between surgery and this multidisciplinary consultation was 8 days, we has 52 sessions of these meeting and a mean of 55 patients was discussed at every meeting.
In our multidisciplinary activity we contributed to collect 922 questionnaires of familiarity and to perform 479 genetic tests.
Our Division is performing a randomized study with two arms comparing the sentinel lymph node biopsy to the simple observation without axillary surgery in patients whose axillary lymph nodes appears to be healthy preoperative ultrasound (SOUND).

We are owner of the AIRC grant for studies of high innovation in multidisciplinary treatment of breast cancer. Cooperation with the Division of Laboratory Medicine allows us to conduct a study on the evaluation of prognostic and predictive value of circulating tumor cells in patients with breast cancer at different stages of the disease. We are also studying the efficacy and safety of HIFU. This study involves a selected population of patients with unifocal breast cancer in sizes up to 15mm. The patients undergo a complete diagnostic evaluation consisting of breast ultrasound, mammography, MRI of the breast and needle biopsy of the nodule to confirm the neoplastic nature. After HIFU treatment, performed in a single session in Day Surgery, patients undergo standard surgical treatment.

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Division of Plastic and Reconstructive Surgery

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Activities 2013. The Division of Plastic Surgery is dedicated to the improvement of quality of life for patients treated for cancer at the EIO. We fully collaborate with the Breast Surgery division and we also support the divisions of Gynecology, Thoracic surgery, General Surgery, and Melanoma and Sarcoma. Our main contribution to breast surgery includes performing all the techniques of immediate breast reshaping after conservative surgery (so called oncoplastic surgery) and all the techniques of total breast reconstructions (immediate and delayed procedures), including the use of tissue expanders or definitive implants, latissimus dorsii flaps, TRAM flaps and microsurgical flaps. We are also developing new approaches such as the use of an Acelullar dermal matrix (ADM) associated with implant breast reconstructions. The use of fat grafting has been also strongly developed in our department; it is more frequently used as a refinement after breast reconstruction or, in selected cases, for total breast reconstruction exclusively with adipose tissue.

The Division also has a role in medical education and each year, in June, organizes a breast surgery course, with three days of live surgery, in order to teach breast surgeons and plastic surgeons to deal with reconstructive surgery.

Ongoing studies:

Several studies are ongoing in our division:

- *Fat grafting clinical study:* in order to verify the oncological safety after breast cancer treatment.
- *Fat grafting laboratory research:* in collaboration with our experimental research lab, we are developing an animal model to study the protective effect of metformine against breast cancer recurrence after lipofilling and breast cancer.
- *Breast reconstruction with biological meshes and implants:* we are carrying out a trial on the use of a Surgimend mesh (derived from bovine pericardium) in 50 consecutive immediate breast reconstructions with implants to evaluate the post operative incidence of complications and benefits. We are also conducting a study with SERI (derived from silk) in immediate breast reconstructions with implants, to optimise the protocol/ indications for this material.
- *Protocols for the use of the (Da Vinci) robot in breast reconstruction:* we are developing a new technique to perform prophylactic mastectomy and breast reconstruction in cases of genetic mutation, using the Da Vinci robot with an axillar incision.
- *Breast reconstruction with pre-molded absorbable scaffold:* we are testing an new re-vascularized absorbable scaffold in lab animals. In the future, this new product will probably replace silicone gel implants.

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Medical Division of Breast Tumors

Marco COLLEONI, MD

Director

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Fellow: Andrea Francesco Sporchia
Research Nurses: Claudia Passoni, Ada Sbriglia
Data Managers: Raffaella Ghisini, Francesco Sangalli, Claudia Sangalli
Secretaries: Simona Puddu, Marcella Netti

Activities 2013/14.

The Division of Medical Senology provides care and conducts research in an integrated fashion in the field of breast cancer. The Division is aimed to provide comprehensive care of all the types and phases (preoperative, adjuvant, advanced disease) of breast cancer with active clinical and translational research, integrating out-patient and in-patient areas through a common support.
The principle of providing the best personalized care for the individual patient with breast cancer, with full respect for quality of life and proper communication, is the best support for competitive and innovative clinical research.
The principle shared by members of the Division is that increased participation in clinical trials would increase learning about the disease and improve patient care.
Weekly multidisciplinary meetings for both the preoperative, adjuvant and advanced setting are planned in order to properly address a tailored clinical and investigational approach.

Research projects are being carried out in close collaboration with other Divisions and Units at the IEO and with National and International Cooperative Groups. International trial cooperation, focused on questions relevant for patient care and biological principles, represents one of the major commitments for the Division. Particularly, large cooperative trials focusing on adjuvant endocrine therapy of premenopausal patients, extended endocrine therapies in postmenopausal patients, maintenance therapy in endocrine non responsive breast cancer are ongoing at the Division of Medical Senology under the umbrella of the International Breast Cancer Study Group (IBCSG). New generation trials concentrate on preoperative endocrine treatment of premenopausal patients and on new chemotherapy approaches in advanced disease.
In addition, clinical trials ongoing in the Division focus on the types and phases of breast cancer in order to better target the specific treatment for each patient. A collaborative approach involving the development of new agents and investigation of their optimal integration in therapy programs will best ensure progress for improved patient care. Studies focusing on safety, quality of life, subjective side effects and personal costs are routinely incorporated in the patients care. Assessment of factors, which are associated with response or resistance to therapy, and exploration of new therapies according to baseline prognostic features are considered as a priority in the development of the best multi-modal strategy including sequence of local and systemic treatments. Research studies are conducted to define the value of new high-throughput technologies in assessing the level of risk and likelihood of response to specific therapies, in order to improve our knowledge and lead to better tailoring of therapies, with a special attention to rare histological types, inflammatory breast cancer chemotherapy regimens delivered in a metronomic fashion and very young patients. We are committed to providing each patient with the best and most personalized treatment options available, taking advantage of the full range of services of a top-ranked cancer hospital and research center. Such an approach brings clinical research closer to the individual patient.

Clinical Trials

- IBCSG 42-12/BIG 2-12 SNAP. “A randomized phase II study evaluating different schedules of nab-Paclitaxel in metastatic breast cancer”. EudraCT Number: 2012-003058-10
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- IEO S582/111. A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients: VEX STUDY. EudraCT 2010-024266-21
- IEO S479/209. Phase II study with Epirubicin, Cisplatin and infusional Fluorouracil (ECF) followed by weekly Paclitaxel plus metronomic Cyclophosphamide ± Trastuzumab and endocrine therapy as preoperative treatment of locally advanced breast cancer EudraCT N.: 2009-012048-18
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Gynecologic Tumor Program

Nicoletta COLOMBO, MD
Director

Components

- Division of Gynecologic Cancer Surgery
- Medical Division of Gynecologic Tumors
- Unit of Preventive Gynecology
- Unit of Procreation and Fertility
- Division of Laboratory Medicine
- Division of Radiology
- Molecular Medicine Program
- Program of Immunotherapy
- Department of Experimental Oncology
- Division of Pathology
- Division of Radiotherapy
- Division of Nuclear Medicine
- Division of New Drugs and Early Drug Development for Innovative Therapies
- Applied Research Unit for Cognitive and Psychological Science
- Unit of Interventional Radiology

Vision

To provide a unique example in Italy of clinical care for patients with gynecological cancers focused on prevention, excellence in care, high quality research and education, in order to improve their prognosis and quality of life.

Mission

To implement an integrated platform of comprehensive multidisciplinary services for diagnosis, treatment and supports of all patients with gynecological malignancies at every steps of their disease.
To create a highly visible community outreach and educational program on gynecological cancers and enhance awareness regarding the importance and the benefits of centralized expert care for advanced cases.
To establish an integrated collaboration between the research and the clinical programs that will advance the science of prevention, early diagnosis, and personalized treatment.

Patient care

The Gynecologic Tumor Program provides servives for prevention, diagnosis, treatment and follow-up of women affected by gynecological malignancies. A clinical coordinator provides patient assistance with triage both within and among the collaborating departments in order to assure expedited access to trans-departmental services. All staff members are involved in multidisciplinary patient management, shared decision making within dedicated tumor boards, pathology discussion and radiological review of the most significant cases. Patients and their families have access to psychological support and decisional counseling, if needed. The division of Gynecologic Surgery at IEO is recognized as a premier national referral center for the most complex surgically cases. More than 300 ovarian cancer patients have undergone cytoreductive surgery in 2013. Moreover, the division of Gynecology has pioneered the use of minimally invasive robotic surgery in the treatment of cervical cancer and endometrial cancer. With 43 active clinical trials in 2013, the majority of patients who need postsurgical treatment have access to experimental therapies. A particular attention is devoted to young patients affected by early stage epithelial ovarian cancer, germ cell tumors, endometrial cancer and cervical cancer, for whom a dedicated clinical pathway has been identified, with a special emphasis in preserving their fertility. Among the out patient activities for prevention, 10.000 Pap Smear / HPV test, 3500 colposcopy and 7300 transvaginal ultrasound have been performed in 2013.

Research Activities

The Program has launched a series of research activities aimed a) at a better understanding of OC biology for the design of novel therapies and b) at defining novel biomarkers for early diagnosis and for predicting the tumor response to therapy. These tasks rely on the integrated efforts the Program members with other IEO members (Prof. Di Fiore, Molecular Medicine Program; Dr. Testa, Dept. Experimental Oncology) and with external investigators (Dr. Giavazzi and Dr. D'Incalci, Ist. Mario Negri; Prof. Fodde, Erasmus Medical Center, Rotterdam; Dr. Gabra, Imperial College, London; Dr. Drapkin, Harvard Medical School).

The ongoing research activities of the Program include:

- The molecular and functional characterization of ovarian cancer stem cells as potential therapeutic target for OC eradication, based on innovative technologies for OCSC isolation.
- The definition of novel OC pathways/biomarkers through functional proteomics.
- Profiling circulating biomarkers as diagnostic and/or disease monitoring tools.
- A patient-derived xenograft platform for basic tumor biology (e.g., cancer stem cells) and translational studies (e.g., preclinical trials of novel therapeutic strategies in collaboration with pharmaceutical companies).
- Participation to a virtual gynecological tumor bank network (with IRFMN, INT, Brescia, Monza, Lecco, Policlinico Gemelli) as an enabling resource for clinical/translational studies on suitable patient cohorts.
- Several clinical trials of new drugs (both pharma sponsored and academic), mainly in ovarian and endometrial cancer. Our recognition as opinion leader and our contacts with the main pharmaceutical companies enable us to be included in most international clinical trials for gynecological cancers.
- Several surgical trials (e.g., a multicenter study to establish the role of secondary cytoreduction in OC and the role of HIPEC after surgical debulking). We will also attempt to define biological and clinical predictive factors to identify those patients more likely to benefit from primary debulking surgery. A better patient selection will in fact not only improve outcome and quality of life but also decrease the high cost associated with this surgical procedure.
- Several studies for cervical cancer prevention are ongoing: a) a large cohort study on HPV vaccination on 750 eighteen years old women with the goal to evaluate the vaccine impact on the natural history of cervical HPV infection. b) A vaccination multicenter project with the aim to evaluate vaccine efficacy in women conservatively treated for cervical cancer precursors who have a risk for cervical cancer 2.5 to 4 times higher than in the general population. c) HPV genotyping to detect early recurrence after treatment. d) a new tissue marker of HPV infection has been developed and patented in collaboration with the Department of Experimental Oncology (dr. Susanna Chiocca) and Pathology (dr. Chiara Casadio); the new marker is being further tested in prospective validation studies.

Educational Activities

The GOP is leader in education with the ESAGON program, that every year offers an advanced post-graduate training, with a particular focus on the recent important progress in the field of oncologic surgery. Thanks to an educational model based on the "Observe and Discuss" approach, ESAGON benefits from the involvement of world-renowned experts from different Institution of excellence.
We have been recognized by ESGO (European Society of Gynecologic Oncology) as a training center and offer a 3-year fellowship program in Gynecologic Oncology.
We offered and will offer a short stage of two days for 15 gynecologic oncologists which includes both formal lectures and practical clinical activities.

Trough the cooperation with ESGO and ESO (European School of Oncology), the program will wide the horizon of education in gynecologic oncology, implementing the first European Master class in 2015. Moreover, the program will include a colposcopy training course, a gynecologic US course and a basic laparoscopic course.

Governance

Prof. Nicoletta Colombo, Dr. Angelo Maggioni, Dr. Mario Sideri, Dr Fedro Peccatori, Dr.ssa Maria Teresa Sandri, Dr.ssa Stefania Rizzo, Dr. Ugo Cavallaro, Prof. Giancarlo Pruneri, Prof. Gabriella Pravettoni, Dr.ssa Maria Rescigno.

Publications

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Midwife: Linda Franzini
Research Nurse: Eugenia Tomas Roldan
Nurse: Patrizia Capodivento

Activities 2013. The Division of Gynecology provides all services involving the diagnosis, treatment and follow-up of gynecologic oncology patients. The staff members are a fully-trained gynecologic oncologist responsible for various activities, including surgery (minor, major and minimally-invasive), research, clinical trials, and early diagnosis.
Among the surgical activities, particular attention is devoted to fertility preserving surgery in young patients with borderline ovarian tumors, early-stage ovarian, endometrial and cervical cancer. The Division has also the facilities and the experience to perform major surgery such as extensive cytoreduction in patients with advanced ovarian cancer and pelvic exenteration with intra-operative radiotherapy (IORT) in patients with recurrent cervical, endometrial and vulvar cancer.
Minimally-invasive robotic and laparoscopic surgery is commonly applied to the treatment of different gyneco-logical malignancies. The foundation of Robotic School in Gynecologic Oncology was promoted in 2009 for teaching innovative minimally-invasive surgical technique.
Members of the Division also have institutional teaching responsibilities that mainly involve training residents and fellows, but they are also involved in Continuing Medical Education (CME) programs.
The foremost educational objective of European School of Abdomino-pelvic surgery in Gynecologic Oncology (ESAGON), founded in November 2009, is to transmit an approach to surgery based upon the natural history of the diseases as well as traditional surgical techniques, and what the relevant technology offers. The School involves both institutions and individuals from different countries.
In July 2010, the Gynecology Department has been recognized as an accredited European Center in Gynecologic Oncology by ESGO (European Society of Gynecologic Oncology) and EBCOG (European Board and College of Obstetrics and Gynecology).

The Unit of Preventive Gynecology encompasses the fields of prevention, surveillance and diagnosis of gynecologic cancerous and pre-cancerous lesions. The clinical activities involve 16 gynecologists. The results of the research activities are published in peer reviewed journals, IF was 62,755 in 2013, with 22 publications.

The Unit has a high experience in laser surgery for cervical, vaginal, and vulvar pre-cancerous and cancerous lesions with approximately 750 laser treatments on lower female genital tract diseases yearly. HPV test and HPV genotyping are used for the management, diagnosis and follow-up of cervical pre-cancers and cancers. P16 and other biomarkers are used in screening and triage of borderline lesions; 2.000 colposcopic exams are performed yearly.
Primary prevention of HPV related pre-cancerous and cancerous lesions is the goal of our HPV vaccination centre, were both adolescents and women in older ages can receive HPV vaccination.

The Unit is involved in the early detection of ovarian cancer as in general population as in high risk of patients with BRCA1/2 mutation or history of previous breast cancer: during 2013 more than 6.000 transvaginal or transabdominal pelvic US have been performed and about one hundred prophylactic salpingo-ophorectomies.
Our team is also dedicated to the diagnosis, management, and follow-up of endometrial abnormalities and early endometrial cancer through transvaginal US and hysteroscopy. More than 350 diagnostic and operative hysteroscopies are performed yearly for uterine polyps and abnormal uterine bleeding.
Conservative treatment includes hormonal therapy of endometrial atypical hyperplasia and early endometrial cancer with progestational agents.

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Medical Division of Gynecologic Tumors

Nicoletta COLOMBO, MD
Director

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Research Fellow: Rosalba Portuesi, MD
Data Managers: Sara Boveri, Abbondanza Montinaro
Secretaries: Gloria Gavioli, Diana Valli
Director Fertility and Procreation Unit: Fedro Peccatori, MD, PhD
Research Fellow: Maria Anna Sarno
Counselor: Eleonora Chiavari

Activities 2013. The Division of Gynecologic Oncology strictly interacts with the Division of Gynecologic Surgery and Gynecologic Prevention to provide diagnosis, treatment and follow-up of women affected by gynecological malignancies. Each staff member is a fully-trained gynecologic oncologist, responsible for various activities within the Division, including the administration of anti cancer agents and supportive care. Clinicians from the Division of Gynecologic Oncology are principal investigators in several international and national trials, addressing new treatment strategies in ovarian cancer, endometrial cancer and cervical cancer. Most of the clinical trials are run in co-operation with MaNGO, Mario Negri Gynecologic Oncology Group, and ENGOT, an organization of European cooperative groups for clinical trials in gynecologic cancers.

Young patients with gynecological malignancies, breast cancer, malignant lymphomas and other solid tumor have the opportunity to freeze ovarian cortex or oocytes prior to chemotherapy, surgery or radiation therapy.
Gamete storage is performed in cooperation with other Istitutions, thus allowing fertility recovery also after gonadotoxic treatments. Last year we conducted several cooperative clinical trials, focused mainly on the treatment of ovarian and endometrial cancer patients. We completed the enrollment in an international phase III trial (TRINOVA-3), evaluating the role of AMG-386 in first line setting of ovarian cancer patients. At the 2013 ESGO Biennial Meeting, the preliminary results of the AGO-OVAR12/LUME-Ovar 1 were reported. This was a phase III randomized placebo-controlled trial, directed to postoperative patients with newly diagnosed FIGO stage IIB-IV ovarian cancer, randomized 2:1 to carboplatin-paclitaxel with or without BIBF 1120 (nintedanib, a potent small molecule triple kinase inhibitor targeting VEGFR 1, VEGFR 3 and FGFR 1). The trial, with 1366 patients enrolled, had met its primary endpoint and demonstrated a significantly longer PFS for patients treated with nintedanib (HR= 0.84; p= 0.0239). Still ongoing are the MITO-8 (PLD compared to CBDCA-PTX) and INOVATYON (PLD-CBDCA compared to PLD-Trabectedin) trials, that could make a significant contribution to the long debate whether the extending of the platinum-free interval with a non-platinum combination prolongs survival in patients with partially platinum-sensitive disease. For resistant/refractory disease, we have recently completed several randomized studies regarding the activity of AMG-386, NGR-hTNF, MM121 (an anti-ErbB3 human monoclonal antibody) and OSI-906 (an inhibitor of insulin-like growth factor 1 receptor - IGF-1) in combination with standard chemotherapy. In this setting of patients, we recently restarted with a phase I trial evaluating the safety of S78454, an H-DAC inhibitor, given with a fixed dose of PLD. The TRINOVA-1 results, presented at the 2013 ESMO congress, showed an improved PFS using trebananib in combination with paclitaxel compared to paclitaxel alone (HR= 0.66, p<0.001) in patients with resistant or partially platinum-sensitive disease. It is still ongoing a randomized clinical phase II trial with Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced (Stage III-IV) or recurrent endometrial cancer. In addition, we recently closed a phase II single-arm study to evaluate the efficacy of oral dovinitib as second line therapy in patients with advanced and/or metastatic endometrial cancer.

Clinical Trials

- MITO16/MANGO-OV2: a multicenter italian study, aimed to identify the clinical and biological prognostic factors of bevacizumab in combination with standard chemotherapy in FIGO stage III-IV ovarian cancers.
- SOLO study: a phase III trial designed to determine the PFS with olaparib as maintenance monotherapy in ovarian cancer patients with BRCA mutation with complete or partial remission following first line platinum-based chemotherapy (SOLO1) and at relapse (SOLO2). Results are expected in 2015.
- PENELOPE: a phase II study that investigate the role of pertuzumab, a monoclonal antibody directed against HER2, in combination with standard chemotherapy, paclitaxel, topotecan or gemcitabine, in recurrent platinum resistant ovarian cancer.
- BEVA-TRABE: a multicenter, randomized, non comparative, phase II study on the efficacy and safety of the combination of bevacizumab and trabectedin with or without carboplatin in patients with partially platinum-sensitive disease.
- PANKOMAB: we just opened a double-blind, placebo controlled, phase II study to evaluate the efficacy and safety of maintenance therapy with PanKoMab-chemotherapy, a monoclonal antibody which recognizes the tumor-specific epitope of mucin-1 (TA-MUC1) to induce antibody-dependent cellular cytotoxicity (ADCC), in recurrent ovarian cancer patients.

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Lung Tumor Program

Lorenzo SPAGGIARI, MD
Director

Components

- Division of Thoracic Cancer Surgery
- Division of Thoracic Oncology
- Division of Pathology
- Division of Radiotherapy
- Dendritic Cell Biology and Immunotherapy Unit
- Applied Research Unit for Cognitive and Psychological Science
- Molecular Medicine Program
- Radiotherapy
- Interventional pulmonology program (diagnosis and palliative treatment of neoplastic obstructions)

Vision and Mission

The Mission of "Lung cancer" program is to offer the patients suffering from thoracic neoplasms a diagnostic and therapeutic course based on a multidisciplinary approach involving oncologists, thoracic surgeons, radiologists, radiotherapists and pathologists.
Main targets of the Program are: developing of a complete way for diagnosis and treatment of thoracic neoplasms; maximizing interactions between clinical and research programs; providing the patients with a personalized clinical care offered by committed staff; implementing research on lung cancer by close cooperations with international scientific societies as IASLC, ESMO, AIOM and AIOT.

Patient care

- Surgery for locally advanced lung cancer
- Surgery for early stage lung cancer (Robot assisted and videothoracoscopy)
- Parenchyma sparing surgery for lung metastases
- Pre- and post-operative chemotherapy for locally advanced lung cancer
- Standard chemotherapy as well as targeted therapy for advanced lung cancer
- Phase II-III clinical trials for thoracic malignancies
- Standard and innovative treatments for soft tissue sarcomas, mesotheliomas and thymomas

Research Activities

Genome sequencing of never-smoker twins with lung adenocarcinoma to identify the genetic alterations that contribute to cancer risk.

About 25-30% of lung cancer cases are not attributable to tobacco smoking. Lung cancer in never smokers ranks as the seventh most common cause of cancer death worldwide.
It is now clear that lung cancer in never smokers is a different entity compared to lung cancer arising in smokers. Indeed, differences in terms of clinical and pathological features make of it a completely different disease with diverse prognosis and strategy of care. Accordingly, molecular features indicate that tumors in smokers and never smokers are biologically distinct. In particular, molecular alterations of EGFR and ALK are present in a relatively high percentage of tumors in never-smokers patients and define response to target treatments.
Several studies have been carried out to investigate possible risk factors that could explain lung cancer in never smokers, but the etiology still remains unclear.
However, given the younger age of onset and the particular geographic distribution of this subtype of tumor, genetic factors could play an important role in the genesis of lung cancer in never smokers since they could contribute to a higher susceptibility to carcinogens or by conferring an "hereditarily predisposition" to lung cancer.
With this project we intend to explore by whole-exome sequencing and Comparative Genomic Hybridization (CGH) the germline and somatic variants present in tumor and normal samples derived from monozygotic twin sisters, both affected by lung cancers bearing EFGR mutations. The ultimate aim is the identifications of the genetic alterations that can contribute to cancer risk, through the development of a bioinformatics strategy able to prioritize rare and novel alterations of cancer genes (oncogene and tumor suppressor) that are uncommon in the general population but common in these cancers.
The alteration of these predisposing genes will be tested in additional never-smoker EGFR-mutated patients.

Epidermal growth factors tyrosine-kinase inhibitors (EGFR-TKI) efficacy in NSCLC patients with high polysomy of chromosome 7 and EGFR/KRas wild type tumors.

More than even before, the efficacy of epidermal growth factors tyrosine-kinase inhibitors (EGFR-TKI) in NSCLC patients carrying EGFR wild-type tumors has been under investigation. EGFR wild-type patients represent a large and heterogeneous group of patients. Since few therapeutic options following first-line therapy are available, defining additional biomarkers that could be used to identify a subgroup of EGFR wild-type patients deriving a benefit from EGFR-TKI is crucial. In this setting, the role played by high polysomy of chromosome 7 still remains controversial. Indeed, previous reports did not discriminate between chromosome 7 high polysomy and EGFR amplification and/or did not investigate the simultaneous presence of EGFR and KRas mutations.
At the European Institute of Oncology in Milan, data from 163 patients analyzed for EGFR status (mutation, amplification, chromosome 7 trysomy and polysomy), in addition to KRas mutation, were retrospectively collected. Among these 163 patients, 72 received EGFR-TKI. All the patients were previously treated with at least one line of chemotherapy. Objective responses and time to progression to EGFR-TKI were evaluated. Among the 163 samples analysed, 25 (15.3%) displayed high polysomy of chromosome 7, in presence of EGFR wild-type, absence of KRas mutation and EGFR amplification. Twelve patients, out of the 25 with high polysomy, received EGFR-TKI. The treatment led to a disease control in 10 of them (80%). One patient was lost to follow-up. In terms of overall response rate, 4 partial responses and 5 stable diseases were observed. Two patients progressed. The mean time to progression was 8.9 months.
In conclusion, high polysomy of chromosome 7 characterizes 15% of tumors without EGFR mutations. Among the EGFR wild-type population, the evaluation of high polysomy of chromosome 7 could be a helpful tool to predict for benefit from EGFR-TKI.

Endoscopic treatment of broncho-pleural fistula by autologous stem cells transplantation.

Lung cancer is the leading cause of cancer death worldwide. Despite the efforts to identify new therapeutic strategies, surgery still represents the only opportunity for cure for patients with NSCLC. Only patients with a loco-regional disease can undergo surgery, since the goal is the complete tumor resection as a definitive primary therapy. Unfortunately, sometimes the excellent long-term results of surgery can be nullified by post-surgical complications, such as bronchopleural fistula (BPF). Indeed, bronchopleural fistula leads the patient to death in an extremely high percentage of cases (up to 71.2%). It appears therefore of paramount interest the development of effective BPF treatment procedures.
We are currently carrying out a project aimed at investigating the safety and the efficacy of bronchoscopic injection of autologous mesenchymal stem cells (MSC) to treat BPFs. Indeed, the creation of artificial BPFs in goats allows us to study the growth and the localization of MSC into the bronchi and to estimate the efficacy of this mininvasive therapeutic approach. Autologous MSCs isolated from the bone marrow were inoculated through bronchoscopy, together with a fibrin-glue, into goats. A control group was inoculated with the fibrin-glue alone. The evolution of BPF was followed using serial bronchoscopy for 15 days and then animals are sacrified after 30 days.

Before inoculation, MSC were infected with a lentiviral vector codifing for a report gene, the galactosidase gene (LacZ) in order to easily detect the MSC into the collected frozen samples.
At present, an experimental bronchopleural fistula was created in nine goats following right upper tracheal lobectomy. The animals were randomly assigned to two groups: one received autologous bone marrow-derived mesenchymal stem cell bronchoscopic transplantation; the other received standard bronchoscopic fibrin glue injection.
All animals receiving bronchoscopic stem cell transplantation presented fistula closure by extraluminal fibroblast proliferation and collagenous matrix development; none (0%) died during the study period. All animals receiving standard treatment still presented bronchopleural fistula; two of them (40%) died. Findings were confirmed by pathology examination, computed tomography and magnetic resonance imaging.
In conclusion, our data suggest that MSC targeted to BPF through submucosal bronchoscopic injection can promote tissue regeneration, thereby occluding bronchial stump dehiscence and preventing pleural empyema. If proven effective in human beings, the technique may serve as an effective mini-invasive approach to BPF treatment, thus representing a potential alternative both to early reoperation when surgery is not feasible and to "open window" thoracostomy.
These preliminary data has already been published by the Annals of thoracic Surgery Journal (Petrella et al. Ann Thoracic Surg, 2013, epub ahead of print).
We are now expanding the study population in order to boost the statistical power of the study, extend the follow-up and more thoroughly evaluate how stem cells work in this field.

Educational Activities

The Program aims to develop a multidisciplinary approach to non-small cell lung cancer diagnoosis, staging and therapy. The 1st Multidisciplinary course of Thoracic Oncology – to be held at the European Institute of Oncology on May, 21st – 23rd 20134 – for oncologists and pulmonologists, will focus on diagnostic and therapeutic strategies, dealing with functional and traditional imaging, biopsy's technique and processing procedures, isthopathologic carachterization and medical and surgical therapeutic approach.

Governance

Lorenzo Spaggiari, Division of Thoracic Cancer Surgery, Filippo De Marinis, Division of Thoracic Oncology, Massimo Barberis, Division of Pathology, Roberto Orecchia, Division of Radiotherapy, Maria Rescigno, Dendritic Cell Biology and Immunotherapy Unit, Gabriella Pravettoni, Applied Research Unit for Cognitive and Psychological Science, Fabrizio Bianchi, Molecular Medicine Program.

Publications

Zagato E, Mileti E, Massimiliano L, Fasano F, Budelli A, Penna G, Rescigno M Lactobacillus paracasei CBA L74 Metabolic Products and Fermented Milk for Infant Formula Have Anti-Inflammatory Activity on Dendritic Cells *In Vitro* and Protective Effects against Colitis and an Enteric Pathogen In Vivo PLoS One. 2014 Feb 10;9(2):e87615

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Perioperative blood transfusion practices in oncologic thoracic surgery: when, why, and how. Ann Surg Oncol. 2012 Jan;19(1):82-8.

Division of Thoracic Cancer Surgery

Lorenzo SPAGGIARI, MD
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Piergiorgio SOLLI, MD
Co-Director

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Assistants: Monica Casiraghi, MD, Adele Tessitore, MD, Stefano Maria Donghi, MD (Pulmonologist)
Fellows: Alessandro Pardolesi, MD, Niccolò Filippi, Roberto Bellini
Residents: Sava Durkovic, MD, Giorgio Lo Iacono
Head Nurse: Ester Spacca
Data Managers: Raffaella Bertolotti, Daniela Brambilla
Clinical Secretary: Enza Adinolfi, Federica Castoldi, Laura Cordini

Activities 2013. The Division of Thoracic Surgery deals with the whole spectrum of neoplastic disease of the lungs, oesophagus, mediastinum, pleura and chest wall.
Surgical treatment of locally advanced tumors is an area of major clinical interest and scientific expertise of the Division, as well as parenchymal – sparing procedures and minimally invasive approach – such as robotic or videoassisted procedures – for early stage diseases.
Another area of clinical interest is palliative approach to advanced neoplastic tracheo-bronchial obstruction and/or compression by laser – assited rigid bronchoscopy; moreover, the development of endobronchial ultrasound during flexible bronchoscopy, optimized preoperative diagnosis and staging of thoracic neoplasms, often skipping more invasive diagnostic procedures.

The Division started, more than 10 years ago, an early-stage lung cancer detection program by low dose multi-detector computed tomography and recently implemented by biomarkers and experimental device (the "electronic nose") potentially able to identify distint characteristics in the exhaled breath of undiagnosed patients with lung cancer.
The Division developed the minimally invasive approach for the treatment of early – stage lung cancers, including robotic technique and video-thoracoscopic major lung resection.
The research activity deals with several translational studies on pharmacogenomics, molecular biology, lung carcinogenesis and angiogenesis.
Following interesting results of experimental bronchial wall restoration in animals, obtained last year, The Division started a clinical airway regeneration program by autologous bone marrow-derived mesenchymal stem cell bronchoscopic transplantation.

Clinical Trials

- Early detection by low-dose computed tomography
- Experimental and clinical airway regeneration by autologous mesenchymal stem cell transplantation
- Limited resection
- Genetic Investigations (miRNA)
- An electronic nose in the discrimination of patients with NSCLC

Publications

Petrella F, Toffalorio F, Brizzola S, De Pas TM, Rizzo S, Barberis M, Pelicci P, Spaggiari L, Acocella F. Stem cell transplantation effectively occludes bronchopleural fistula in an animal model. Ann Thorac Surg. 2014 Feb;97(2):480-3.

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Perioperative blood transfusion practices in oncologic thoracic surgery: when, why, and how. Ann Surg Oncol. 2012 Jan;19(1):82-8.

Division of Thoracic Oncology

Filippo DE MARINIS, MD
Director

STAFF Chair of the Unit of Sarcomas, Thymomas and Mesotheliomas: Tommaso De Pas, MD
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Assistant: Gianluca Spitaleri, MD
Translational Research: Francesca Toffalorio, MD, PhD
Research fellow: Ester Del Signore, MD
Clinical Fellows: Fabio Conforti, MD, Chiara Lazzari, MD, Antonio Passaro, MD, Matilde Strudel, MD
Data Managers: Sabrina Boselli, Letizia Sirica, Daniela Brambilla
Scientific Secretary/Personal Assistant: Deborah Console
Secretary: Monica Croce

Activities 2013.

Clinical activity. The Division was established to guarantee the best of care to patients with thoracic malignancies; a dedicated staff takes care of the patient in each stage of disease. A close collaboration with the Division of Thoracic Surgery and Radiotherapy make sure the correct follow-up of the patient from the pre- to the post-surgical time.
The clinical practice of the Division consists of in- and outpatients treatment, according to the complexity of the therapy, and of consultations for second opinions.
Clinical research activity. The Division gives the opportunity to participate to appropriate clinical trials; the novel drugs and therapies currently under study vary among targeted therapy (the drugs target specific proteins of pivotal pathways altered in NSCLC), combined therapy and immunotherapy.

Basic research activity. A long and successful collaboration with Italian and foreign researchers led to the publication on international peer-review journals of several studies, including those dealing with pharmacogenomics/genetics and with low grade neuroendocrine tumor of the lung; now the research program is focused on whole genome sequencing of lung adenocarcinomas and on the activity of molecular drugs in specific subsets of patient.

Activity of the unit of soft tissue sarcomas, mesotheliomas and thymomas. The daily clinical practice of the Unit entails the treatment of patients affected by pleura and thymus neoplasias as well as soft tissue sarcomas, through outpatients consultations as well as inpatients and outpatients treatment care.

Clinical Trials (target selected):

- **ALK (Anaplastic Lymphoma Kinase) pathway**
  - LDK378 plus AUY922 (phase Ib/II heat shock protein 90 inhibitor in patients with advanced NSCLC progressed to ALK-inhibitors)
- **EGFR (Epidermal Growth Factor Receptor) pathway**
  - INC280 (phase IB/II study of INC280, a Met inhibitor, in association to gefitinib, in patients progressed to EGFR inhibitors carrying cMet amplification)
  - Dacomitinib (phase III study of dacomitinib versus gefitinib as first line treatment in patients with EGFR mutated tumors)
- **c-MET pathway**
  - SAR125844 (phase IB study of SAR 125844, a Met inhibitor, IV in patients with advanced solid tumours, c-MET positive)
- **Ras pathway**
  - GSK2118436 (phase II study of dabrafenib, a BRaf inhibitor, in patients with advanced NSCLC carrying BRaf mutations)
- **Immunotherapy**
  - VX-001 (phase IIb study of optimized criptic human telomerase reverse transcriptase peptide PTERT572Y in patients with local or advanced NSCLC not progressing to chemo- or radio-therapy)

Publications

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Urogenital Tumor Program

Ottavio DE COBELLI, MD
Director

Scientific Board

- Prof. O. de Cobelli, Division of Urologic Cancer Surgery
- Prof. B. A. Jereczek, Division of Radiotherapy
- Prof. S. Pece, Program of Molecular Medicine for Care
- Dr. F. Nolè, Medical Oncology Unit of Urogenital Tumors
- Dr. G. Curgliano, Division of New Drugs and Early Drug Development for Innovative Therapies
- Dr. G. Renne, Division of Pathology
- Dr. G. Petralia, Division of Radiology

Vision and Mission

The Program P.U.R.E. (Prostate Urogenital Research Excellence) was born from the desire to achieve a multidisciplinary and translational approach in the management of patients with prostate cancer or other diseases in uro-oncology, moving quickly and efficiently scientific discoveries into clinical practice, through the identification and validation of new diagnostic, prognostic and therapeutic biomarkers.
The program according to ongoing development of well-timed prevention and individual therapy-planning, aims to build an integrated approach to urological cancer patients' care, reducing the risk of "overdiagnosis" or drug toxicity, improving quality of life without a deep impact on the health budget.

Objectives

- Early detection and identification of genetic and environmental factors, identifying patients at risk.
- Integration of clinical and laboratory variables able to predict the potential risk of neoplastic progression, allowing the construction of more and more effective nomograms in the management of patients undergoing active treatment or surveillance programs.
- Identification of the molecular mechanism underlying carcinogenesis, discovering new molecular targets and new targeted therapy.
- Identification of biomarkers of therapeutic response for modulation of cancer therapies, reducing drug toxicity.

Division of Urologic Cancer Surgery

Ottavio DE COBELLI, MD
Director

STAFF Senior Deputy Director: Deliu Victor Matei MD, PhD
Deputy Directors: Gennaro Musi, MD, Danilo Bottero, MD
Assistants: Giovanni Cordima, MD, Giacomo Galasso, MD, Antonio Brescia, MD, Federica Mazzoleni, MD, Antonio Cioffi, MD, Matteo Ferro, MD, PhD
Residents: Sara Melegari, MD, Roberto Bianchi, MD
Secretaries: Elena Collarin, Adriana Barioli
Data Manager: Serena Detti
Head Nurse: Enza Dossena

Activities 2013. The Division of Urology is concerned with the treatment of all urological tumours, including prostate, bladder, kidney, testis and penis cancer. In 2013, 1622 patients were admitted for surgical treatment. Among these we performed both endoscopic, open and robotic surgery. Among open procedures we performed 6 radical retropubic prostatectomies, 21 radical nephrectomies, 3 nephron sparing procedures and 61 cystectomies. Of these procedures, 43 were with urinary reconstruction.
We had a further increase of robotic surgery, with 503 robotic assisted prostatectomies and 109 kidney surgery (49 robotic radical nephrectomies and 60 nephron sparing procedures). Our experience in urologic oncology was extended in all the items such as testis cancer and penis cancer. There were also performed urinary diversions for patients who underwent pelvic exenteration in other divisions (Gynaecology, General Surgery).

Many patients underwent endoscopic procedures, like trans- urethral resection of bladder (380 patients) and ureteral stent insertion (81 patients). Accurate follow-up procedures, following international guidelines, are strictly observed. We had a great development of robotic surgery, as it was the more frequent surgical treatment for prostate cancer. The oncological results with a medium follow up of 34 months are similar to the open radical prostatectomy; however, the main advantage of this surgical technique is the shorter time required to reach urinary continence and sexual potency, and the better overall outcome for both functional domains, comparing to the open surgery. Moreover, Robotic Surgery offers better perioperative outcomes: blood loss, catheterization, surgical time. The recent development of multiparametric MRI, which combines anatomical T2W images with functional techniques, such as diffusion-weighted MRI and dynamic contrast-enhanced, has significantly improved local staging of prostate cancer, and has shown the potential to influence the decision to preserve neurovascular bundles and the extent of surgical margins in robotic prostatectomy The intraoperative frozen-section procedure, which provides histological assessment of the surgical margin, is attractive as it enables the surgeon to intraoperatively demonstrate the oncologic safety of an nerve sparing radical prostatectomy procedure. In light of the promising results reported for mp-MRI and IFS separately, we hypothesized that their combined use would improve the oncological outcome and functional results.
Plans for research projects in 2014/15 include a further increase of MRI and IFS in order to validate these kind of treatments in patients with prostate cancer. The standard treatment for invasive bladder cancer remains radical cystectomy. The indication for orthotopic bladder substitution has greatly increased over the last decade and in suitably selected patients, quality of life is excellent and morbidity is comparable to that with other forms of urinary diversions. The intestinal bladder sub- stitute should be a low-pressure, capacious and highly compliant reservoir, with a state of fullness that can be appreciated by the patient, allowing him to void at a socially appropriate time

Clinical Trials

- European multicenter protocol to assess tumor heterogenicity with cell cycle progression assay in tumor tissue of patients with prostate cancer stage T1-3, No, Mo. Empathy-P.
- Post marketing multicenter retrospective clinical investigation for assessing long term outcomes on Coloplast ureteral double loop stents BIOSOFT® DUO

Publications

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Medical Division of Urogenital, Gastrointestinal, Head and Neck Tumors

Aaron GOLDHIRSCH, MD
Director (ad interim)

STAFF Medical Oncology Unit of Urogenital Tumors Director: Franco Nolè, MD
Senior Assistants: Elena Verri, MD, Maria Cossu Rocca, MD, Daniela Cullurà, MD
Assistant: Gaetano Aurilio, MD, PhD

Activities 2013. Medical team of our Division consists of specialists in the area of urogenital tumors. The cooperation among the professionals involved in the urogenital program allow our team to develop a competent and comprehensive treatment program for each patient. Cancers of prostate, bladder, kidney and testis are diseases that are included in the spectrum of clinical and research programs of the Division.

Prostate Cancer

Prostate cancer is the most common cancer among males in the Western World and is the second leading cause of male mortality.
The course of prostate cancer from diagnosis to death is categorized as a series of clinical states defined by extent of disease (localized disease, rising PSA after local therapy, advanced disease with absence or presence of detectable metastasis) and by response to androgen deprivation.

Systemic therapies of prostate cancer, include hormonal treatment, chemotherapy, biologic therapies, targeted approaches, and treatments specifically designed to attack prostate cancers that have spread to the bone.
In our Division, patients are considered for treatment after a multidisciplinary discussion and after a clinical evaluation, to determine which treatment or combination of treatments will be most effective, considering the specific features of disease, offering the possibility to participate to national or international clinical studies with innovative treatments or a standard treatment.
In 2013, at our Medical Division of Urogenital Tumors we have taken care of 250 patients with prostate cancer treated in clinical research programs or with standard therapies.

Kidney Cancer

Treatment options and recommendations for kidney cancer, depend on several factors, including the type and stage of cancer, possible side effects, the patient's preferences and overall health. Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment have shown promise in treating metastatic kidney cancer.
In 2013, at our Medical Division of Urogenital Tumors we have taken care of 150 patients with advanced kidney cancer treated in clinical research programs with innovative treatments or with standard therapies.

Bladder Cancer

Bladder cancer is the 4th most commonly diagnosed cancer in men and 9th in women. Patients with bladder cancer or with upper urinary tract cancer, have their situation discussed weekly by urologic oncologists, surgeons, radio-oncologists who evaluate x-ray images, pathology reports and patient history to determine the best treatment option for the patient. One of the most interesting option that we offer to the patient with muscle invasive bladder cancer, who refuse cystectomy or with comorbidities that contraindicate surgery is a bladder sparing program, in collaboration with the Division of Radiotherapy and Urology. In this program, patients with muscle invasive bladder cancer, are treated with IG-IMRT radiotherapy plus chemotherapy with cisplatin or platinum salts. Our preliminary results support this treatment modality in select patients with muscle invasive bladder cancer.
In patients with stage IV bladder cancer, platinum-based combination chemotherapy regimens are the standard of care. Together, with the patients with bladder cancer we discuss treatment options, offering to the patients the best treatment option.
In 2013, at our Medical Division of Urogenital Tumors we have taken care of 100 patients with bladder or urinary tract cancer treated in clinical research programs or with standard therapy.

Testicular cancer

Testicular cancer is the most common solid tumor diagnosed in men between the ages of 15 and 34. In Italy, testicular tumors are the most common malignancy (11%) in males less than 50 years. Thanks to advances in the treatment of testicular cancer, the prognosis is excellent for most men diagnosed with testicular cancer. When found and treated early, more than 95 percent of men are cured.
The drugs most commonly used to treat testicular cancer are bleomycin, etoposide and cisplatin. This combination is known as BEP chemotherapy. Other combinations of drugs are also used depending on the stage of the cancer, or if it's come back after treatment. Chemotherapy for testicular cancer is given: after surgery as adjuvant treatment; to treat testicular cancer with distant metastases; to treat recurrent testicular cancer (salvage chemotherapy).
In 2013, at our Medical Division of Urogenital Tumors we have taken care of 130 patients with testicular cancer.

Ongoing Research Activity

Prostate Cancer

Our research activity on prostate cancer addresses the issues commonly encountered by the practicing oncologists.
The research themes include:

- Development of surrogate markers that may have utility in predicting prognosis and monitoring the antitumor effects of treatment in castration-resistant prostate cancer.
- Clinical trials addressing new drugs in patients with prostate cancer.
- Clinical trials including biological agents targeting different critical points of the signaling cascade or proteins of the mitotic machine

Despite its limitations, PSA is the best tumor marker of prostate cancer currently available in clinical practice. We are developing an alternative biomarker strategy, testing the prognostic and predictive value of Circulating Tumor Cells (CTCs) in prostate cancer, using the CellSearch System®, approved by the FDA for routine clinical use in metastatic breast cancer, colorectal cancer and in castration-resistant prostate cancer (CPRC).
We investigated the role of CTCs in:

- Patients with CRPC who are starting first or second line systemic treatment for advanced disease. (manuscript in preparation).
- Patients with clinically localized prostate cancer eligible for radical prostatectomy (clinical stage T1-3NxMo, any Gleason score) with the aim to investigate the prognostic value of CTCs before and after curative treatments, the correlation between CTCs and other known prognostic factors and biomarkers.
- Patients with PSA failure, following definitive treatment of prostate cancer.

Ongoing Clinical Trials

- A Multinational, Phase III, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Non metastatic Castration-Resistant Prostate Cancer
- Phase Ib dose finding study of abiraterone acetate plus BEZ235 or BKM 120 in patients with castration- resistant prostate cancer
- A randomized, parallel-group open-label Phase II trial of the immunological effects of a new vaccine in castration-resistant prostate cancer
- Selective Bladder Preservation Therapy for Patients with Muscle-Invasive Bladder Cancer and who are candidate to Cystectomy

Publications

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Division of Otolaryngology Head and Neck Surgery

Mohssen ANSARIN, MD
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Speech Pathologist: Giovanna Baracca MD
Speech Therapists: Valeria Zurlo, BS
Pietro Grimaldi, Anna Ieronimo
Data Manager: Maria Angela Massaro
Secretaries: Paola Maggioni, Anna Maria Manti

Activities 2013. The clinical research of the Division is focused on the early diagnosis of head and neck cancers, the development of new treatment modalities and molecular medicine through a multidisciplinary approach. The main topics are oral and laryngeal precancerous lesions, cancer of the oral cavity, pharynx, larynx, salivary and thyroid glands.
The Division has established national and international collaboration with many world-wide institutions. Several fellows attend our department in order to improve their knowledge of Head & Neck Oncology. We are developing organ and function preservation protocols of the larynx, compartmental surgery of oral cancer; intraoperative ultrasound guide lymphadenectomy of the neck, and endoscopic robotic-and laser-assisted surgery for laryngeal and oropharyngeal malignancies. We are also developing conservative and video-assisted (MIVAT) thyroid surgery.

Clinical activity during 2013 included 981 surgery admitted in the 14 beds of the Division. Among them 199 underwent laryngeal surgery, 338 oral and oropharynx surgery, 166 thyroid surgery and 66 for a salivary glands cancer. Patients usually undergo preoperative staging in out-clinic regimen and, in most cases, are then admitted to the hospital on the same day of surgery.
In 2013, mean patients' stay in the hospital was 5 days. Furthermore, 14500 patients were checked in the out-patient head and neck clinic. Treatment programmes of 603 patients were discussed and planned in the weekly multidisciplinary meetings (held on Wednesdays).
The division is coordinating two prospective trials: The first is the Pioglitazone study (S500/409). This is a multicentric chemoprevention trial on oral precancer lesions involving 12 USA institutes and 1 European institute. The second is the Lymphatic Mapping study (S629/411), a monocentric study in which we are studying the lymphatic drainage of the neck with indocyanine dye in advanced oral cavity cancers. Moreover 6 retrospective studies on head and neck cancer are ongoing.
The Division is also involved in a multi-center international study "Role of human papillomavirus infection and other co-factors in the aetiology of head and neck cancer in Europe and India" (HPV-AHEAD) that has been recently funded by the Seventh Framework Programme (FP7) of the European Commission in the Cooperation Work Program - Health 2011, specific call "Epidemiology and etiology of infection-related cancers". In this study, coordinated by IARC/WHO, we expect to provide novel and crucial insights for both HPV and non-HPV associated Head and Neck cancer and to further clarify the role of HPV infection in the etiology of a subset of HNC.
The Division published 8 papers on peer-reviewed journals, with an overall IF = 10.5, and 6 chapters in books in the head and neck oncology and surgery fields.
The Division is involved in the organization of basic and advanced courses on head and neck and thyroid cancer for ENTs, dentists and GPs in collaboration with the Italian ENT Society (SIO) and the IHNS.
The Division has an agreement with the ENT post-graduate school of the University of Pavia: each resident attends the Division and participates to the clinical and research activities for 6 months. Physicians of the Division are involved in the teaching activities of the school.
The Division organised:
1) A Resident Course: in this, 5 specialists spent a week attending lectures on head and neck oncology and observing the clinical activities of the Division; a full immersion experience in head and neck oncology.
2) In collaboration with the Institute of Anatomy of the University of Paris, ENT Clinic of Pavia, Ferrara and Brescia we organize in Paris two courses of head and neck surgical techniques using cadavers.

Publications

Navach V, Zurlo V, Calabrese L, Massaro MA, Bruschini R, Giugliano G, Ansarin M, Chiesa F. Total glossectomy with preservation of the larynx: oncological and functional results. Br J Oral Maxillofac Surg. 2013 Apr;51(3):217-23. doi: 10.1016/j.bjoms.2012.07.009. Epub 2012 Aug 9.

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Medical Division of Urogenital, Gastrointestinal, Head and Neck Tumors

Aaron GOLDHIRSCH, MD
Director (ad interim)

STAFF Medical Unit of Head & Neck Cancer:
Director Franco Nolè, MD
Senior Assistants: Maria Cossu Rocca, MD, Elena Verri, MD, Daniela Cullurà, MD
Assistant: Gaetano Aurilio, MD, PhD

Activities 2013. The Head and Neck Cancer Program of our Division, provides medical treatment for this type of cancer, including tumors affecting tongue, tonsils, mouth, palate, jawbone, sinuses, pharynx, larynx, salivary glands and thyroid.
All patient cases are presented at a multidisciplinary tumor board comprised of the patient care team, as well as radiologists and pathologists. We provide state-of-the-art treatment options, including postoperative chemotherapy after surgical treatments or chemo-radiation therapy with curative intents. In addition, programs of chemotherapy are offered to the patients for advanced disease. The Unit participates in innovative multicentric clinical trials investigating new treatments options and new drugs for head & neck cancer. Our programs, are conducted in collaboration with Division of Head & Neck Tumors and with Division of Radiotherapy and are aimed to develop new treatment modalities and to develop molecular medicine.

In 2013, treatment programs of 500 patients have been discussed and planned in the weekly multidisciplinary meetings and 150 patients, with different stages of disease have been treated with medical therapy alone or in combination with radiation therapy in programs of “curative” or “post-operative” chemo-radiation therapy.
The Unit is also involved in the organization of basic and advanced courses on Head and Neck and thyroid cancer.

Publications

Future challenges in head and neck cancer: From the bench to the bedside?_
L. Calabrese A. Ostuni, M. Ansarin, - G. Giugliano, F Maffini, D. Alterio M. Cossu Rocca, G. Petralia, R. Bruschini, F. Chiesa on behalf of AROME 1, Crit Rev Oncol Hematol. 2012.

Research Activities

DIVISION OF OTOLARYNGOLOGY HEAD AND NECK SURGERY

Clinical Trials

Phase IIB Randomized, Placebo Controlled Trial of Pioglitazone for Oral Premalignant Lesions: An Inter-Consortium Collaborative Study (IEO S500/409).

This is an inter-consortium collaboration between two Consortium Lead Organizations (CLO), MD Anderson Cancer Center (MDACC), Houston, TX and University of Wisconsin Paul P. Carbone Comprehensive Cancer Center (UWCCC), Madison, WI with a total of 13 participating clinical sites.
The central hypothesis of this protocol is that the PPAR gamma agonist pioglitazone (Actos®) may have activity against tobacco-related intraepithelial neoplasia (IEN) in humans, and this activity may be suggested by clinical or histologic response to pioglitazone treatment of oral premalignant lesions (OPL), namely dysplastic oral leukoplakia, hyperplastic leukoplakia in high risk locations (dorsal, lateral or ventral tongue or floor of the mouth) or erythroplakia of any histology. So, the primary objective of this Phase IIB randomized, placebo-controlled trial is to assess the efficacy of pioglitazone 45 mg qd given for 24 weeks in subjects with oral premalignant lesions.
The IEO is supposed to include 9 patients in three years. The study started in Novembre 2010 (March 2011) and as of 31/12/2013, 9 patients underwent randomisation.

Lymphatic mapping in oropharyngeal cancer: integration of dynamic lymphoscintigraphy - lymphoscintigraphy fluorescent indocyanine green (IEOS629/411).

Neck treatment in cNo tongue squamous cells carcinoma is still debated. Sentinel node (SN) technique could help the decision making, but is still unclear which kind of neck dissection must be performed in SN+ cases. Moreover, the pattern of cervical metastases has wide intra-individual variation and up to 5% of nodal metastases are found to be contralateral. In 2006 we published the lymphatic mapping study on 14 No patients affected by advanced tongue cancer. Contralateral drainage occurred in 11 patients and in two of them metastatic nodes were found on the contralateral side only. Metastases were found only in radioactive lymph nodes. The limits of this technique were the need of lymphoscintigraphy of specimens as to compare preoperative and postoperative imaging and the impossibility to visualize the lymphatic ways during surgery. Our purpose is to overcome these limits comparing lymphoscintigraphy with Tc-99 and near-infrared fluorescence imaging using indocyanine green die.
The sample size is 14 patients and we enrolled 6 patients as of 31/12/13.

Role of human papillomavirus infection and other co-factors in the aetiology of head and neck cancer in Europe and India. (Retrospective multicentric study granted by the CEE VII Framework) (IEO N101/11).

Human papillomavirus (HPV) is responsible for approximately 25% of head and neck cancer (HNC) worldwide and appears to be associated with a better response to treatment and improved prognosis. Evidence suggests that HPV-induced HNC has steadily increased in the USA and some European countries in the last decades. However, whether this is a worldwide phenomenon and specific risk factors are associated with it remains to be proven.
In addition, little is known on the natural history and risk factors of oral HPV infection. HPVAHEAD network aims to address these and other unanswered questions on HNC aetiology and epidemiology with a focus on the role of HPV. We will assemble and analyze a large collection of plasma/sera and HNC tissues from 42 entres in 16 European countries as well as HNC tissues from 7 Indian centres together with epidemiological and clinical data. HPV status in human specimens will be evaluated by different assays in central laboratories.
This proposal will be focused on the elucidation of the role of HPV types and other environmental risk factors in HNC in Europe and in India. The study will take 3 years and started in October, 2011 and we enrolled. Up to December 2013 the slides of 350 patients operated on for an oral cancer at IEO were evaluated for HPV and other predictive biomarkers.

4. Treatment of Early Oropharyngeal cancer (cT1-T2, cNo): robotic surgery vs radiotherapy. Incidence of Oropharyngeal cancers is increasing in time, expecially in young people. In the last decades Radiotherapy (RT) on the oropharynx and the neck was considered the choice treatment in these patiens. Long term Side effects of radiotherapy are often severe and affect swallowing and quality of life. Trans-oral Robotic surgery (TORS) showed good reliability in mini-invasive treatment od orropharyngeal and supraglottic cancers. This approach allows to compeletely remove early cancers and superficial local recurrences. The aim of this study is to evaluate the effectiveness of TORS vs RT in treating these cancers, and to evaluate oncological and functional results of the two approaches. Hundred patients with an oropharyngeal cancer will be recruited and randomised. The study design has been approved by the Oncological Lumbard Network (Rete Oncologica Lombarda – ROL) and is now under evaluation by the IEO Ethic Committee.

Ultrasound Score (US) of thyroid nodules (IEON90/11)

The present study arises from the objective difficulties of histological examination in some particular and borderline conditions, such as follicular neoplasm.. Its main proposal are: a) to identify the US features of benign and malignant thyroid nodules, in order to define different group risk and to assign a specific score; b) to correlate US characteristics with pre-surgical cytological data and post-op histological data; c) to propose a new reliable score accounting for pre-surgical clinical, cytological and echo graphic evaluations.

Comparison between CT and MR imaging with pathological findings in T2/3 laryngeal cancer in terms of accuracy in thyroid cartilage involvement: a prospective non randomized study. Conservative and functional surgery of laryngeal cancers is increasing in the last years. Laser surgery is considered yhe treatment choice in early glottis cancers (cT1); recently mini-invasive techniques (laser and robot –assisted surgery) showed to be technically feasible in treatment of cT2 and selected cT3 laryngeal cancers. Functional and oncological results are satisfactory.
In these medium advanced cases complete removal of the tumour depends on a correct stadiation and particularly on the status of the cartilages. In the past TC scan was considered the best diagnostic examination for studying the laryngeal cartilages. Recently new MRI devices allowed to better evaluate this important anatomical site. Aim of the study is to compare pre-operative CT and MRI scan and post-op specimen on patients with a cT2/scT3 laryngeal cancer in order to evaluate cartilage status and its impact on complete surgical removal of the tumour and on the outcome. Fifty patients will be included in the study; it started in 2013 and as of 31 /12/2013 40 patients were included.
Questo è lo studio che nell'ambito del H&N task force stiamo facendo con divisione di radiologia e anatomia patologica. Mancano pochi casi per raggiungere i 50 casi ipotizzati.

MEDICAL DIVISION OF UROGENITAL, GASTRO-INTESTINAL AND HEAD AND NECK TUMORS

Ongoing Research Activity

The Unit started collaboration with other Research Institutes deeply involved in the field to improve our ability to obtain new advances in research and to improve the network power, which is essential in Head and Neck cancer management. We are also working on radiobiology issue to improve results of combined conservative treatments as radiotherapy+ target therapy.

Projects

- Long term responders to first line chemotherapy plus cetuximab in recurrent/metastatic Head and Neck cancer: a genomic landscape approach to identify predictive biomarkers.
- Evaluation of feasibility and efficacy of alternative schedules in patients treated with cetuximab + platinum based therapy for recurrent/metastatic squamous cell carcinoma of Head and Neck.
- Collaboration to define national and shared guidelines in the management of main toxicity due to chemo-radiation therapies.

Ongoing Clinical Trials

A randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of afatinib (BIBW 2992) as adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced head and neck squamous cell carcinoma.

European, Observational, Prospective Study to Evaluate the Benefit/Risk of Vandetanib (CAPRELSA™) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer (MTC).

Phase II multicenter randomized, double blind, placebo controlled study assessing the efficacy of BKM120 + paclitaxel vs paclitaxel + placebo in pts with recurrent or metastatic Head & Neck squamous cell carcinoma.

Cetuximab and Cisplatin with or without Paclitaxel in recurrent/metastatic head and neck cancer phase II b, randomized study.

Neoadjuvant docetaxel,cisplatin and 5- fluorouracil (tpf) followed by radiotherapy plus concomitant chemotherapy or cetuximab versus radiotherapy plus concomitant chemotherapy or cetuximab in patients with locally advanced squamous cell carcinoma of the head & neck.

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of E7080 in 131I-Refractory Differentiated Thyroid Cancer.

Division of General and Laparoscopic Surgery

Bruno ANDREONI, MD
Director

STAFF Director, Hepatobiliopancreatic Unit: Antonio Chiappa, MD
Assistant: Emilio Bertani, MD,
Scientific Secretary: Nordiana Baruzzi
Clinical Secretary: Paola Italia
Data Manager: Darina Tamayo
Secretary of the Lu.V.I. Foundation: Rocco Ditaranto
Head Nurse: Marina Mancini

Activities 2013. The Division of General Surgery started its activities in 1994 through an agreement with the Milan University School of Medicine, recently renewed (December 2013). Among the IEO Divisions directed by a University Professor, the Division of General and Laparoscopic Surgery has been temporarily closed pending the appointment of a new University Director (as of February 2014 Prof. Andreoni is the University Director of the new Palliative Care Division). The medical staff of the Division of General and Laparoscopic Surgery has documented clinical experience in the treatment of upper and lower gastrointestinal tumors (from the esophagus to the anus), including hepatobiliopancreatic, renal and adrenal cancers, abdominal sarcomas and neuroendocrine digestive tumors.
All clinical activities are performed with particular attention to a multimodal, multidisciplinary approach, involving a close cooperation with medical oncologists, endoscopists, interventional radiologists and radiotherapists within the institutional "Digestive Tumors" Task Force.

In 2013, 304 major surgical procedures (general anesthesia) were performed with a total income of 3,387,500€: very satisfying results, when compared to the limited available resources (number of surgeons, beds and operating sessions assigned to the Division). Fifty-one per cent of patients came from outside the region, sure sign of "attractiveness".
In 2013 the personnel's main clinical aim was to provide appropriate services in accordance with international and local (Regional Oncological Network (Rete Oncologica Lombarda – R.O.L.) guidelines.

Hepatobiliopancreatic Unit (Director: Antonio Chiappa)

The IEO-HPB Unit proposes novel and multidisciplinary approaches to the treatment of liver, pancreas and biliary tract cancers. The main aim of the dedicated team is an accurate analysis of each and every case in order to offer the best treatment among all possible options.
The IEO-HPB works in close collaboration with other departments (medical oncology, diagnostic and interventional radiology, radiotherapy, nuclear medicine, endoscopy) to study and treat these particular diseases, offering "tailored" solutions that can guarantee long term survival and adequate quality of life.

Educational Activities

Both Directors are University professors, therefore they carry out an intense pre- and post-graduate educational activity as required by the IEO-Milan University agreement.
The Division of General and Laparoscopic Surgery of the European Institute is part of the training network of the Specialization School in General Surgery of the Milan University.

Research Activities

In his capacity as Coordinator of the R.O.L. Group "Appropriateness, quality and costs of surgical procedures for digestive tumors", the Director of the Division is the Scientific Coordinator of the following observational multicentric studies:

- "Clinical pathway (PDTA) in radically-resected rectal tumors, reconstructed through BDA (Regional Patient Database) methodology". It is a multicenter study by the Regional Oncology Network (ROL), approved by the Ethical Committees of the 49 participating Surgery Units (including IEO). The main aim of the study is to verify if treatments performed in clinical practice for locally advanced rectal cancer comply with ROL guidelines (that were drawn by all local oncologists based on international guidelines). 455 Patients with locally advanced rectal cancer were enrolled. An interim analysis is planned for 2014.
- "Comparison of clinical results after surgery and biomolecular characteristics of screening detected- vs non-screening detected vs interval colo-rectal cancers". It is a multicenter study approved by the Ethical Committees of the 34 participating Surgery and Pathology Units (including IEO, which is the coordinating Center). The main aim of the study is to verify if colorectal tumors have different clinical and biological characteristics according to the way of diagnosis. 235 Patients were enrolled. Biomolecular tests (K-RAS and BRAF mutation, microsatellite instability, DNA methylation, Whole Exome Sequencing) are ongoing.
- "Comparison of appropriateness, quality and costs of surgical procedures for colo-rectal tumors with open vs laparoscopic vs robotic techniques". It is a multicenter study by the Regional Oncology Network (ROL) coordinated by IEO aimed at verifying quality and costs of surgical procedures for colorectal cancer. The present protocol is based on a 2009 IEO monocentric study (results published in Int J Colorectal Dis 2011, 26:1317). The IEO Surgery Units have so far enrolled 25 Patients. A group of IEO experts (Surgeons, Anesthesiologists, Case managers, ward and operating room Nurses, Data Managers, administrative personnel - Health Services Head Office, Pharmacy, Purchase department, Business Management, IT department, etc.) was formed to carry out the present study. An interim analysis is planned for September 2013 to define improvement actions to be implemented during the second part of the study. A final verification of results in terms of procedure appropriateness is planned.

The Director of the Hepatobiliopancreatic Unit and the other surgeons of the division take part (as principal investigators or co-researchers) in a number of multicentric studies in collaboration with other prestigious Centers for Digestive Surgery, both national and international. The list of these studies can be found in the Clinical Disease-Oriented Research (Abdominal Tumors) section.

Publications

Biffi R, Botteri E, Bertani E, Zampino MG, Cenciarelli S, Luca F, Pozzi S, Cossu ML, Chiappa A, Rotmensz N, Bazolli B, Magni E, Sonzogni A, Andreoni B. Factors predicting worse prognosis in patients affected by pT3 No colon cancer. Long-term results of a monocentric series of 137 radically resected patients in a 5-year period Int J Colorectal Dis. 2013;28 (2): 207-2015 [Epub ahead of print 19 August 2012]

Division of Abdomino-Pelvic Surgery

Roberto BIFFI, MD
Director

STAFF Unit of Minimally Invasive Surgery Director: Paolo Pietro Bianchi, MD
Unit of Integrated Abdominal Surgery Director: Fabrizio Luca, MD
Deputy Director: Simonetta Pozzi, MD
Senior Assistant: Sabine Cenciarelli, MD
Assistants: Wanda Petz, MD, Manuela Valvo, MD
Clinical Researchers: Igor Monsellato, MD (Fondazione Umberto Veronesi), Massimiliano Zuccaro, MD (Fondazione IEO) up to December 7th 2013
Fellows: Marcos Guerra Cogorno, MD, Kemal Atahan, MD
Residents: Giovanna Scifo, MD (up to December 31st 2013), Marco Marino, MD, Andrea Gatti, MD (since Jan 1st, 2014)
Data Managers: Sergio Volpe, up to July 2013, Darina Tamayo
Clinical Secretary: Benedetta Clementelli
Personal Assistant to Dr Biffi: Paola Lonati
Head Nurse: Marina Mancini
Case Manager Nurse: Chiara Foroni

Activities 2013. Established on May 2007, the Division of Abdomino-Pelvic Surgery included since December 2011 the Unit of Minimally Invasive Surgery (Director: Dr Paolo P. Bianchi), becoming Division of Abdomino-Pelvic and Minimally Invasive Surgery; in the same time, a new Unit was established (Integrated Abdominal Surgery), directed by Dr Fabrizio Luca.
More than one thousand five hundred oncology surgical procedures were carried out during 2013, aimed at treatment of the following conditions: oesophageal, gastric, small bowel, colorectal, liver and pancreas carcinomas. In addition, staff Physicians maintained specific expertise and know-how in integrated surgical treatment of trunk and limb-roots sarcomas, gastro-intestinal stromal tumours (GIST), primitive and metastatic tumours located in kidneys and adrenal glands, neuro-endocrine tumours of the gastrointestinal tract. A significant portion of routine clinical activity usually involves a close cooperation with other IEO clinical Divisions (Gynaecologic Surgery, Thoracic Surgery, Urologic Surgery, Melanoma) in order to provide comprehensive care for oncologic diseases demanding skills and medical knowledge from different specialties (advanced ovarian carcinomas, oesophageal neoplasms extending into the abdomen, high-grade male pelvis tumours, visceral deposits of melanomas). Treatments of pelvic recurrences and peritoneal carcinomatosis with cytoredcutive surgery (CRS) and Hyperthermic Peritoneal Chemoptherapy (HIPEC) are regularly part of the surgical activity of the Division; the activation on 2009 of the Ovarian Cancer Center for Excellence by the Gynaecologic Oncologic Surgery Division offered the opportunity for an even closer cooperation between gynaecologists and abdominal surgeons, as shown by more than two hundred surgical high-complexity procedures per year, carried out with a multidisciplinary approach. A significant clinical research activity was carried out, and a number of papers were published in close cooperation with Gynecology Oncologists of IEO.
A close collaboration with the Division of Genetics and Oncologic Prevention was established, and clinical and pathology features of the first patient undergoing total prophylactic gastrectomy in Italy for a CDH1 mutation were provided.
A significant part of the surgical procedures are carried out with a minimally invasive approach (laparoscopic and robotic), at present time regularly applied to the treatment of tumors arising from colon and rectum, stomach, liver, spleen, pancreas and adrenal glands. Therapeutic choices are routinely made in agreement with other specialists, such as medical oncologists, radiotherapists, endoscopists, nuclear medicine specialists and interventional radiologists, by means of team case-discussing within a dedicated task-force. Taking responsibility for highly complex oncology cases, a strong link with the Anestesiology and Intensive Care Division is demanded, in order to provide intensive treatments for critically ill surgical patients.
Minimally invasive colorectal cancer surgery using a surgical robot started during 2007; a study on robot-assisted rectal cancer resection using the da Vinci system, a newly developed four-arm robotic device, was concluded, and a paper, collecting a relevant clinical series of fully robot-assisted rectal and left colon cancer resection, was published in Annals of Surgical Oncology-2009. More than 800 patients were so far treated with this technique. On January 2010 a collaborative paper with US and Italian groups was published, again in Annals of Surgical Oncology, investigating the impact of robotic approach on mesorectal excision for cure of rectal cancer. Extension of this minimally invasive approach to other surgical oncology applications (stomach, adrenal gland, liver, spleen and pancreas) is currently matter of active clinical investigation. More recently, a paper was published in Journal of Robotic Surgery, investigating the pros and cons of robotic approach in treatment of rectal cancer, comparing this innovative technique with open,traditional technique. A recent paper was published in Annals of Surgery, aiming at prospectively evaluate the impact of robotic surgery for rectal cancer on sexual and urinary functions in male and female patients. A preservation of urinary and sexual functions was demonstrated, due to the superior movements of the wristed instruments that facilitate fine dissection, coupled with a stable and magnified view that helps in recognizing the inferior hypogastric plexus. A very recent paper, published in Eur J Surg Oncol, compared short and long-term outcomes of robotic vs open TME (Total Mesorectal Excision).Eight editions of a 2-days full immersion Master Course in Robotic Abdomino-Pelvic Surgery were held since October 2010 to December 2013, with participation of attendees of surgical teams coming from Italy, France, Belgium, The Netherlands and Pakistan. In September 2012 Dr Luca's Unit of Integrated Abdominal Surgery has earned the distinction of being named a Colorectal Epicenter, a designation given to hospitals that have excellent surgical outcomes and advanced research and teaching programs. Moreover, Dr Bianchi is Member of the Research Committee of the EAES (European Association for Endoscopic Surgery and other Interventional Techniques), and dr Biffi is elected Fellow of the Society of Pelvic Surgeons, established on 1950 in Cleveland-OH.
Finally, the Division maintained specific expertise on long-term central venous accesses for chemotherapy and total parenteral nutrition administration. A training course for physicians, dealing with diagnosis and treatment of complications associated with central venous access placement and utilization in oncology, was provided on November 2013. Dr Biffi was member of the panel of international experts who provided guide-lines for this topic by ESPEN (European Society of Clinical Nutrition and Metabolism) and the International Group who provided clinicians with an evidence-based overview of all topics related to ultrasound vascular access. In addition, Dr Biffi was Investigator in a multi-center Italian observational study – enrolling more than 1,000 patients – dealing on the prevalence of caloric-proteic malnutrition in the oncology outpatient setting (SCRINIO Project). Preliminary data were published on Supp Care Cancer - 2009, whereas final results were published on Supp Care Cancer - 2012.

Publications

Biffi R, Botteri E, Bertani E, Zampino MG, Cenciarelli S, Luca F, Pozzi S, Cossu ML, Chiappa A, Rotmensz N, Bazolli B, Magni E, Sonzogni A, Andreoni B.
Factors predicting worse prognosis in patients affected by pT3 No colon cancer: long-term results of a monocentric series of 137 radically resected patients in a 5-year period.
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Division of Endoscopy

Cristiano CROSTA, MD
Director

Giancarla FIORI, MD
Co-Director

STAFF Deputy-Director: Davide Ravizza, MD
Senior Assistant: Cristina Trovato, MD
Assistants: Giuseppe de Roberto,
Research Fellow: Ivana Bravi, MD
Data Manager: Darina Tamayo
Secretaries: Paola Colli, Elena Degani
Head Nurse: Fiorella Zoccatelli

Activities 2013. The Division continues as a leading center for Italian Colorectal Cancer Screening Programme and for prevention and early diagnosis of esophageal, gastric, duodenal tumors. As part of the program of International Medical Education, the division provides the advanced training for interventional endoscopy and innovative techniques. Advanced techniques enable us to offer a minimal invasive treatment for oncologic patients. During the last year a total of 13,725 endoscopic procedures were performed. The main interventional procedures included:

- curative endoscopic therapy of early digestive cancer as mucosectomy and submucosal dissection of early cancer and large gastrointestinal lesions and treatment of bleeding lesions
- palliative endoscopic treatment of advanced obstructing tumors to restore the digestive tract patency as debulking and stenting of malignancies

- endoscopic treatment of neoplastic obstruction of biliary tract to relieve jaundice
- preoperative diagnosis and staging of esophageal, gastric, duodenal mediastinal, bilio-pancreatic and colorectal tumors, including endoscopic ultrasonography with fine needle aspiration

The main goal of the Division is patients' satisfaction through the adequate diagnostic-therapeutic pathway/s. Patient's monitoring before, during and after endoscopic procedures, together with the reprocessing of endoscopes and endoscopic devices, are imperative goals.

Sperimentazioni cliniche

- Study on Post-polipectomy Complications. SPOC Trial
- Confocal laser endomicroscopy in the gastrointestinal pathologies.
- Identification of Genetic Circulating Biomarkers for the Early Diagnosis of Colorectal Cancer. MiRNA Trial
- A Multicenter, Open, Prospective Study on Modified Resect and Discard Strategy of Small Colonic Lesions using the WavSTAT4 Optical Biopsy System. MORDIS Trial.
- Patient acceptance and compliance with a split-dosing preparation for colonoscopy in clinical practice

Publications

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Medical Division of Urogenital, Gastrointestinal, Head and Neck Tumors

Aaron GOLDHIRSCH, MD
Director (ad interim)

STAFF Medical Unit of Gastrointestinal and Neuroendocrine tumors
Director: Nicola Fazio
Senior Deputy Director: Maria Giulia Zampino
Assistant: Francesca Spada
Fellows: Salvatore Galdy, Simona Ravenda

Activities 2013. Our global clinical activity is mainly outpatient- and research-based. More commonly it is included within an integrated multidisciplinary approach, involving other specialities. Intravenous and oral chemotherapy, molecular targeted agents, and biotherapy are usually managed.
Regular weekly multidisciplinary meetings have been ongoing for more than ten years, one for GI tumors and one for NETs.
We have also a regular mono- and multi-disciplinary second-opinion out-patient activity.
We consider local and international guidelines and recommendations, and we are included in regional and national clinical networks.

Upper GI

In locally advanced esophago-gastric and bilio-pancreatic cancers we perform perioperative treatment involving chemotherapy +/- radiotherapy, usually after a baseline multidisciplinary discussion based on biological characteristics of the tumor, clinical characteristics of the patient and goals of treatment. In metastatic stage we usually propose first-line chemotherapy +/- biotherapy possibly within a clinical trials. A close collaboration with the Unit of palliative care is usual.
In NET we have a specific team, including the following specialities: medical oncology, surgery, endocrinology, gastroenterology/endoscopy, diagnostic and interventional radiology, pathology, nuclear medicine, radiotherapy. For each specialty there are one or more specific referrals for NET. Over the years the number of clinical discussions, new patients, and second opinions have been markedly increasing. For most patients with NET who come to our Institute, spontaneously or, more frequently, referred by other physicians/hospitals, we discuss within the board three main points: diagnosis reliability, staging completeness, and prognosis evaluation. After that we share early and late goals of treatment and a possible global therapeutic strategy. A pathology revision by the referral pathologist is usual.

Lower GI

Systemic treatment of colorectal cancer (CRC) is performed in adjuvant and metastatic setting tailored by biomolecular profile, appropriate instrumental workup and clear and specific objective of cure. Different settings of metastatic CRC are usually differently considered: resectable, potentially resectable or unresectable. In liver-dominant metastatic disease we collaborate with interventional radiologists for liver-directed procedures, including arterial chemoembolization or intra-arterial chemotherapy. In locally advanced rectal adenocarcinoma we are involved with radiotherapists and surgeons in a preoperative multidisciplinary approach with neoadjuvant intent for conservative surgery. In squamous cell anal carcinoma we collaborate with radiotherapists for chemoradiation as first option for cure. We are also particularly involved in treatment of small bowel rare tumors.

Publications

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Research Activities

RESEARCH ACTIVITIES

Factors affecting prognosis in colon cancer. Histological grade III and mucinous histotype were found to impact on cumulative incidence of colon-related events in a cohort of 137 patients undergoing curative surgery for adenocarcinoma, final stage pT3 No. Risk was found inversely proportional to the number of dissected lymphnodes. Results were published in Int J Colorectal Dis. 2013.

Metagenomics of colorectal cancer. Microbiota of colon cancer patients. These projects are carried out with IFOM-IEO Researchers, aiming at identification of new biological markers in the blood and feces of colon cancer patients. A correlation between neutrophils, coagulation defects and HMGB1 is postulated in colorectal cancer, as well as a specific pattern of colonic microbiota.

Robot-assisted minimally invasive surgery for rectal cancer. An international, randomized clinical trial comparing laparoscopic vs robotic rectal resection for rectal cancer (ROLARR trial) was started on 2012; 45 patients were so far enrolled by IEO investigators. A total of 400 patients is expected from all participating centers worldwide.

Laparoscopic radioguided detection of colon cancer with the use of a portable gamma camera. The aim of this trial is to evaluate the utility of radiotracers in detection of small colon cancer lesions during minimally - invasive surgery and even to map the lymphatic pathway in order to study sentinel lymphnodes.

Preservation of the genito-urinary function in patients undergoing surgery with robotic technique for rectal cancer. Aim is to assess prospectively the genito urinary function preservation in patients undergoing nerve sparing robotic surgery for treatment of rectal cancer. Preliminary data were published in Ann Surg 2013.

Integration of Diffusion-Weighted magnetic resonance imaging in surgical planning for robotic nerve sparing total mesorectal excision. A new MRI technique (DW-MRI) might improve the identification and depiction of the hypogastric plexus, thus having potential benefits on preservation of genito-urinary function in patients receiving robotic surgery.

Totally implantable central venous access devices. A cost analysis of a randomized trial on best approach to central veins for chemotherapy deliverance was completed. A new revision of the International Guidelines is programmed.

UPPER GI

Confocal Laser Endomicroscopy in early detection of esophagus dysplasia. A trial was activated to investigate the diagnostic potential of Confocal Laser Endomicroscopy in detecting the dysplasia associated to the Barrett's esophagus. A comparison with the standard Seattle biopsy protocol will be done.

Lymphadenectomy in gastric cancer. We analysed data of 114 patients who underwent gastrectomy and extended lymph node dissection for node-negative adenocarcinoma of the stomach between 2000 and 2005, extracted by our Tumor Registry. As more extended lymph node resection offered survival benefit, lymphadenectomy involving more than 15 lymph nodes should be performed. A paper was published, and a new investigation is foreseen.

Metastatic gastric cancer. HER2 positive tumors: we are studying whether pertuzumab can ameliorate the results of trastuzumab (international randomized, JACOB trial).
We are comparing two different regimens of three-drug polychemotherapy (GISCAD trial: low TOX vs EOX).
We are participating in a biological international study to analyze the association between MET copy number gain (CNG) and overall survival (OS) of patients with HER2 positive metastatic gastric cancer treated with first-line chemotherapy plus trastuzumab.

Hereditary Diffuse Gastric Carcinoma. In collaboration with the Division of Genetics and Oncology Prevention, a study for detection of CDH-1 germ-line mutation in patients under 45 affected by diffuse gastric carcinoma is currently run.

Pancreatic and biliary tract carcinoma. In pancreatic adenocarcinoma we are conducting a randomized, double-blind, phase 3 study of the JAK1/2 inhibitor, ruxolitinib or placebo in combination with capecitabine in subjects with advanced or metastatic adenocarcinoma of the pancreas who have failed or are intolerant to first-line chemotherapy (The JANUS 1 Study)
In biliary tract carcinoma, we are conducting a retrospective biological study to detect the expression of ROS-1.

Liver metastases. An observational, prospective, multicenter study entitled "Analysis of phosphoproteomics for targeted therapy of colorectal liver metastases (TASK 2)" is now ongoing.

LOWER GI

Factors affecting prognosis of colon ancer. Retrospective evaluations are ongoing on patients resected with stage II-III colorectal adenocarcinoma who underwent curative (open or mini-invasive) surgery at our Institute between the last ten years. The data will be extracted by our institutional Tumor Registry. The aim of this analysis is to investigate clinical-pathologic and molecular features affecting outcome in this setting of patients.
A retrospective analysis of 199 patients, treated with surgery in IEO for colorectal lung metastases during the last ten years, was conducted for evaluating clinical and bio-molecolar prognostic factors affecting oucome.

Circulating Tumor Cells (CTC). An observational, prospective, IEO monocentric study has been recently completed on identification and possible prognostic significance of CTC in patients affected by locally advanced rectal cancer candidates to neoadjuvant treatment for curative surgery.
We evaluated 90 patients with stage II-III rectal cancer underwent neoadjuvant chemo-radiotherapy and analyzed the presence of CTC in peripheral blood at specific time points, by using CellSearch System. In 19% of patients we detected CTCs at baseline and we found a reduction in CTCs number in case of objective remissions. Furthermore the proportion of CTCs patients decreased over the time as the therapeutic course proceeded. In conclusion CTCs might play a possible future role for the selection of patients who might benefit to more conservative surgery.
Our findings are currently under review for publication.

Medical oncology - Adjuvant setting. TOSCA trial is a prospective study evaluating the impact of 3 versus 6 months of FOLFOX/XELOX regimens in patients with colon cancer staged as II-high risk or III and the accrual has recently been completed. We have actively participated at the enrollment of patients in this clinical trial by including 90 patients and then we are among the top ten Italian centers for enrollment. Data monitoring of the study is in progress.

Medical oncology - Metastatic setting. The role of immunogenic response after EGFR-inhibitors (in collaboration with IFOM) and the mechanism of primary and acquired resistance to biological agents is under investigation.
New anticancer drugs and combinations are tested within international multicenter trials like GILEAD phase II study evaluating Simtuzumab/FOLFIRI or FOLFIRI/placebo in patients with K-RAS mutated colorectal tumour. In liver-dominant colorectal cancer patients with unresectable or borderline resectable metastases, we are participating in a multicenter first-line clinical trial (ABOVE study) with the aim to evaluate the percentage of conversion to surgery obtained with bevacizumab/FOLFOX regimen and to evaluate the maintenance role of one-year bevacizumab use after chemotherapy-combined administration.
Furthermore, throughout 2013, we took part in a prospective, phase IIIb/IV, international, single arm study to evaluate the safety and health-related quality of life of Aflibercept in patients with metastatic CRC previously treated with an oxaliplatin-containing regimen.
Together with IEO interventional radiologists, we are investigating hepatic intra-arterial injection of drug-eluting bead (MIRACLE III trial) in patients with liver-dominat disease pretreated with conventional systemic approaches.

Radiation therapy - rectal cancer. We actively participated to the phase III trial -INTERACT-, regarding treatment of patients with locally advanced rectal cancer suitable for neoadjuvant chemo-radiotherapy. The accrual is recently completed and data monitoring is in progress.
A trial evaluating the role of conservative surgery after primary chemoradiotherapy is upcoming, aiming to reduce the morbidity of extended surgery and to contribute to a better patient's quality of life. Other upcoming trials are investigating the role of adjuvant therapy after radically resected metastases and the role of "induction" chemotherapy in locally advanced rectal cancer with the aim to reduce radiotherapy use.

Squamous cell anal carcinoma. At our Institute we have high team-work expertise in the management of squamous cell anal carcinoma, especially related to chemo-radiotherapy conducted with curative intent in locally advanced disease. In this setting we are involved in the research of potential bio-molecular prognostic or predictive factors affecting outcome.
Thoughout 2013 we conducted a retrospective analysis of anal cancer patients treated in our Institute and we studied the correlation between HPV-positive tumours and outcome.
The results of this study are in progress.

NEUROENDOCRINE NEOPLASMS (NENs)

Low-intermediate pancreatic NEN
We are studying whether the addition of a somatostatin analog to everolimus gives a benefit; the accrual in the international randomized phase II multicenter trial (COOPERATE-2) is now completed. Moreover we are validating efficacy and tolerability of sunitinib in the phase IV, international, single arm trial (A6181202).
We are also carrying out a study on the angiogenetic effect of everolimus, focused on three levels: tumor molecular imaging (diffusion MRI), circulating factors (e.g. endothelial circulating cells) and tumor tissue. Finally we are studying the role of BEZ235 in patients refractory to everolimus (trial CBEZ235Z2201); the accrual has been recently completed. Results are pending.
In non-functioning non-pancreatic NET we participated in the RADIANT-4 trial, a regulatory, international, randomized, phase III study comparing everolimus with placebo; accrual has been recently completed. Results are pending
In Low-intermediate grade NET from different origins we are studying a combination of capecitabine and temozolomide. Both drugs are given metronomically. MGMT, TS, and other biological factors will be studied.

Low-grade NET with progression after somatostatin analog: b) a higher dose of somatostatin analog (lanreotide 180 mg/4 weeks) in patients progressive at conventional dose of octreotide/lanreotide (multicenter Italian trial).

In advanced lung/thymus NETs we are participating in an international randomized phase II trial comparing everolimus with pasireotide with everolimus + pasireotide. Accrual is ongoing.

Finally, we are conducting two biological projects: a) A pharmacogenetic/pharmacokinetic modelling approach to the prediction of everolimus tolerability, in patients with pNET treated with everolimus; b) set-up and molecular analysis of models of tumor xenograft in NET.

A phase II trial in advanced Merkel Cell Carcinoma with a anti-PDL-1 agent is upcoming.

OTHERS

Totally implantable central venous access devices. A cost analysis of a randomized 3-arm trial on best approach to central veins for long-term chemotherapy deliverance is under evaluation.
A new revision of the International Guidelines on evidence-based overview of all topics related to ultrasound vascular access is programmed.

Home Enteral Nutrition. A randomized prospective trial investigating nutritional and clinical impact of prolonged home enteral nutrition vs dietetic counseling in surgical oncology patients was recently closed. A data analysis is ongoing.

Modulation of postoperative insulin resistance. A randomized, prospective multicenter trial is ongoing, aimed at evaluation of the metobolic effects of preoperative oral carbohydrate ingestion on postoperative insulin resistance and infections' rate in surgical oncology patients. It is entitled PR.O.C.I. (PReoperative Oral Carbohydrate Ingestion).

Soft Tissue Sarcoma

Elisabetta PENNACCHIOLI, MD
Director

STAFF Fellows: Sara Coppola, MD, Antonio Intelisano, MD

Activities 2013. The clinical and research activity is carried out according to a model of multidisciplinarity. This reflects the spirit of our group, where the presence of spikes of true excellence in some areas does not obscure the collegial work that permits the expression of this excellence.
Our team approach to sarcoma brings together medical, surgical and radiation oncologists; orthopaedic, thoracic and reconstructive surgeons; specialized pathologists and diagnostic radiologists; as well as other specialists.
In a staff meeting, which is perfomed once a week, the clinical situation of every patient is collegially examined, and the most appropriate diagnostic/therapeutic plan is chosen. The patients are then also collegially re-evaluated during the treatment, and eventual decisions on the therapeutic layout stem from the discussion of the relevant experts. These meetings, beyond their importance for the management of the clinical situation of the patients, are also fundamental opportunities to generate new and foster existing scientific collaborations.

The cooperation with plastic surgeons is integrated in all phases of surgical planning and allows to obtain wide-margin function–sparing excisions, in locally advance tumors or anatomical difficult sites. Another important tool is isolated limb perfusion, that is used as a means to deliver high doses of chemotherapy and permit limb salvage in unresectable primary or recurrent extremity soft tissue sarcomas that would otherwise require amputation. It is our intention to introduce isolated limb infusion, as a less invasive and repeatable procedure, in cooperation with the interventional radiologists.
Radiation plays an important role in limb-sparing therapy and to improve local control in STS. Pre- and postoperative external-beam radiation therapies (EBRT/IMRT), as well as brachytherapy, are commonly used and have been shown to decrease the risk of local recurrence. Intraoperative radiation therapy (IORT) is also used. Because this treatment is conducted during surgery and can be targeted to a precisely defined area, higher-than-usual doses of radiation can be used, while sparing nearby healthy tissues. During brachytherapy, tiny radioactive seeds are implanted in or near a tumor.
Another valuable option is the proton therapy, which delivers high radiation doses directly to the tumor site, sparing nearby healthy tissue and vital organs. For some patients, this therapy results in better cancer control with less impact on the body. The Proton Therapy Center (CNAO) is one of the largest and most advanced centers Europe and is a direct cooperation in our Institute.
In our practice, we refer to the Memorial Sloan Kettering Cance Center prediction tools to predict which approaches to treating soft tissue sarcoma will result in the greatest benefit. The Sarcoma nomograms are available online and can calculate probabilities of survival and disease recurrence based on specific information about the patient and the tumor (ref. Synovial Sarcoma Survival Nomogram, Liposarcoma Survival Nomogram and Local Recurrence Risk after Limb-Sparing Surgery without Radiation Nomogram).
Soft tissue sarcomas, although sharing a mesenchymal origin, are a heterogeneous group of diseases. Recent developments suggest that a histotype-taylored approach may be more adequate. This is being studied in a trial of the Italian Sarcoma Group. Genetic profiling studies have indicated that some soft tissue sarcoma subtypes, despite a distinct histo-pathological difference, may be closely related. Molecular biology research in addition has identified several subtype-specific oncogenes and their protein products that could serve as treatment targets. Since many of the new molecularly targeted agents do not induce tumour regression, but mainly result in growth inhibition, it is therefore necessary also to change the study end-point in screening studies in the search for active treatments. By using databases from large cooperative groups it should be possible to identify progression arrest rates for each specific subtype, as soft tissue sarcoma treatment and research could require a change of approach and necessitate global cooperation. To be part of this process, we are involved in a collaborative program at the national and international level.

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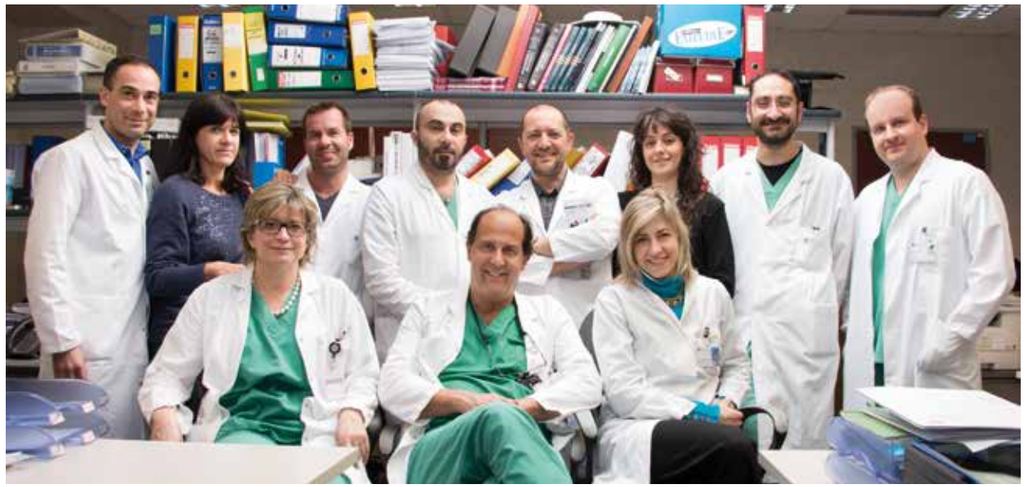
Surgical Division of Dermato-Oncology

Alessandro TESTORI, MD
Director



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Activities 2013. The treatment of melanoma and other skin cancers is tailored on the stage of disease. Procedures include: diagnostic excisional biopsies of the primaries, re-excision plus sentinel node biopsy in stage I-II melanoma patients, complete lymph-node dissection in the case of metastatic spread to the nodes, isolated limb perfusion with TNF and Melphalan or electrochemotherapy with bleomycin in patients with in-transit metastases and systemic treatments within or out of clinical trials for stage IV disease. Interestingly, new technologies have been recently introduced in order to improve the accuracy of the diagnosis of skin tumors. A high resolution digital dermoscopy is available for mapping of nevi and follow- up of suspicious pigmented lesions.

Furthermore, a reflectance confocal laser scanning microscopy (RCSLM) is available for the *"in vivo"* evaluation of clinically difficult skin lesions. This is is a new diagnostic technique which allows non-invasive imaging of the upper portion of the skin at a resolution that permits visualization of cellular details with near histological resolution in real time. Outlines of cells and their architecture are imaged and may be analyzed both horizontally and vertically
to the skin surface. The method has been proved to be highly useful in early melanoma and other skin neoplasms detection. From a surgical point of view, chemosaturation therapy with percutaneous hepatic perfusion is a new technique which represent a unique, repeatable catheter-based regional approach. It is indicated in all those patients with an exclusive hepatic involvement by different cancers but in particular by ocular melanoma, since they do not have any alternative valid therapeutic option. It has many advantages compared to other loco regional treatments since it permits to treat the entire liver (including invisible micro-metastases), it reduces systemic toxicities by drug filtration, thus improving safety, it is repeatable as many as ten times in one single patient and it is minimallyinvasive allowing treatment for sicker patients. From a medical oncologist point of view, the availability of 2 drugs, Vemurafenib and Ipilimumab, impacting on survival have revolutionize our therapeutic approach, widening the options and expanding hope for a cure in many patients affected by extended disease. In the future, combination of targeted therapies with chemotherapy and/ or immunotherapies will offer more opportunity to induce durable responses impacting on duration and quality of life of our patients.

Activities 2014

The division is devoted to the diagnosis and treatment of skin cancers and softtissue sarcoma. The activity ranges from sophisticated diagnostic procedures, dermatologic and molecular biology researches, to the surgical and medical treatments of melanoma and soft tissue sarcoma patients. Because of the complexity of these items, there is a clear indication for a multidisciplinary approach.
That's the reason why, not only in soft tissue sarcoma but also in melanoma patients, optimal care requires coordination between a variety of specialties, which may include:

- Dermatology
- Dermatopathology/Surgical Pathology
- Surgical Oncology
- Medical Oncology
- Radiology
- Radiotherapy
- Psycho-oncology
- Basic Research and Immunology

In our Institution, comprehensive services, available through an out- or in-patient choice, include:

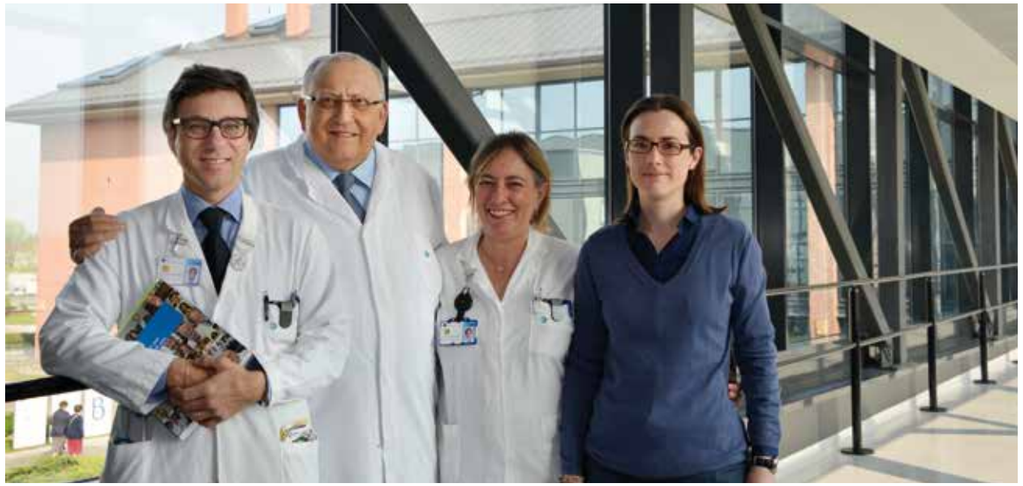
- Complete medical, dermatological and surgical evaluation
- Diagnosis of suspicious skin lesions with the aid of dermoscopy and digital dermoscopy.
- Diagnosis of clinically difficult skin lesions with Reflectance Confocal Microscopy (RCM)
- Participation to surgical, chemo- and immunotherapeutic National and International clinical trials.
- Pathological review of skin biopsies by dermatologists, surgical pathologists and dermatopathologists.
- Surgical treatment of melanomas: excision of the primary, sentinel node biopsy, complete lymphnode dissection, Electrochemotherapy, limb Perfusions and liver Perfusions (1st in Europe).
- Genetic counseling and Psychology support.
- Multidisciplinary follow-up for patients with a history of melanoma.
- Adjuvant immune therapy within clinical trials for high-risk melanoma patients.
- Standard and Investigational therapies for the treatment of advanced melanoma, including tumor vaccines.
- Molecular biology and immunology research.

To coordinate all these activity we created the Melanoma Cancer Center (MCC) within the EIO, with the aim of ameliorating this comprehensive, multidisciplinary approach for the cure of skin cancers. The most recent and ongoing Melanoma clinical trials are described in the dedicated chapter of the annual report.
Loco-regional treatments, as Isolated limb perfusion, are used in locally advanced tumors, by associating TNF to chemotherapeutic agents and treatments with electrochemotherapy..

During 2013, more than 8000 patients were examined in the outpatient clinics. The surgical procedures conducted on melanoma patients were almost 400. Moreover, approximately 1600 non melanoma skin cancer or various other cutaneous lesions were operated under general or local anesthesia.
The Division published 20 articles on peer-reviewed journals with a general impact factor equal to 81,165. Further steps will include the development of new drugs combinations, new surgical procedures and new dermatological diagnostic approaches in order to achieve the best standard of care for patients affected by melanoma and sarcoma.

Medical Division of Melanoma

Aaron GOLDHIRSCH, MD
Director (ad interim)



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The Division and the incorporated Unit are devoted to the treatment of locally advanced and metastatic skin cancers and soft tissue sarcoma in strict cooperation with the EIO Division of Melanoma and soft tissue Sarcomas and the Unit of Sarcoma, Timoma and Mesothelioma. The activity ranges from diagnosis, staging and medical treatments of melanoma and soft tissue sarcoma patients with special attention to clinical features, molecular biology and translational research. The latter two aspects of the work are integrated with each other and represent a core activity of the staff.
The complexity of clinical, biological and molecular details is a clear indication for a multidisciplinary approach with strict coordination between various specialists, in order to recommend proper comprehensive treatment options for each patient. In particular, for patients with Melanoma, an intense integrated activity of all specialists involves dermatologists, surgeons, medical oncologists and biologists, all committed to create a complete evaluation of the single patient and the clinical and biological aspects of the disease. This setting has motivated the creation at the IEO the "Melanoma Center", incorporating different specialists who work in the same disease oriented program under the same direction. Interestingly, our Team includes a molecular biologist working on basic research at IEO-Campus and a Psycho-oncologist offering support to all patients undergoing specific surgical or medical treatments and their families.
The treatment of melanoma and other skin and soft tissue cancers is tailored according to the stage of disease and follows the guiding principle of IEO, i.e. the minimum effective treatment to reach the maximal therapeutic efficacy with the quality of life as a fundamental target.
Cooperation between specialties includes:

- Dermatology
- Dermatopathology/Surgical Pathology
- Surgical Oncology
- Medical Oncology
- Radiology
- Radiotherapy
- Nuclear Medicine
- Psycho-oncology
- Basic Research and Immunology

Activities 2013.

Melanoma

In the context of the Multidisciplinary team and the Melanoma Cancer Center, patients with advanced disease are mainly enrolled in chemo-, targeted and immuno-therapeutic clinical trials and treated within the Medical Oncology Unit of Melanoma. The group participated to the development of the anti-BRAF/anti-Mek combination targeted therapy and anti-CTLA4/anti PD1 combination immunotherapy. These drugs shown ability to impact on survival in advanced melanoma and revolutionized our therapeutic approach, widening the options and expanding hope for a cure in many patients affected by this disease.
In the meantime, new phase II and III clinical trials exploring other combination of targeted therapies with chemotherapy and/or immunotherapies and/or Vaccinations are ongoing, offering new opportunity to induce durable responses which could impact on quality of life of our patients. Moreover, spontaneous studies, supported by grants to dr. Ferrucci and Martinoli, are focused mainly on translational research.
Finally, adjuvant targeted therapy options as per histology are under evaluation through participation in 3 international clinical trials.
Interestingly, our Team include a molecular biologist working on basic research at IEO-Campus and a Psycho-oncologist offering, if requested, support to all the patients undergoing specific surgical or medical treatments and their family.

Basal Cell Carcinoma

Patients affected by basal cell carcinoma usually receive surgery and/or radiotherapy as the only curative approach. When the disease rarely become metastatic or could not be approached by surgery or radiotherapy any more, systemic options were lacking. Recently, a new drug, Vismodegib, is being tested by our group in an international clinical trial with interesting results.

Sarcoma

The Task Force on Sarcoma involves medical oncologists, surgeons, pathologists, radiotherapists and radiologists in order to offer a comprehensive approach to patients in all different stages of disease. Clinical trials and innovative treatments are offered as part of this strict collaboration within different professionals in a multidisciplinary setting.

Description of Clinical Practice

Most of the patients were evaluated and treated in ambulatory and day hospital facilities after a coordinated visit of each patient in one of the dedicated clinics, including those dedicated to patients in clinical trials or outside clinical trials. In 2013: Clinical ambulatory visits were 1047; Clinical Day Hospital treatments were 482 and 134 new patients were enrolled in clinical trials.

Publications

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Research Activities

Clinical Trials

- A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.
- A Phase III, randomized, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma.
- Phase III, randomized, double blind, placebo-controlled study of vemurafenib (ro5185426) adjuvant therapy in patients with surgically resected, cutaneous braf-mutant melanoma at high risk for recurrence.
- A multicenter, open label, randomized Phase II trial of the MEK inhibitor pimasertib (MSC1936369B, formerly known as AS703026) or dacarbazine in previously untreated subjectswith NRAS mutated locally advanced or metastatic malignant melanoma.
- A Randomized Double-Blind Phase III Study of Ipilimumab Administered at 3 mg/kg vsat 10 mg/kg in Subjects with Previously Treated or Untreated Unresectable or MetastaticMelanoma.
- Randomized phase III open label study of BMS-936558 versus chemotherapy in patients affected by advanced melanoma patients progressing after a stabilization of disease with anti-CTLA4 treatment.
- Randomized phase III open label study of Nivolumab monotherapy versus Nivolumab/Ipilimumab combination versus Ipilimumab monotherapy in previously untreated patients affected by advanced or metastatic melanoma patients.
- Randomized phase II open label study of Ipilimumab retreatment versus best investigator choice in patients affected by advanced melanoma patients progressing after anti-CTLA4 treatment.
- A prospective, multicenter, randomized, open-label, active controlled, two-parallel groups, phase 3 study to compare the efficacy and safety of masitinib at 7.5 mg/kg/day to dacarbazine in the treatment of patients with non-resectable or metastatic stage 3 or stage 4 melanoma carrying a mutation in the juxtamembrane domain of c-kit.
- A single arm, open label, phase II, multicenter study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma.
- Multicentric, open lable of expanded access to assess the safety of RO 5185426 (VEMURAFENIB) in patients affected by metastatic melanoma.
- BRF115252: dabrafenib (gsk2118436) for compassionate use in BRAF V600E mutation- positive metastatic melanoma.
- Compassionate Supply of Pazopanib for Patients with Advanced Soft Tissue Sarcoma (aSTS) through a Named Patient Program.

Basic and Translational Research

The most interesting opportunity for us is to bridge basic research to the clinical one.
Through the IEO bio-bank, the laboratories of IFOM dedicated to basic or immunology research receive biological material to be utilized for specific collaborative research projects.
Moreover, a molecular biologist is working at IEO-Campus under the Grazia Focacci Foundation support. She reported interesting data on Maspin expression during melanoma progression and metastatization, which could allow to use this protein as a surrogate marker that may have utility in predicting prognosis and monitoring the treatment antitumor effects in melanoma. In fact, Patients expressing maspin in the cytoplasm and not in the nucleus have a better prognosis, while those with expression of maspin in the nucleus and not in the cytoplasm have a worse prognosis.
In this setting, other biomarkers of tumor progression and response to therapy are under research by evaluating hematochemistry of patients receiving different treatments and procedures. Another study is performed in collaboration with the Genova INT on the analysis of CTLA4 polimorphisms which could allow the predict response to Ipilimumab.
Our research program is also focused, this time in collaboration with the Milan INT, on molecular evaluation of the microenvironment and angiogenesis in patients enrolled in a specific protocol and receiving an antiangiogenic drugs combined with chemotherapy (Bevacizumab and Dacarbazine). In particular, this is a satellite study evaluating IL-8, IL-10, IL12p70, IL-17, IL-23, IFN-g, TNF-a, CXCL10, VEGF-A, VEGF-C, VEGFR1, VEGFR2, E-selectin, P-selectin, sICAM-1, CRP and comparing the results on the basis of the clinical response observed in the clinical trial. Data are being submitted for publication.
Finally, we are studying the specific effect of various drugs and combinations on the immune system by monitoring the level of expression of target molecules involved in the induction of an immune response.
In the near future we are planning to investigate the role of circulating tumoral cells (CTCs) in melanoma patients receiving different locoregional and systemic treatments.

Division of Clinical Haemato-Oncology

Giovanni MARTINELLI, MD
Director

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Director of Transplantation Unit: Rocco Pastano, MD
Deputy Director: Alberto Agazzi, MD
Senior Assistant: Anna Vanazzi, MD
Assistants: Giovanna Andreola, MD, Paola Bertazzoni, MD, Angelo Gardellini, MD, Federica Gigli, MD, Simona Sammassimo, MD
Fellow: Niccolò Frungillo, MD
Data Managers: Liliana Calabrese, Mara Negri
Secretaries: Daniela Antoniotti, Tiziana Masala
Head Nurse: Laura Orlando
Scientific Nurse: Sarah Liptrott

Activities 2013. Created in December 1997, the Division of Clinical Haemato-Oncology provides care for patients with haematologic malignancies (non-Hodgkin's lymphomas, acute leukaemias and multiple myeloma) and for patients with solid tumours for whom high-dose chemotherapy and autologous peripheral blood progenitor cell (PBPC) support is a standard or investigational treatment option.

Within the Division of Clinical Haemato-Oncology, the Allogeneic Transplant Unit performs allogeneic transplants with reduced conditioning or myeloablative regimens, from sibling and unrelated donors, principally for patients with haematologic malignancies. In order to improve clinical results and reduce acute toxicities, including Graft Vs Host disease, the use of TLI / ATG in malignant haematological diseases was implemented. This regimen, first developed at Stanford University, has the peculiarity to skew graft activity toward host tolerance, maintaining high anti tumor activity and reducing overall transplant related mortality.
We activated a study to determine if engraftment can be achieved safely in patients with high-risk hematologic malignancies who undergo non-myeloablative BMT from HLA-haploidentical donors. The protocol includes the immunological monitoring of patients with haematological malignancies after allogeneic transplant.

At the Division of Clinical Hematoncology, a JACIE accredited unit Center has been set up for collecting stem cells from peripheral blood. All procedures are managed by physicians and nurses specifically trained in allogeneic and autologous donor evaluation, stem cell and lymphocyte collection by aphaeresis, coding and labelling cellular therapy products.

Since 2010 we have been performing extracorporeal photopheresis (ECP) to treat patients with acute/chronic GVHD or coetaneous lymphomas. Early introduced in the treatment of steroid-refractory acute and chronic GvHD, ECP is a well tolerated procedure, with very low incidence of side-effects that often allows more rapid reduction of concomitant immunosuppressive therapy.
In order to better elucidate the immunomodulating effects of ECP, we are performing *in vitro* analysis nfocusing on the apoptosis process and on cytokines expression in patient blood samples before and after theprocedures.

Clinical Research Activity

Multicenter, comparative study to evaluate the role of mediastinal radiotherapy after chemotherapy regimens containing rituximab in patients with a new diagnosis of lymphoma in primary mediastinic large B-cell.

The study is sponsored by IELSG and is designed for patients with a new diagnosis of non-Hodgkin lymphoma in primary mediastinal large B-cell (PMLBCL). The PMLBCL is a curable disease when treated properly. In recent years it has been possible to recognize the crucial role of the initial therapeutic choice in obtaining the healing: in fact, the cases that recur are often resistant to treatments and then becomes very difficult to achieve durable remissions. For this reason, the initial treatment is carried out with aggressive regimens (next-generation combination chemotherapy + rituximab), with the aim to get as many possible remissions.
The purpose of the study is to evaluate the role of the residual mediastinal radiotherapy in patients that at the end of chemo-immunotherapy have a negative PET / CT. It is not clear the role of radiotherapy mediastinal complementary, at the end of first-line chemoimmunotherapy. Some retrospective studies with few patients had initially suggested that the complementary radiotherapy could improve therapeutic outcomes and reduce the number of relapses.
These results have not been confirmed, however, and the role of radiotherapy is not defined for patients who achieved remission, as demonstrated by PET / CT negative, at the end of chemoimmunotherapy. This clinical study could save in patients with complete remission of the disease a complementary radiotherapy that might not be required and therefore carry a risk (reduced), of long-term toxicity. These risks relate mainly cardiac toxicity and the onset of second cancers (lung, thyroid, breast, etc.) That represent the most common adverse events of late mediastinal radiotherapy.

Phase II study of the use of the scheme of intensified chemotherapy ChlVVP / ABVVP in patients with advanced-stage Hodgkin's lymphoma.

The main objective of this study is to reach a progression-free survival (PFS) at 3 years 80% in patients with Hodgkin's disease. The scheme ChlVVP / ABVVP intensified using also pegfilgrastim, is increased in the dose intensity of the scheme (in particular of certain drugs such as adriamycin and etoposide, particularly active in Hodgkin's lymphoma) decreasing the risk of any delays in the course of treatment due to haematological toxicity which in our case has been greatly reduced. This increase could result in a greater effectiveness of the scheme. The clinical study is therefore proposed to the patients for the proven efficacy and good tolerability of the treatment, also for what concerns the late side effects. Another advantage for the patient is that treatment will be administered in Day Hospital.

Non-myeloablative transplantation of hematopoietic stem cells for patients with metastatic solid tumors or relapsed, resistant / refractory to conventional therapy, using HLA-matched family donors or HLA-haploidentical family donors.

The purpose of the study is to determine whether engraftment can be achieved safely in patients with metastatic solid tumors or relapsed, resistant / refractory to conventional therapy, underwent transplantation with non-myeloablative peripheral blood stem cells from HLA-identical family donors or HLA-apoloidentici.
It would be important to extend the option of hematopoietic stem cell transplantation (HSCT) for the potential curative effect of solid tumors at high risk to patients who do not have an HLA-compatible donor.
Until now, transplantation of non-myeloablative hematopoietic stem cell transplantation from partially HLA-incompatible donors were associated with a high rate of graft rejection and graft-versus-host disease (GVHD). The research involves patients with metastatic solid tumors or relapsed, resistant / refractory to conventional therapies, offering the possibility to use a potentially curative treatment for patients with solid tumors at high risk who can not benefit from more active treatment that is able to increase the life expectancy of the patient.

These patients have already failed a poly- chemotherapy and their disease state does not allow the use of active treatments, so the only alternative for these patients is a treatment to supportive care and palliative care.

Prospective observational study on donors of stem cells in ambito familiare.

Observational study that does not include an experimental treatment and is for providing data for the standardization of the criteria for eligibility to donate peripheral HSC at GITMO centers. It is not available a prospective study for evaluating jointly (Blood Center and Transplant Centers) the selection criteria for the choice of HSCs familiar donor and the incidence of severe adverse events early and late time.

Observational study with, Cyclophosphamide, Doxorubicin liposomal non- pegylated (Myocet), Vincristine, and Prednisone in frail patients with diffuse large cell lymphoma.

At our Institute patients with diffuse large cell lymphoma are treated with CHOP-like therapy, the regimen R-ACOD. It is usually well tolerated, but the presence of doxorubicin that carries a risk of cardiac toxicity limits its use in elderly patients and in patients with cardiovascular disease. In this particular subset of patients there is the possibility of administering such a scheme by replacing the normal Doxorubicin therapy with non-pegylated liposomal doxorubicin (R-MCOD scheme). the aim of the study is to verify that such replacement allows to safely administer a CHOP-like therapy in patients that because of age and / or comorbidities can not receive a standard therapy. It also evaluates the effectiveness of R-MCOD compared to R-ACOD.

Rituximab + 2 - CDA and rituximab maintenance in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma.

Despite the important progress made in recent years, the LLC is unfortunately a disease not treatable and even the latest immuno-chemotherapies are able to prevent relapse.

For many years, the first-line treatment of patients with CLL was based by the use of Chlorambucil and other alkylating agents with whom they obtained less than 10 % complete response (CR) with a low, almost zero impact, on survival. The objective of this study is to confirm the efficacy of the R-2CDA and to evaluate the effectiveness of the addition of rituximab as monotherapy for maintenance, in increasing molecular responses and prolong the duration of response. The only maintenance therapy with monoclonal antibody is well tolerated and is substantially free of side effects.

Our research group was invited as a member of REL, a network established by the Lombardy Region for optimizing assistance and cure for patients affected by haematological disease. REL also defines criteria for the accreditation of transplant centers operating at regional level. We collaborate actively with participation in registries for collecting data to standardize the diagnostic and the therapeutic approach in certain diseases such as leukemia and myelodysplasia.

Publications

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Department of Pathology and Laboratory Medicine

Giuseppe VIALE, MD
Director

Vision and Mission

The Department of Pathology endorses and maintains the founding principles of the IEO (central role of the patient, continuous improvement of diagnostic and therapeutic activities, regard of the human resources, fostering of clinical and translational research, international collaboration, educational activities, safety in the working place, technological advancement), and provides all the services for the diagnosis of the diseases and for informing the local and systemic treatments in a timely fashion, ensuring the best possible accuracy in the assessment of all the clinically useful prognostic and predictive parameters.
This is granted by the involvement of all the staff members in the definition of the departmental objectives, in the continuous educational processes, and in the monitoring of the clinical and research outputs as compared to defined standards.
The vision of the Department is to achieve and maintain the status of reference laboratory for the neopastic diseases and clinical research within the National and International scientific community.

Clinical activities

The services provided by the Department using the resources of its Divisions and Units (Division of Pathology, Division of Laboratory Medicine, Division of Laboratory Haematology-Oncology, Unit of Cytopathology, Unit of Histopathology and Molecular Diagnostics) include:

- diagnostic activities on histological and cytological samples for in- and out-patients
- assessment of biological variables with prognostic and predictive value
- mutational analyses of actionable genetic aberrations
- autopsy service
- hematology, biochemistry, coagulation, tumor markers, infectious disease serology, drug monitoring and microbiology
- flow cytometry and cell sorting
- stem cell processing for transplantation

Research activities

The Department of Pathology is actively involved in clinical and translational research activities, with an extensive network of internal and external collaborations. A dedicated unit (Pathology for Clinical Trials) serves as the Central Pathology Office of the International Breast Cancer Study Group, and as the reference laboratory in the conduct of several multicentric international clinical trials.
Internal research programmes are mainly devoted to the molecular segmentation of breast and lung cancer, in the prognostication of prostate carcinoma with gene expression profiling.
The Department is also actively involved in the maintenance of a frozen tissue bank.
The Division of Laboratory Medicine is involved in researches aimed at the detection and characterization of circulating tumor cells in different malignancies, with particular reference to breast cancer; at the implementation of new methods of detection of HPV and on new algorithms for the follow-up of the patients with cervical cancer; at the early diagnosis of chemotherapy-induced cardiotoxicity; and at the evaluation of new circulating tumor markers for different malignancies.

The Laboratory of Hematology-Oncology has developed innovative preclinical models of local and metastatic neoplastic diseases, including breast and hematological malignancies. These tools are used to investigate the contribution of different cell types to cancer progression and to study new therapeutic strategies and targeted drugs. Moreover, the Laboratory is developing new approaches for the enumeration of cancer-specific DNA transcripts in the peripheral blood as a non-invasive biomarker for cancer detection and follow-up after therapy.

Educational activities

Educational activities of the Department include teaching for pre- graduate students of the School of Medicine and of the School of Physiotherapy of the University of Milan, it hosts the post-graduate Medical School in Pathology, and it is involved in the teaching activities of the European School of Molecular Medicine (SEMM).

Division of Pathology

Giuseppe VIALE, MD
Director

Giuseppe RENNE, MD
Co-Director

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Director, Histopathology and Molecular Diagnostics Unit: Massimo Barberis, MD, MIAC
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Activities 2013. The Division of Pathology includes the Units of Histopathology and Molecular Diagnostics, of Cytopathology, and of Laboratory Haematology-Oncology. This report focuses on the activity of the first two Units, which has included 21,835 histological diagnoses and 15,100 cytologic diagnoses (6,500 fine needle aspiration or extravaginal exfoliative cytology samples and 8,600 Pap tests) with 3,823 cases seen in consultation for a second opinion and 4,923 cyto-istological intraoperative diagnosis (4440 of them were frozen section examinations).
Among the different tumor types, we have examined 3,546 breast samples, 2,066 biopsies of sentinel lymph nodes, 3,011 surgical specimens of gynaecological pathology, 1,422 specimens of thoracic pathology and 407 malignant melanomas.
Besides a diagnostic laboratory supplied with the most updated equipments for histologic and cytologic investigations, the Division includes two functional sections of immunohistochemistry and molecular pathology supplied with automatized instruments able to offer extensive immunophenotyping and molecular characterization of normal and tumor tissues by using a large array of monoclonal and polyclonal antibodies, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) techniques. More than 60,000 immunohistochemical reactions, 1,344 FISH assays, 1,594 molecular reports with 6,874 PCR analyses and 9,204 direct sequencing have been routinely carried out in 2013 for tumor genophenotyping, including the immunohistochemical evaluation of estrogen and progesterone receptors, HER-2 and EGFR expression in tumors for tailoring individual therapy; the characterization of malignancies from unknown primary sites; the assessment of gene amplification in carcinomas and gene translocation in malignant non-Hodgkin lymphomas and soft tissue tumors;and the mutational analysis assessment of several genes.
The research activities during 2013 have mainly focused on the modelling of predictive factors for breast cancer addressing both the pathological complete remission and the long term survival in patients undergone neo-adjuvant chemotherapy, as well as the long term survival of patients treated in the adjuvant setting. In particular, the value of a model to predict the magnitude of benefit of adjuvant letrozole, as compared to tamoxifen, has been documented in more than 5,000 patients enrolled in the BIG1-98 clinical trial. Furthermore, genetic analyses of the polymorphisms of the CYP2D6 gene have been carried out to assess the response of the patients with endocrine responsive breast cancer treated with tamoxifen.
The suitability of needle core biopsy for the diagnosis of malignant lymphomas has been established in a series of more than 400 cases. In primary pulmonary MALT lymphomas we have evaluated prevalence and clinical implications of re-arrangements of the MALT-1 gene.
These activities have required extensive immunophenotyping and molecular characterization of tumor tissues, using automatized immunostainers, PCR-, real time PCR-based and FISH techniques, tissue microarrays, and microdissection for tumor cell enrichment.
The research activities of the Division, including the studies performed in collaboration with several Divisions of the European Institute of Oncology, as Experimental Oncology, Senology, Medical Oncology, Head&Neck Surgery, Gynaecology, Thoracic Surgery, and Chemoprevention, have resulted in 69 full articles published during 2013 in peer-reviewed international journals, with an overall IF of 399.5 (mean IF: 5.7).
The Division hosts the Postgraduate Medical School in Pathology of the University of Milan.

Histopathology and Molecular Diagnostics Unit

The 2013 clinical activity of this Unit has regarded the consultation and revision duties on fellows, residents and staff pathologists working at the Division of Pathology and Laboratory Medicine.
The Unit play a role as a referring center for lung cancer and neuroendocrine tumors.
It participates as referral center for the Italian Association of Medical Oncology (AIOM) and the Italian Society of Anatomic Pathology and Cytology (SIAPEC) in the national quality control system for molecular testing.
Recommandations and guidelines for the detection of ALK rearrangement and the results of the Italian Quality Control Procedures for the detection of EGFR mutations in non small cell lung cancer have been published and discussed in International Symposia.
The activity has been totally optimized with the validation of diagnostic protocols running on the genetic analyzer ABI 3500 Dx, on pyrosequencer Qiagen PyroMark and on the 7900 HT fast real time PCR. A MassArray platform has been introduced to support mutational analysis in clinical trials.
We can proudly state that our Division proposes to our stakeholders (in and out-patients, oncologists, pharma industries) a fully integrated system of molecular diagnostics based on automatized platforms for immunohistochemistry, in situ hybridization, RT-PCR, qRT-PCR and Sequencing respecting standards, rules, approvals requested for clinical testing.
All the reagents, disposables, instruments are validated for IVD according to the 98/78CE directive of the European Council and satisfying the requisites of CE label. Moreover, our ISO-approved Unit is engaged in developing a robust QC and QA program.
In conclusion we can offer a wide test spectrum to detect patients with solid tumors candidate to targeted therapies.
The main results of our specific clinical research have been published in peer reviewed journals.

Cytopathology Unit

The Unit of Diagnostic Cytology performs cytologic diagnoses for both in- and out- patients. The total number of tests in 2013 was 15,100; 6,500 of them were fine needle aspiration or extravaginal exfoliative cytology samples and 8,600 were Pap tests (mainly liquid based samples).
The four technologists are involved in the preparation of the slides and of the cell blocks while all the cytotechnologists perform the screening of the slides, both of vaginal and extra-vaginal samples.
Since March 2011 we started to support thoracic surgeons and digestive endoscopists while performing fine needle aspiration (FNA) samples assessing their adequacy during the endoscopic procedures (R.O.S.E.: rapid onsite cytotologic evaluation).
Both the technologists and the cytotecnologists are involved in this field together with the pathologist/s intraoperative charged with the diagnosis. During 2013, 47 adequacy procedures were performed with the digestive endoscopists, mainly on pancreatic lesions, while 420 adequacy procedures were performed with the thoracic surgeons, under fluoroscopy or ultrasound guide.
Cytotechnologists are also encouraged to actively participate in updating courses. In the last year a work was accepted for oral presentation at the 18th International Congress of Cytology in Paris.
FNA of palpable breast nodules and of superficial lymph nodes were performed by three cytopathologists.
One of them performed also ultra sound guided FNA of non palpable breast lesions. FNA of superficial lymph nodes were completed with cell block preparations, stained with immunocyto-chemistry and used for driving therapy in breast cancer follow up.
The daily internal quality control system, based on the review of 10% randomly selected cases according to a computer-mediate selection, guarantees the reliability and accuracy of the test results.
A computerized system online connects the department with the wards, so that the diagnoses are immediately available to the physician, just after the validation process. Moreover the Cytology Laboratory has implemented and maintains a quality management system, which fulfills the requirements of JCI and ISO.
Besides diagnostic cytology, the Unit is involved in different research activities, including the studies performed in collaboration with the Laboratory Medicine Division on circulating tumor cells in breast cancer, with the Division of Chemoprevention on Breast Ductal Lavages (DL) and HALO tests and with the Lab of Viral control of cellular pathways and biology of tumorigenesis, trying to understand how oncogenic viruses like HPV exploit the SUMO pathway.

Division of Laboratory Medicine

Maria Teresa SANDRI, MD
Director

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Fellow: Christian Mauro, DSc
Technician Fellow: Chiara Tigano
Secretaries: Elena Campanato, Erika Platano

Activities 2013. The Division of Laboratory Medicine encompasses the fields of hematology, biochemistry, coagulation, tumor markers, infectious disease serology, drug monitoring and microbiology. It serves both in- and out-patients, and the total number of tests performed during the 2013 was about 981.000. Moreover, the Division organizes the supply of blood products through a dedicated team.
Highly trained technologist perform the tests with automated analyzers, and expert personnel perform manual microscopic and analytical procedures necessary to provide accurate test results.
The everyday internal quality controls, and the participation to external quality assessment programs organized by the Regione Lombardia or by Private Companies, guarantees the reliability of the test results. Moreover, the laboratory has implemented and maintains a quality management system which fulfills the requirements of the ISO 9001:2000 standard.

A very recent computerization system online connects the lab with the wards, so that the results of the tests are very rapidly available for the physician, immediately after the validation process.
To facilitate the management of critically ill patients, a Point of Care Testing (POCT) system has been implemented, with blood gas analyzers and glucometers installed in different guards, controlled and supervised by the lab.
The laboratory is in charge of the organization of the Transfusional Service, which derives its technical procedure from the Centro Trasfusionale e di Immunologia dei Trapianti di Milano.
The laboratory also provides support to other clinical divisions for research protocols, both in terms of aliquoting and storing samples and in terms of performing esoteric tests, when requested.
It has organized a Service for external gynecologists and outpatients clinics related to the HPV testing, used for the management and prevention of cervical cancer.

Clinical Trials

- Prospective characterization of circulating tumor cells in patients with hormone receptor positive metastatic breast cancer. The aim of the study is to evaluate the presence of circulating tumor cells, isolated from whole blood, in women with metastatic breast cancer treated with hormonal therapy. The cells will be characterized and a special focus will be on the detection of specific markers which may be used to guide a personalized therapy.
- Evaluation of the prognostic role of Circulating Tumor Cells (CTCs) in patients with HER2 positive or triple negative tumor, during neoadjuvant chemotherapy. The aim of the study is the evaluation of the presence of circulating tumor cells in women undergoing or pre-operative chemotherapy or directly surgery. Two methods will be used: one which allows the enumeration of the cells, and a second method which allows the evaluation of the presence of cells presenting EMT or stemness characteristics.
- Use of new molecular tests in the diagnosis and follow-up of women with cervical lesions. The study will compare different methods for the detection of HPV in cervical samples from women with a lesion undergoing conservative surgery with the aim of identifying a more specific approach to detect those women who will present a relapse.
- Impact of prophylactic vaccination with Gardasil in a eighteen-year old women. Women will be vaccinated with a prophylactic vaccine against the genotype 16, 18, 6 and 11 of HPV. The women will be followed for 5 years with annual visit, HPV testing and in case of positivity genotyping. Aim of the study is to evaluate the change in HPV infection, with genotypes related or non-related to the vaccine, the incidence of HPV test positivity and of high grade lesions during the follow-up.

Publications

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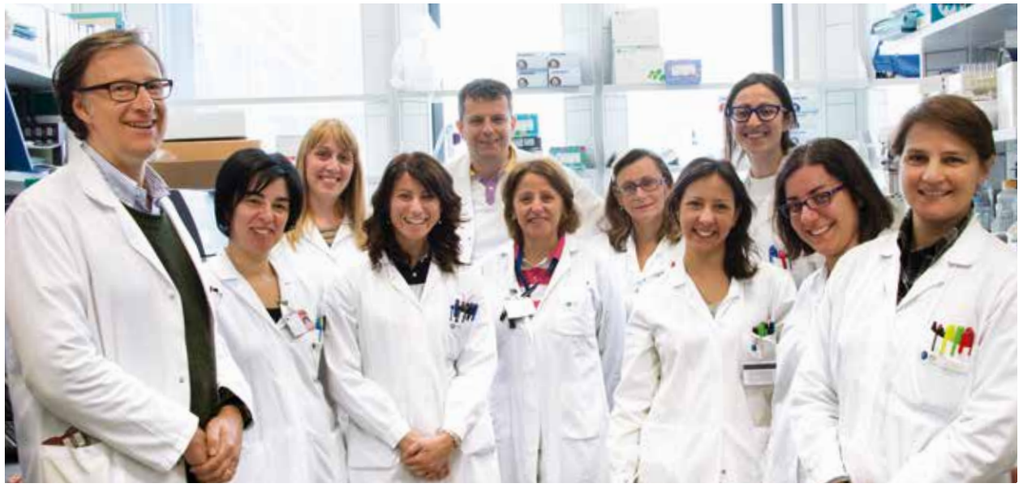
Division of Laboratory Haematology-Oncology

Francesco BERTOLINI, MD, PhD
Director



STAFF Senior Vice-Director: Patrizia Mancuso, Biol Sci D
Vice-Directors: Cristina Rabascio, Biol Sci D, Chiara Corsini, Biol Sci D
Senior Assistant: Angelica Calleri, Biol Sci D
Assistant: Giuliana Gregato, Biol Sci D
Fellows: Stefania Orecchioni, Biol Sci D, Valentina Labanca, BIol Sci D, Giovanna Talarico, Biol Sci D
Technicians: Cinzia Massaro, Pierluigi Antoniotti, Jessica Quarna
PhD Student (SEMM): Francesca Reggiani, Biotechnol Sci D
Secretary: Patrizia Passeri

Activities 2013. The Laboratory has two main clinical activities, both ISO9001, JACIE and JC Lab certified: a) diagnosis of haematological malignancies; and b) stem cell processing for transplantation.
Since 2011, the lab is also offering cell sorting and purification forclinicians and scientist interested in translational research. In 2013, the lab performed more than 600 cell sorting procedures, more than 70 stem cell collections were processed for autologous or allogeneic use and more than 1,200 blood and marrow sampleswere studied by flow cytometry, PCR, immunohistochemistry, FISH, cytogenetics and circulating tumor-specific DNA. The repository of plasma, serum and whole blood samples from leukaemia, lymphoma and myeloma patients includes nearly 8,000 frozen samples from untreatedpatients at first diagnosis and from patients longitudinally followed after remission or relapse.

Trafficking and angiogenic potential of cancer, stem and endothelial cells are the main research interests of the laboratory. We have developed and validated at the preclinical and clinical level a number of surrogate assays of angiogenesis and anti-angiogenic drug activity that arecurrently used worldwide in many clinical trials where cancer patients are treated with anti-angiogenic therapies. These assays have been found to predict the clinical outcome of breast cancer patients treated with anti-angiogenic therapies and to be of help to define the most activecombination of anti-angiogenic drugs and cytotoxics.
We are currently leading an international effort toward the standardization of the measurement of these surrogate markers.
In collaboration with IEO Department of Experimental Oncology we are investigating novel preclinical models of human haematological malignancies that are used to investigate new prognostic markers and new therapeutic procedures.
Along with Pfizer the Laboratory has recently described that targeting ALK1 kinase inhibits angiogenesis and tumor growth through a mechanism of action complementary to anti-VEGF therapies. Finally, we have described that progenitor cells from the human adipose tissue may promote breast cancer growth, angiogenesis, migration and metastases in several preclinical models of breast cancer.

Ongioing studies

- The role of Biguanides in controlling adipose-tissue support to tumorigenesis and metastatization
- Standardization of the enumeration of Circulating endothelial cells and progenitors
- Liquid biopsies: enumeration of cancer-specific DNA transcripts in the peripheral blood
- Validation of new biomarkers in acute leukemia
- Investigation of novel cell populations in the adipose tissue involved in tumorigenesis and metastatization.

Publications

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Department of Medical Imaging and Radiation Sciences

Roberto ORECCHIA, MD
Director

Vision and Mission

The collaboration between all the components of the Department lead to the optimization of the process of diagnosis and cure of patients. While a multidisciplinary approach to the diseases is mandatory nowadays, all departments participate at several scheduled meetings. The combination of metabolic and functional imaging offers the possibility of a more accurate diagnosis and therapy because imaging represents the optimal way to stage, treat and follow patients. Teams of specialists are in fact dedicated to each tumor site and in such a manner, through the collegial evaluation of images and clinical informations and evaluating different approaches, will be possible the best choice in each particular clinical situation. Also the process of enrolling patients to the different therapeutical strategies, once decided, will be easier and faster and each treatment will be personalized.

Patients care

All the Divisions and Units do participate to the process of diagnosis and treatment of patients. The purpose has always been to define the strategy that leads to an early diagnosis and that could easily let the start of the future steps. It is well known that to an early diagnosis correspond less aggressive treatments and how an high level of accuracy can also be crucial to avoid the risk of inappropriate procedures.
In this sense the PDP (Percorsi Diagnostici Preferenziali) are the first step with which we enroll patients to a scheduled series of actions to reach the aim of a faster, easier and complete approach to the different diseases. For all pathologies, those well defined steps drive the patient from all the exams, even pre intra or postoperative, straight to the treatments and it is to be noted that also the risk of loss of time between the two moments can be reduced having as much as possible an adequate idea of the whole scenario of each patient. A multidisciplinary approach is always followed during the whole diagnostic and therapeutic process but also during the follow up. In fact early and late toxicities and possible recurrences can be better and easily managed if immediately and accurately detected.

Research Activities

Research activities are of a great importance and do involve all the Divisions and Units that are part of the Department.
We investigate every step of the process that patients undergo from diagnosis to treatments. At the time of the diagnosis the research of new biomarkers made by the Division of Nuclear Medicine could bring to a better definition of the extent of diseases. The Radiologic Department has a lot of ongoing studies especially about breast cancer, but also about prostate cancer. It is more and more necessary to make an adequate and precise diagnosis of the breast itself but also of the clinical state of the axillary nodes. In this sense more accurate mammoghaphies and ultrasounds exams are of main importance and do bring important results in terms of future approaches to the patients with less invasive surgeries and chemo-radiotherapy treatments. Prostate cancer can easily be cured with conformal treatments if well defined in its extent with magnetic resonance.
Out of the diagnostic steps even in the subsequent therapies new innovations are ongoing. Regarding radiotherapy, conformal and image guided treatments do let a more and more adequate and accurate conformation of the fields.
Thanks also to the processes of quality assurance on the fully equipped machines, made by the Division of Medical Physics, and to the developments on new treatment planning software we are able to deliver higher doses per treatments and finally a lower number of fractions, so giving the patients the possibility to reduce the total treatment time. Giving a highly conformal treatment even the acute and late side effects should be reduced and we are recording data about it.
Considering all kind of patients a particular attention is about pregnant women and breast cancer. Even in these cases an accurate diagnosis and less invasive treatments, such as Intra Operative Radiation Therapies (IORT), could help in giving the higher chances to cure the disease.
Due to the therapeutical innovations there is a growing number of patients affected by oligometastatic disease and long survivals if compared to the past. Particular attention is taken about this group of patients because small amounts of disease can be controlled with the new strategies of treatments.
Both the Radiotherapy Department and the Unit of Interventional Radiology play a leading role in this field.

Educational Activities

Educational activities of the Department include teaching for pre- and postgraduate medicine, physics and biotechnology students and radiology & radiotherapy technicians RTTs at which participates the Politecnico of Milan. The Division of Radiotherapy is the main site of the post-graduate residency program in Radiation Oncology of the University of Milan and also participates to several research activities in several European Projects on improvement in radiotherapy for cancer patients: the most recent ones are ULISSE and EUREKA-2 of European Atomic Energy Community's Seventh Framework Programme and projects of the Italian Ministry of Health, University of Milan, and Italian Association of Cancer Research (AIRC). These studies directly and fully involve the Division of Medical Physics. There is also a strict collaboration with the CNAO (Centro Nazionale Adroterapia Oncologica) to share research protocols of treatments in very selected tumours
The Unit of Interventional Radiology is involved into the ESIR (European School of Interventional Radiology) and is an active member of CIRSE (Cardiovascular and Interventional Radiology Society of Europe) that has recently asked the Division to participate in writing a clinical document for "Guidelines on Ablation of Small Renal Tumours".

Division of Radiotherapy

Roberto ORECCHIA, MD
Director

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TECHNICIANS (RADIOTHERAPY TECHNOLOGISTS, RTTs)

Chief Technician: Massimo Sarra Fiore, MSc
Technician referent for Brachytherapy Unit: Andrea Guido, MSc
RT Technicians: Francesca Baldini, MSc, Jennifer Bona Rivas, MSc, Enrica Borghetti, MSc, Manuela Cannella, MSc, Lucia Casanova, Saudia Castagna, MSc, Fabiana Castelluccia, MSc, Fabio Castellini, MSc, Roberto Corea, MSc, Guglielmo Gatto, MSc, Saverio Greco, MSc, Verlie Ann Jones, Olena Kuts, MSc, Assuntina Leppa, MSc, Francesca Picca, MSc, Claudio Pobbiati, MSc, Alberto Rampinelli, MSc, Daniela Rozza, MSc, Elena Strata, MSc, Andrea Vaccari, MSc, Ilona Vecchio, Msc, Giulia Piccinini, MSc

NURSES E AUXILIARIES

Referent nurse: Gianni Buffi
Nurses: Rodolfo Cendamo, Milena Lucic, Loredana Murra, Iacob Radu Daniel
Auxillaries: Elena Rubio, Cosimo Persichella

Secretaries: Ida Muraca, Maria Ersilia Viscusi
Secretary, Reception: Nadia Zanoni

Activities 2013. The Division of Radiotherapy called since the beginning of 2012 Advanced Radiotherapy Center (ARC) is an university department with 65 employees including 14 radiation oncologists, 8 physicists and 1 bioengineer committed to the high quality care delivery enhanced by research activities and resident and student education. The Division has the convention with the Faculty of Medicine of the University of Milan for postgraduate teaching in radiation oncology.
The Division has the latest equipment available for the high-precision radiotherapy like Intensity Modulated Radiotherapy (IMRT, including dynamic arc IMRT using RapidArc technology), Image-Guided Radiotherapy (IGRT), respiratory gating, intra- and extra-cranial stereotactic radiotherapy and 3-D conformal radiotherapy. High precision radiotherapy allows for excellent tumor targeting and maximum sparing of normal tissue. In consequence, several clinical protocols with dose escalation and accelerated hypofractionated schedules (higher dose per fraction, leading to the reduction of the overall treatment time) have been activated. In particular, the FAST project (Frazionamenti Accelerati dello Schema Terapeutico, i.e. Accelerated Fractionation of the Therapeutic Schedule) has been applied to the breast, prostate cancer and other cancers.
Brachytherapy Unit is a full-profile unit equipped with both low-, pulsed- and high dose rate systems. The unit is committed to the integrated approach in the field of radiotherapy.
The Department collaborates with the National Centre for Oncological Hadrontherapy (CNAO) in Pavia for the definition of the clinical research protocols on the particle therapy in selected cancer patients. There is also an active collaboration with the Department of Experimental Oncology, IEO and with Politecnico of.
During 2013, 3366 new patients were treated in our Division: 2801, 352 and 213 with external beam radiotherapy, intraoperative irradiation (mainly for breast cancer) and brachytherapy, respectively.
Educational activities of the Division include in-department teaching for pre- and postgraduate medicine, physics and biotechnology students and radiology&radiotherapy technicians RTTs (University of Milan and Politecnico of Milan). The Division is the main site of the post-graduate residency program in Radiation Oncology of the University of Milan.
The Division has numerous research activities, including internal studies and institutional multidisciplinary or multicentric studies. The Division is involved in several European Projects on improvement in radiotherapy for cancer patients. The most recent scientific commitments include research projects like ULISSE and EUREKA-2 projects of European Atomic Energy Community's Seventh Framework Programme and projects of the Italian Ministry of Health, University of Milan, and Italian Association of Cancer Research (AIRC).
In research activities of the Division the emphasis is placed on breast cancer, urological tumors and head and neck and other adult solid tumors. The main accent is focused on the combined modality approach, high precision radiotherapy, hypofractionation and ablative radiotherapy, oligometastatic disease and new prognostic and predictive factors. Last but not least, quality of life and reduction of radiotherapy toxicity is extensively studied. In breast cancer, along with 3D conformal RT, IMRT is routinely used in the adjuvant setting. Our clinical practice has always been based on hypofractionation. IMRT has increased this attitude due its potential to achieve superior dose homogeneity and normal tissue sparing, especially for targets and organs at risk. Several clinical protocols are going on, using either helical or direct tomotherapy modality allowing for reduction of overall radiotherapy duration.
Every year the Division publishes about 30 full papers with an overall Impact Factor of about 150.

Clinical Trials

- Multicenter phase IIb/III randomized trial in patients with breast cancer, on the postoperative external beam radiotherapy comparing conventional fractionation with 2 accelerated hypofractionation with concomitant boost schemes. MIRA-SOLE trial. IEO S639/311
- Randomized phase II clinical study in patients undergoing intraoperative boost to the tumor bed witrh electrons (ELIOT) followed by postoperative accelerated hypofractionated external beam radiotherapy after conservative surgery for early-stage breast cancer. IEO S676/61
- Prospective research grant of the Italian Association of Cancer Research (Associazione Italiana per la Ricerca sul Cancro, AIRC) IG-13218: Short-term high precision radiotherapy for early prostate cancer with concomitant boost on the dominant lesion
- Prospective research grant of the Italian Association of Cancer Research (Associazione Italiana per la Ricerca sul Cancro, AIRC) IG-N14300: Carbon ions boost followed by pelvic photon radiotherapy for high risk prostate cancer
- Prospective current research projects of the Italian Ministry of Health on breast, prostate and head and neck malignancies.

Publications

Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. ‹http://www.ncbi.nlm.nih.gov/pubmed/24225155› Lancet Oncol. 2013 Dec;14(13):1269-77.

Jereczek-Fossa BA, Santoro L, Zerini D, Fodor C, Vischioni B, Dispinzieri M, Bossi-Zanetti I, Gherardi F, Bonora M, Caputo M, Vavassori A, Cambria R, Garibaldi C, Cattani F, Matei DV, Musi G, De Cobelli O, Orecchia R. Image guided hypofractionated radiotherapy and quality of life for localized prostate cancer: prospective longitudinal study in 337 patients. <http://www.ncbi.nlm.nih.gov/pubmed/23313200> J Urol. 2013 Jun;189(6):2099-103.

Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Dell'Acqua V, Ferrari A, Rotmensz N, Sangalli C, Luini A, Veronesi U, Orecchia R. Accelerated partial breast irradiation with intraoperative electrons: using GEC-ESTRO recommendations as guidance for patient selection. <http://www.ncbi.nlm.nih.gov/pubmed/23218711> Radiother Oncol. 2013 Jan;106(1):21-7.

Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Rotmensz N, Sangalli C, Luini A, Veronesi U, Orecchia R. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. <http://www.ncbi.nlm.nih.gov/pubmed/22245196> Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):806-13.

Jereczek-Fossa BA, Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, Zerini D, Gherardi F, Ascione C, Bossi-Zanetti I, Mauro R, Bregantin A, Bianchi LC, De Cobelli O, Orecchia R. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. <http://www.ncbi.nlm.nih.gov/pubmed/21277113> Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):889-97.

Division of Radiology

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Roberto Di Filippi, Alessandro D'Incecco, Simone Fasulo, Roberto Labruna, Ferdinando Laserra, Manuela Martino, Obregon Valeria, Ubaldo Piccolo Longo, Filippo Raccosta, Cinzia Resta, Riccardo Simone, Emanuella Veneziano, Bollini Elena, Marco Gavarini, Prisco Gennaro
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Activities 2013.

In 2013 the Department of Radiology performed 100.000 different diagnostic examinations and interventional procedures, 8% of them in patients enrolled in clinical trials.

The scientific activity is coordinated by a specialized staff of radiologists, technicians, secretaries, data managers, physicists, bio-engineers and statisticians. The main researches are dedicated to early diagnosis and functional imaging which led to clinical applications.
The early diagnosis studies allowed to develop an extraordinary tool in oncological screening: the whole-body diffusion is able to diagnose the presence of asymptomatic tumors through a special exam of Magnetic Resonance.

The observational study performed since 2000 on 6000 volunteers with low dose CT for early diagnosis of lung cancer, is recognized as one of the most important research project worldwide, showing the possibility to offer an effective secondary prevention of lung cancer for smokers.
The use of latest generation CT equipment allows to perform virtual colonoscopy examinations with a very low dose of radiation.
Being between pioneers of functional imaging studies gave us the opportunity of developing a state-of-the-art techniques in Magnetic Resonance ad the Multi-parametric Magnetic Resonance Imaging (mp-MRI) in Prostate, which is the current most advance technique in the study of this organ.

The Division of Radiology is member of the European Institute of Biomedical Imaging Research (EBIR) and of the European School of Radiology (ESOR), and strict co-operation, in research and medical education, is maintained with Insespital University of Berne, University of Sussex, the Royal Marsden Hospital in London and Massachusetts General Hospital in Boston. The Division is deeply involved in educational programmes, being part of the teaching activities of the Department of Health Sciences at School of Medicine, School of Radiographers and Post-graduate School of Radiology of the University of Milan.

In 2013 we organized 7 residential courses, with a total of 204 ECM credits.

Interventional Radiology Unit Activities

The Interventional Radiology Unit is one of the very few European Units of Interventional Radiology that manages its own beds in a dedicated ward; 275 Ordinary Admissions and 288 Daily Admissions (Day Surgery) were performed in 2013. 1328 main interventions (such as liver, renal and lung thermal ablations; liver embolizations and radioembolizations), 2530 minor procedures (such as image guided biopsies and port placements) were performed in three distinct dedicated interventional rooms. Clinical activity also included more than 1000 outpatient consultations in a dedicated clinical room twice a week and more than 100 concomitant surgical interventions (both during laparoscopy and open surgery before or after liver resection).

The Interventional Radiology Unit is also involved in the management of urgency and emergency procedures that may occur in the daily clinical and surgical activity with the oncological patient thanks to a new overnight on-call service: more than 300 bedside urgent interventions have been performed in 2013 such as central venous catheterization and pleural drainage under ultrasound guidance, 12 arterial coil or glue embolizations for post surgical life threatening bleedings, 34 biliary drainage for malignant jaundice, 7 caval filter deployments for deep venous thrombosis and more than 150 nephrostomies for urinary tract obstruction. Moreover as a comprehensive cancer center more than 100 patients have been treated with ultrasound-guided HIFU (focused ultrasound), within a feasibility study phase. All patients included in this study were deemed not candidate for surgery, nor suitable for local ablative techniques such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization or embolization (TAE), or were unwilling to have any of those treatments. Finally also non surgical treatment of symptomatic uterine fibroids is managed by the Interventional Radiology Unit, with both: a non invasive option (ultrasound-guided HIFU) and a more aggressive treatment that is trans arterial fibroid embolisation.

Innovation, clinical research and development of newer treatment strategy in multimodal management of tumor disease, are the backbone of daily practice of the Unit, which represents today one of the pillars of clinical management at the European Institute of Oncology.
Unit of Interventional Radiology is involved into the ESIR (European School of Interventional Radiology) and is an active member of CIRSE (Cardiovascular and Interventional Radiology Society of Europe). The CIRSE Standards of Practice Committee has recently ask for writing a clinical document for "Guidelines on Ablation of Small Renal Tumours" in order to: help create high-quality interventional radiological guidelines, based on the most up-to-date scientific data available allow for the document to undergo strict peer review in the journal CVIR and by CIRSE's Executive Committee.

Research Activity

DW-MRI

- FDG PET/CT e Diffusion Weighted Imaging in squamous cells cancer of head and neck: prognostic values of SUV and ADC
- Spectroscopy and DWI in carcinoma of the cervix
- Comparing DWI and PET in patients with advanced carcinoma of the cervix
- Comparison multi detector CT and MRI with surface coils and DWI in diagnosis of neoplastic infiltration of laryngeal cartilage
- Laryngeal MRI with surface coils: T2 and DWI imaging vs contrast enhanced T1

Imaging guided Biopsy

- Accuracy and costs of percutaneous biopsy of laryngeal and hypopharyngeal lesions guided by US
- Accuracy and safety of CT guided biopsies of mediastinal masses
- Feasibility of CT guided biopsy of lung nodules < 1cm

Prostate imaging

- Prognostic role of Multi-parametric MRI (mp-MRI) in Nerve-Sparing Robotic Assisted Laparoscopic Prostatectomy (NS-RALP) Outcomes
- Can mp-MRI in low risk subjects predict negative outcome?
- PI-RADS and Gleason scores: are they associated? Experience in 244 operated patients

Lung cancer

- GGO detection at ultra-low-dose CT with a new model-based iteractive reconstruction algorithm (MBIR): an anthropomorphic phantom study'
- Radiological features of pulmonary benign lesions detected at lung cancer screening.
- Existing problems and possible solution for lung cancer screening (review)
- 10-year CT lung cancer screening: cumulative-dose in 5201 asymptomatic smokers
- Tracking of stem cells used to repaire bronchopleural fistula
- Comparing CT-designed lung volume and postpneumonectomy pulmonary function

Interventional Radiology

- Unit is actually involved in more than 10 clinical trial regarding imaging guided percutaneous biopsies for re-assessment of metastases biological behavior.
- MIRACLE trial for trans arterial liver metastases embolisation with Irinotecan loaded Embozene TANDEM® Microspheres

Selected Publications

G. Petralia, A. Padhani, P. Summers, S. Alessi, S. Raimondi, M. Bellomi - W¬hole-body diffusion imaging for the early detection of metastases in patients with advanced melanoma - Eur Radiol (2013) 23:3466–3476

S. Rizzo, G. Calareso, F. De Maria, V. Zanagnolo, R. Lazzari, A. Cecconi, M. Bellomi - Gynecologic tumors: How to communicate imaging results to the surgeon - Cancer Imaging (2013) 13(4), 611-625

Monfardini L, Della Vigna P, Bonomo G, Orsi F, Tullii M, Disalvatore D, Monfardini S. - Interventional oncology in the elderly: complications and early response in liver and kidney malignancies. - J Geriatr Oncol. (2013) 4(1):58-63

Aurilio G, Monfardini L, Rizzo S, Sciandivasci A, Preda L, Bagnardi V, Disalvatore D, Pruneri G, Munzone E, Della Vigna P, Renne G, Bellomi M, Curigliano G, Goldhirsch A, Nolè F. - Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. - Acta Oncol. (2013) 52(8):1649-56

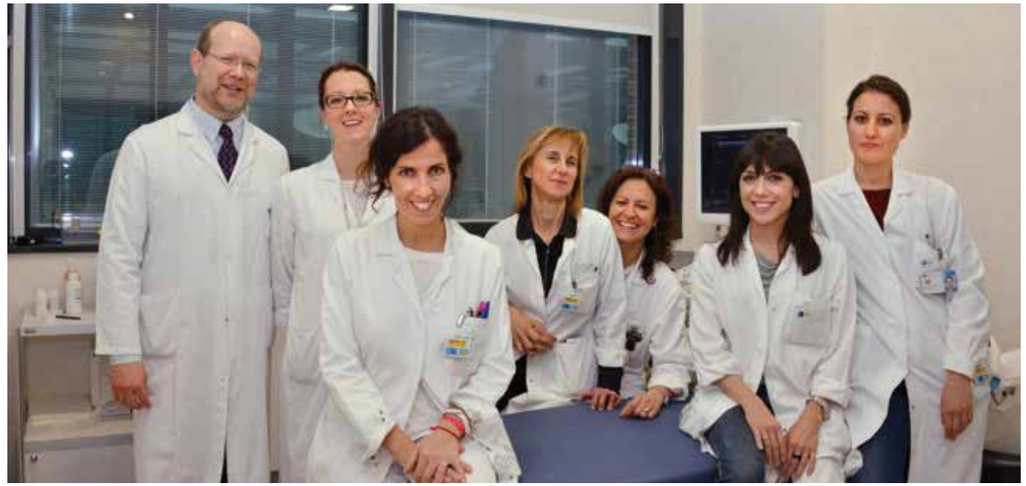
C.Rampinelli, D.Origgi, M.Bellomi (2012) Low-dose CT: technique, reading methods and image interpretation - Cancer Imaging (2012) 12(3), 548_556

G.Petralia, P.Summers, S.Viotti, R.Montefrancesco, S.Raimondi, M.Bellomi - Quantification of variability in perfusion CT analysis of HCC: a step towards clinical use - Radiology (2012) 265; 448-456

C. Rampinelli, L. Preda, M. Maniglio, L. Sirica, L. L. Travaini, G. Veronesi, M. Bellomi - Extrapulmonary Malignancies Detected at Lung Cancer Screening - Radiology (2011) 261; 293-299

Division of Breast Imaging

Enrico CASSANO, MD
Director



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Data Managers: Cristiana Fodor, Simona Menna

Activities 2013. The significant reduction in breast cancer mortality in the population is attributable to improvements in treatment, but even more so to the increasingly accurate and timely diagnosis of the disease.
Every action undertaken, above all, every investment dedicated to this end, is therefore of pivotal importance.
To implement early diagnosis, it is important that breast centres avail themselves of appropriate equipment and dedicated staff.
It is on this first step – that of accurate and early diagnosis – that the subsequent treatment pathway is based.
In the field of breast diagnosis today, the important objective is not however just the "timeliness" of the diagnosis, but also its "completeness".

It is necessary to diagnose a neoplasm when it is still small, and yet one must also provide contextual data regarding its biological characteristics. It is these characteristics in particular that will determine the treatment plan.
These are the principal objectives of the clinical, scientific and educational activities undertaken by the Breast Imaging Division of the European Institute of Oncology.

The well-established investigations routinely carried out are:
- breast examination
- mammography
- breast ultrasound
- magnetic resonance
- cytological sampling
- microhistological sampling

A recent addition to the Division is tomosynthesis. This is a three-dimensional high-definition mammography technique that enables the breast to be examined in "layers": this has the great advantage of facilitating the understanding of radiology reports which may be non-immediate or incompletely visualised with classical 2D mammography. Tomosynthesis, according to initial reports in the scientific literature, increases the sensitivity of mammography by 25%-30%.

Some Division study protocols and related clinics

SOUND study

Sentinel node vs. observation after axillary ultrasound

This is a prospective observational study for the definition of the parameters of negativity in axillary ultrasound.
Lymph node removal in breast disease is not performed for therapeutic purposes, but is exclusively aimed at disease staging.
Sentinel lymph-node biopsy (SLNB) is a useful procedure for axillary staging when there is a lack of clinical evidence for lymph-node involvement.
Currently, SLNB is a technique that enables axillary dissection to be avoided in approximately 70% of breast cancer patients. It is nonetheless necessary to better define the indications for SLNB.
Furthermore, identifying diagnostic methods that enable lymph node status to be ascertained, as an alternative to SLNB, is a matter of priority.
The combined use of ultrasound and of ultrasound'guided cytology could enable the identification of a certain number of lymph nodes affected by neoplastic disease: this would enable some patients to be sent directly for axillary dissection, avoiding having to recourse to SLNB, with a consequent reduction in health expenditure and in surgical time.
In summary, the study aims to assess whether the ultrasound method, with the latest developments in medical semiology and new equipment can permit pathological oncology signs to be identified at the lymph-node level.
In this way the negative predictive value of the method can be established as can the possibility to use it in axillary staging.
The study is aimed at patients with a cytohstological diagnosis of small-dimension breast disease (T1) with a clinically-negative axilla (N0) and who are candidates for breast-conserving surgery. These patients undergo dedicated axillary ultrasound at the preoperative stage. If the ultrasound detects a suspect lymph node, an ultrasound-guided cytological sampling is carried out on it.
A dedicated database stores the data relating to axillary ultrasound, lymph node cytology and the outcome of the histological biopsy of the sentinel node.

Image-guided percutaneous biopsy

For years now, mini-invasive biopsy procedures via the percutaneous route for non-palpable suspect breast lesions, have replaced surgical biopsy for diagnostic purposes: vacuum-assisted biopsies have become more widespread with respect to traditional core-biopsies.
Vacuum-assisted biopsies in fact have the main advantage of avoiding the multiple needle passages of the core needle biopsy; furthermore, greater quantities of breast tissue are sampled with respect to those in core biopsies, facilitating the pathologist's interpretation. Also the greater quality of sampled tissue enables immunohistochemical analyses and analyses of prognostic markers, such as Ki-67, and oestrogen, progestin and Herb-B2 receptor status.
The disadvantages of vacuum-assisted biopsy are essentially a certain invasiveness, high costs and a learning-curve for the radiologist which more demanding than that for FNAC and core biopsy.
Such biopsies have few complications (<10%), these essentially being haematomas and venous bleeding.
Vacuum-assisted biopsies are conducted in the Division with stereotactic guiding, ultrasound and NMR.
The needles used vary in size from 7G to 14G, and some studies have not reported significant differences between the different calibres. In the last two years we have been able to use and test different equipment from different manufacturers with various interesting techniques aimed at greater comfort for the patient and less invasiveness, a faster procedure and the improvement of the quality of removed tissue.

Outpatient clinic for pregnant women

SIGA Senologia Integrata in Gravidanza e Allattamento (Integrated Senology in Pregnancy and Lactation).
The clinical and instrumental approach to pregnant or lactating symptomatic patients has been defined and duly applied, after having included it in the FONCaM protocols.
Given the considerable diagnostic difficulties regarding the breast in pregnant women, and a scarcity of clinical experience, there being few scientific publications in the purely

diagnostic sphere, a multidisciplinary outpatients clinic was launched in the Division for pregnant symptomatic women. The difficulties in arriving at a timely and accurate breast diagnosis are linked essentially to the known hormonal, and therefore morphological, changes in the breast during pregnancy, the limited experience of specialists and an inexact knowledge in the area of radioprotection when examining pregnant patients.
Hence the initiative on the part of some radiologists of the Division to create an outpatient clinic dedicated to breast diagnosis in pregnant patients. The clinic is interdisciplinary and works both in a clinical and a scientific context.
In addition to the radiologist, also involved are oncology, surgery, pathology, epidemiology, gynaecology, paediatrics and health physics specialists.

Contrast-media mammography

A study of particular interest which may have wide-ranging development and important clinical applications is contrast-media mammography. The examination is conducted like a normal mammography but with the concomitant intravenous injection of iodine contrast medium (Visipaque 320, 1.5 ml pro kg, 3ml\sec flow). The study is aimed at patients with dense breast and a verified diagnosis of breast neoplasia. Informed consent is necessary for these patients.
Two images are used for each projection. One is low-energy and the other is obtained by subtraction, combining the two acquisitions at low and high energy. The first mammography scan is carried out at two minutes from the endovenous injection of the contrast medium and the others at two minutes apart.
By means of this technique, two images are used for each projection; the images obtained by subtraction highlight the nodules that show the contrast and which are therefore suspicious for cancer. This type of assessment is proving useful in dense breasts where mammography is known to be of reduced sensitivity. An initial association between contrast-media mammography and tomosynthesis is under way and it is envisaged that this could increase the sensitivity and specificity of mammography still further, and yield useful information regarding the local extent of the neoplasia.

Publications

Breast ductal lavage for biomarker assessment in high risk women: rationale, design and methodology of a randomized phase II clinical trial with nimesulide, simvastatin and placebo
Matteo Lazzeroni, Aliana Guerrieri-Gonzaga, Davide Serrano, Massimiliano Cazzaniga, Serena Mora, Chiara Casadio, Costantino Jemos, Maria Pizzamiglio, Laura Cortesi, Davide Radice and Bernardo Bonanni
BMC Cancer 2012, 12:575

The biological features and prognosis of breast cancer diagnosed during pregnancy: a case-control study.
Azim HA Jr, Botteri E, Renne G, Dell'orto P, Rotmensz N, Gentilini O, Sangalli C, Pruneri G,
Di Nubila B, Locatelli M, Sotiriou C, Piccart M, Goldhirsch A, Viale G, Peccatori FA.
Acta Oncol. 2012 May;51(5):653-61

Stereotactic vacuum-assisted breast biopsy is not a therapeutic procedure even when all mammographically found calcifications are removed: analysis of 4,086 procedures.
Penco S, Rizzo S, Bozzini AC, Latronico A, Menna S, Cassano E, Bellomi M.
AJR Am J Roentgenol. 2010 Nov;195(5):1255-60

A neurilemmoma in the brachial plexus was found incidentaly with breast intraductal papilloma
Latronico A, Mazzarol G, Trentin C, Meroni S, Abbate F, Cassano E, Bellomi M
Am J Case Rep 2010; 11:195-197

Breast ductal carcinoma and metastatic lymphoma to the contralateral breast in patient with cutaneous non-Hodgkin lymphoma
B. Di Nubila, S. Meroni, L. Bonello, F. Peccatori, E. Cassano, M. Bellomi
Hippokratia 2011;15(1):84-86

Ultrasound challenge: secondary breast angiosarcoma mimicking lipoma
Meroni S, Moscovici O, Renne G, Sosnovskikh I, Rossi V, Menna S, Cassano E..
Breast J. 2013 Jul-Aug;19(4):437-8

Underestimation rate of Lobular Intraepithelial Neoplasia (LIN) in Vacuum Assisted Breast Biopsy (VABB)
Meroni S, Bozzini AC, Pruneri G, Moscovici OC, Maisonneuve P, Menna S, Penco S, Meneghetti L, Renne G, Cassano E.
Accepted at European Radiology

Division of Nuclear Medicine

Chiara Maria GRANA, MD
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Data Managers: Ines Tedeschi, Cristiana Fodor
Nurse: Francesca Fassari
Medical Physicists to Nuclear Medicine: Francesca Botta, Mahila Ferrari
Secretaries: Laura Brambilla, Anna Lucia Tusini

Activities 2013. The Division of Nuclear Medicine is certified ISO 9001-2008 and is devoted to the early localization and treatment of tumors, by means of functional imaging and targeted radionuclide therapy. The Division offers traditional nuclear medicine techniques as well as new diagnostic exams, such as sentinel node lymphoscintigraphy in breast, gynecologic, tongue cancer and melanoma, radioguided occult lesion localisation (ROLL) in breast, lung and colon lesions, perfusion procedures in melanoma and sarcoma patients, peptide-guided whole body scans and PET scans.
18FDG-PET scans are routinely performed in the diagnosis, staging, follow up and radiotherapy planning of various types of cancer, applying ROL criteria in PET/CT scan acquisition. Since July 2008 PET/TC scans with 68Ga-octreotide are performed.
The Division is one of the few in Europe having protocols of radionuclide therapy of solid tumors and lymphomas with new radiolabelled molecules that show high affinity for tumor cells, such as monoclonal antibodies and radiolabelled peptides.

Our Division has been one of the pioneers in the development of peptide receptor radionuclide therapy (PRRT) in NETs, where clinical studies have been carried out for over 15 years. Currently we are participating to an international registrative phase III study on PRRT.
Our previous therapy experience focused on Radioimmunotherapy in patients with recurrent glioblastoma, obtaining important results on survival, and also on the development of an innovative radionuclide treatment for breast cancer (IART®).
The Division is also involved in the treatment of Non-Hodgkin Lymphoma with radioimmunotherapy with Zevalin and in the radioembolization treatment of primary and secondary liver tumors. Other fields of activity include benign and malignant thyroid diseases and the treatment of painful bone metastases and prostate cancer with radium-223. We have also out-patient activity for thyroid and neuroendocrine patients. As Nuclear Medicine is a cross discipline, we participate in different multidisciplinary teams.
The Division is equipped with two PET/CT scanners, one double-head gamma-camera and one single head gamma-camera. Moreover, the Division is fully equipped for the synthesis of 18FDG and 68Ga-peptides and their quality controls and possesses three hot labs for the preparation of radiopharmaceuticals with different types of emission (gamma, beta+ and beta-), both for diagnosis and therapy.
In 2013, 9685 diagnostic studies were performed, of which 4127 were PET/CT with 18FDG and 482 with 68Ga-octreotide, and over 650 outpatients were visited.
The research activities include the development of a new albumin macroaggregate suitable for labeling with long lived isotopes to be used in the ROLL technique in alternative to the currently available products labeled with 99mTc with the goal to increase the flexibility of the procedure and expand its clinical application.
In the field of new radiopharmaceuticals for application to receptor mediated therapy, we are investigating a new class of peptides with affinity for somatostatin receptors which have been developed in collaboration with the University of Florence.

These research efforts are in the frame of a wider project by IAEA entitled "Development and evaluation of 177Lu and 90Y labeled cancer specific radiopharmaceuticals in a kit form suitable for targeted therapy". One of these new somatostatin analogues has been labeled with 68Ga and injected in tumor bearing mice showing a superior uptake in the tumor compared to a radiolabeled analogue routinely used in the clinical practice.
During 2013, the Division published 16 articles on peer-reviewed journals, with an overall 58.274 Impact Factor. The Division has an agreement with various Universities in Italy, for the educational activity in the School of Specialization in Nuclear Medicine, Oncology and Basic Radiopharmacy Principles to spread new therapeutic modalities in the field of Radionuclide Therapy and Radiopharmaceuticals. Nuclear Medicine Division is hosting many young fellows from different countries, for preclinical and clinical Research activities, to foster future collaborations.

Clinical Trials

- IEO S685/112
  A multicentre, stratified, open, randomized, comparator-controlled, parallelgroup phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours

- IEO S738
  A phase 3, open-label, multicenter, randomized study of sequential Zevalin (ibritumomab tiuxetan) versus observation in patients at least 60 years of age with newly diagnosed diffuse large B-cell lymphoma in PET-negative complete remission after R-CHOP or R-CHOP-like therapy

- IEO S 724/512
  A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL).

- Protocollo RADIOMEN (submitted to C.E.)
  Studio esplorativo, monocentrico non controllato in aperto, volto a sviluppare e valutare l'applicazione di una tecnica innovativa di rimozione radioguidata dei tumori cerebrali.

- IEO 73
  "Valutazione dei marcatori di tossicità a lungo termine in pazienti con tumori neuroendocrini sottoposti a terapia radiorecettoriale (PRRT) mediante analisi PCR."

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Activities 2013. The activities of the Medical Physics Unit concern the applications of physics in the medical field. For this purpose the physicists of the Unit regularly and continuously cooperate with the physicians and the technicians of the Department of Medical Imaging and Radiation Sciences for the implementation and optimization of new diagnostic and therapeutic techniques involving the use of ionizing and non-ionizing radiation, the dosimetric evaluations of radiation fields produced by radiological equipments and radioactive sources, the execution of radiation treatment planning, the commissioning of new equipments and the quality assurance of radiotherapy and diagnostic imaging systems, the radiation safety of operators and patients.

The main activities, listed by field of application, are:

Radiotherapy

- dosimetry of radiation beams produced by accelerators and radiation sources in use: conventional and advanced linear accelerators (Trilogy, TomoTherapy, CyberKnife, Vero) for external beam radiotherapy, mobile linear accelerators for Intra Operative Radiation Therapy (IORT), remote after-loading projectors for brachytherapy with sealed radioactive sources, 125I seeds for interstitial permanent prostate brachytherapy;
- implementation and application of advanced irradiation techniques: 3D-Conformal Radiotherapy, Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), stereotactic treatments, Image Guided Radiotherapy (IGRT), 4D treatments with tumour tracking;
- treatment planning for patients undergoing external beam radiotherapy and brachytherapy;
- quality assurance of radiotherapy equipments (linear accelerators, brachytherapy equipments, etc.).

Nuclear Medicine

- internal dosimetry evaluations for loco regional radionuclide therapies with resin 90Y-microspheres (radioembolization);
- leakage monitoring in perfusion procedures;
- optimization of nuclear medicine procedures and assessment of doses to patients;
- study of radiobiological models applied to radionuclide therapies, especially for radioembolization of liver tumours with 90Y-resin microspheres;
- analysis by home-made software (Matlab support) of the activity distribution in scintigraphic images and evaluation of dose distribution at the voxel level (voxel dosimetry); analysis of the dose-volume histograms, Biological Effective Dose histograms and Equivalent Uniform Dose;
- development of a software for the segmentation of PET volumes and evaluation of standardized uptake value to facilitate patients' diagnosis and follow-up assessment;
- quality assurance of equipments (SPECT, PET/CT, etc.).

Diagnostic Radiology

- optimization of diagnostic imaging procedures (conventional radiology, mammography, CT, angiography, ultrasound, MRI, etc.) and treatments with high intensity focused ultrasound (HIFU);
- evaluation of doses to patients undergoing radiological procedures;
- optimization of patient dose in screening and follow up procedures with multislice CT;
- development of a quality assurance program for HIFU (High Intensity Focused Ultrasounds);
- quality assurance of radiological, magnetic resonance and ultrasound equipments.

Radiation Protection

- risk assessment in activities with ionizing radiation, magnetic resonance imaging and laser sources;
- individual and environmental monitoring in activities with ionizing radiation;
- monitoring of the disposal of radioactive waste in the environment.

Research Projects

- "Dosimetry for Ultrasound Therapy". Collaboration within the EMRP Joint Research Project 'Dosimetry for Ultrasound Therapy (DUTy)'

- "Adult and Paediatric Patient Radiation Doses From Multidetector Row Computed Tomography Scans: a National Survey (MCTDOSE)"
- "Dosimetric evaluations in patients undergoing radiation therapy with 177Lu-DOTATATE" within the "Dosimetry, Pharmacokinetics and ECG substudy" as part of the multicenter study "A multi-centre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTAo-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours."
- "Image analysis" as part of the multicenter study "Generation of scintigraphic images in a virtual dosimetry trial based on Monte-Carlo modeling."
- "New and innovative technologies in the integrated surgical treatment of breast carcinoma."

Publications

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Division of Early Drug Development for Innovative Therapies

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Activities 2013. The mission of our Division is to accelerate the development of new anticancer drugs (including biologics, and cellular therapies) that will improve survival and quality of life for patients with cancer. Our drug development program is not only furthering cancer research, but it also offers hope to patients facing the toughest cancer battles. Our personal commitment is devoted to build up an alternative, personalized, disease and pathway oriented model to develop drugs for cancer disease and to ensure equitable access to new and field-relevant health tools. We are committed to develop therapeutics for biomarker-defined subpopulations, to develop new drugs or new less toxic formulations of existing drugs. We are strongly motivated to innovate approach to cancer treatment. Innovation refers to the testing and implementation of novel approaches (clinical trial designs and operations, funding mechanisms, resource utilization, data collection, data analysis, etc) to developing more effective therapeutics more efficiently than existing methods.

We need to innovate through interconnectedness. We are involved in a complex international network with cooperative efforts across institutions, industry, and organizations to conduct clinical trials that will have the greatest impact on cancer care more efficiently. The breadth and technical complexity of new technologies that could advance personalized oncology care demand a more interconnected approach to the development of diagnostics and therapeutics. Consortia of institutions that can standardize the acquisition, processing, and shipping of patient specimens may interconnect, with each having a laboratory that specializes in different methods of specimen analysis. Such interconnected facilities may expedite the development of personalized cancer therapeutics more powerfully than single centres.
As therapeutics are developed to treat small subsets of individual disease populations, the operations to perform trials in isolation with old methods become inefficient, almost untenable. We cooperate with the internal Drug Discovery Program to advance unprecedented targets, for orphan indications and high medical needs. We support conduction of pre-clinical and translational trials to enable rational selection of optimal drug candidates for human testing. We are conducting activities in collaboration with basic science labs (involved in drug discovery and target identification, mechanism of action and resistance, and structure-function analyses). Our Division also provides training for new generations of physicians, designs programs that promote knowledge particularly among high-risk and underserved populations, and disseminates innovative patient therapies and scientific discoveries to our patients across Italy and throughout Europe. We pursue excellence relentlessly and with integrity in all that we do, adhering always to the highest standards of conduct and good clinical practice. We provide compassion and respect for those in our care and for one another. We foster the spirit of inquiry, promoting collaboration and innovation across traditional boundaries while celebrating individual creativity.
The Division will be embracing aspects of both academic and industrial research (phase I-II trials): focus on scientific excellence, team working, and hypothesis-driven goal-oriented research. It will bring together scientists with complementary expertise and professional backgrounds in the areas of cancer genomics and bioinformatics, cancer biology and genetics, cancer drug discovery and pharmacology as well as clinical trial expertise.
Choices of programs will be driven by unequivocal evidence of their role in disease control and treatment in clinically relevant settings.
The clinical Division consists of a team of highly trained physicians and staff with extensive experience in internal medicine, cancer treatment, translational medicine, Phase 0-I, early phase II clinical trials and clinical pharmacology research.

Our clinical research platform is based on:
1) The speed and efficiency of the design, launch, and conduct of trials
2) The innovation in science and trial design with strong translational background
3) Trial prioritization, selection, support, and completion
4) Dedicated clinical, pathology and laboratory platform integrated with a molecular screening program

Facilities of the Division include

Ambulatory Service for patients screening: 3 days per week (24 slots).
Outpatients Day Hospital Service for patient treatment: 3 days per week (33 slots).
In patients hospitalization: 36 beds for patients on phase I studies and for critical patients with adverse events following experimental treatment.

Research Nurses / Study Coordinators

The Research Staff consists of Research Nurses and Study Coordinators who are responsible for protocol management and patient care. Our research staff is responsive to both patient and study sponsor needs. Each study is assigned a research team member to ensure continuity of care for study patients as well as the needs of the study sponsor. The research staff is closely involved with patient screening, enrollment, education, and patient follow up. They maintain constant communication with study sponsors, physicians, clinical staff, and patients. Annually trained on ICH GCP, Clinical trial procedures, regulatory questions as well as on specific pathologies, our team provides in-depth therapeutic expertise at every level of your study process.

Early Drug Development Research Program

Early drug development research program is equally committed to scientific discovery and patient care. Our world-class young clinical investigators work across disciplines, departments, and institutional boundaries to translate research findings into new diagnostics and therapeutics for patients. The cornerstone of translational research of medical oncology staff is collaboration: close interactions among basic scientists, computational biologists, chemists, clinical investigators, and others. The group also enjoys fruitful partnerships with pharmaceutical and biotechnology companies, which have the complementary resources needed to help transform promising compounds into drugs and biologics.
A major departmental research theme is linking knowledge of the genes that cause cancer to the discovery and testing of new therapeutics, involving both small-molecule drugs and immune approaches. Other key themes relate to developing personalized medicine strategies by using genetic, epidemiologic, and population-based studies to determine risk and ideal treatment for individual patients.
The early drug development team currently has nearly 40 open adult therapeutic clinical trials. It accrues several patients to therapeutic and non-therapeutic clinical protocols each year. Disease center members play a major role in the IEO research programs and in international cooperative group trials, such as the International Breast Cancer Study Group (IBCSG) and the Breast International Group (BIG). Department investigators focus on testing new drugs in Phase I and II trials, particularly first-in-human studies that have the potential to move the boundaries of solid tumors oncology care. Technologies being offered include the isolation, enumeration, and genotyping of circulating tumor cells, determination of plasma cytokine levels, and genotypic analysis of plasma-based tumor DNA. All these technologies are applied in clinical trials

The milestones of our clinical research are here summarized:

1. Identification of biological features of disease predictive of response to a target-oriented approach within a molecular screening program
2. Identification of mechanisms of resistance to anti- HER2 positive breast cancer disease and development of new strategies to target HER2 positive breast cancer
3. Molecular screening with next generation sequencing technologies to evaluate potential “molecular drivers” of resistance to standard treatments in patients with luminal B and triple negative breast cancer
4. Exploring the combination of endocrine therapy with biological agents targeting HER2, src or insulin growth factor receptor (IGFR)
5. Exploring the role of dual targeting (multiple antibodies or antibodies conjugated to chemotherapeutics agents) in patients with HER2 positive breast cancer
6. Generation of human-xenograft models to predict response to targeted agents in patients with metastatic breast cancer
7. Selecting cancer vaccine targets for individual cancers. Analyzing the immunogenicity of T-cell and B-cell peptide epitopes and performing cytokine immune assessments to identify epitopes and cytokines that enhance immune responses
8. Exploring the role of antigen specific immunotherapeutics fro patients with triple negative breast cancer with residual disease after a neoadjuvant chemotherapy

Future research should achieve the goal to recognizing the diversity of targets in each subtype of breast cancer, taking advantage from molecular characterization tools. New prospective trials will specifically address the questions of targeting multiple pathways in each breast cancer subtype, to maximize response to treatment and minimize the toxicity. Recent large-scale tumor sequencing studies, including wide genome analysis studies, have identified a number of mutations that might be involved in breast cancer tumorigenesis. Analysis of the frequency of specific mutations across different tumors has been able to identify some, but not all of the mutated genes that contribute to tumor initiation and progression. One reason for this is that other functionally important genes are likely to be mutated more rarely and only in specific contexts. Thus, for example, mutation in one member of a collection of functionally related genes may result in the same net effect, and/or mutations in certain genes may be observed less frequently if they play functional roles in later stages of tumor development, such as metastasis. The biggest challenge for the future will be to apply a network reconstruction and coexpression module identification-based approach to identify functionally related gene modules targeted by somatic mutations in cancer.
The ultimate goal of this approach is to identify network of pathways and potential crosstalks within pathways. Dual or multiple targeting in order to shutdown “drivers” pathways will be the future of breast cancer treatment within several subtypes. This method was applied to available breast cancer sequence data, and identified several pathways as targets of rare driver mutations in breast. These mutations do not appear to alter genes that play a central role in these pathways, but rather contribute to a more refined shaping or “tuning” of the functioning of these pathways in such a way as to result in the inhibition of their tumor-suppressive signaling arms, and thereby conserve or enhance tumor-promoting processes.
We believe a gene network reconstruction, strategy-based approach can successfully identify cancer driver mutations through enrichment of mutations within modules. We should describe highlight a few important caveats in the field. Next generation sequencing technologies used to reconstruct genetic networks can be altered to generate networks of different sizes, or reflecting different coexpression relationships, depending upon the investigators requirements and/or sample size and likelihood that module enrichment will be observed in different-sized modules. Specifically genome remodelling during cancer progression or upone resistance to therapies can up-regulate pathways due to downregulation of current driver pathways. Additionally, this approach probably does not capture all of the secondary driver mutations, which may require either additional complementary systems biology approaches, or larger sample sizes to capture other mutation-enriched coexpression modules. Overall, we believe that this approach shows tremendous promise for the identification of rare tumorigenic driver mutations, which is a crucial task for upcoming large-scale cancer resequencing projects, as it is these more private mutations that may be driving intra-tumor heterogeneity, inter-patient heterogeneity, and ultimately altering response to therapeutic intervention. The future of many investigational therapeutics in cancer is therefore linked to our ability to identify the most druggable target in each disease segment.

Clinical Trials

- A phase 1b open-label three-arm multi-center study to assess the safety and tolerability of pf-05212384 (pi3k/mtor inhibitor) in combination with other anti-tumor agents.
- A phase Ib, open-label study of oral BGJ398 in combination with oral BYL719 in adult patients with select advanced solid tumors.
- A randomized pre-surgical pharmacodynamics study to assess the biological activity of LEE011 plus letrozole versus single agent letrozole in primary breast cancer (MONALEESA).
- Phase 1B study of docetaxel + PF-03084014 in metastatic or locally recurrent/advanced triple negative breast cancer.
- A Phase 2, Single-Arm, Open-Label, Multicenter Study of the Clinical Activity and Safety of Enzalutamide in Patients With Advanced, Androgen Receptor-Positive, Triple-Negative Breast Cancer.
- FINESSE An open, 3-cohort, phase II trial testing oral administration of lucitanib in patients with FGFR1-amplified or non-amplIfied oestrogeN rEceptor poSitive metaStatic breast cancEr.
- Pertuzumab + trastuzumab (PH) versus PH plus metronomic chemotherapy (PHM) in the elderly HER2+ metastatic breast cancer population who may continue on T-DM1 alone following disease progression while on PH / PHM: an open-label multicentre randomized phase II selection trial of the EORTC Elderly TaskForce and Breast Cancer Group.
- Phase 2, open-label, multicenter, randomized study of PD0332991 (oral CDK 4/6 inhibitor) monotherapy and PD 0332991 (oral CDK 4/6 inhibitor) monotherapy and PD 0332991 in combination with the endocrine therapy to which the patient has progressed in the previous line for ER-positive, HER2 negative postmenopausal advanced breast cancer patients (TREND).
- MEDI4736-1108 A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors.

Publications

Curigliano G, Pivot X, Cortés J, Elias A, Cesari R, Khosravan R, Collier M, Huang X, Cataruozolo PE, Kern KA, Goldhirsch A. Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer. Breast. 2013 Oct;22(5):650-6.

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Division of Cancer Prevention and Genetics

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Activities 2013. The Division of Cancer Prevention and Genetics is essentially dedicated to clinical research on the prevention of solid tumors and clinical management (risk assessment, surveillance and preventive treatment) of subjects at higher-than-average risk for various types of cancer. In order to develop new strategies of cancer prevention the Division's multidisciplinary staff (including oncologists, geneticist, biologists, research nurses, counselor, data managers) is committed to conduct clinical trials with the main aim to validate various drugs, micronutrients, natural compounds as preventive agents. Most of the research efforts are currently focused on chemoprevention trials on breast, ovarian, colorectal, oral and lung cancer. The target population is heterogeneous but includes mainly two groups of risk: 1) patients with (previously resected) precancerous conditions (such as breast ductal intraepithelial neoplasia, or colon adenoma or oral leukoplakia); 2) healthy individuals

who carry one or more risk factors (such as family history, germline mutations, high levels of androgens or estradiol or IGF-I, use of HRT, metabolic syndrome, insulin resistance, athypical hyperplasia, high mammographic density, peripheral lung "ground glass opacities" etc). These at-risk subjects are screened, followed and, when possible, enrolled in chemoprevention trials.
We have an established experience on various types of trials, including: a) phase II studies on surrogate endpoint biomarkers; b) larger phase III, multi-institutional trials on clinical endpoints (cancer incidence); c) pre-surgery WOP ("window-of-opportunity") studies in patients candidate to surgical treatment for primary breast cancer in order to test the efficacy of new and "old" drugs on breast cancer cell proliferation (measured by Ki-67 on baseline biopsy and then on the specimen after 3-4 weeks of drug treatment), and other tissue and circulating biomarkers. Since phase III trials typically last several years before providing results, we put much effort in the creation and conduction of phase II trials, studying how candidate biomarkers of risk (in different organs and in the blood) are modulated by preventative compounds.
We utilize a large spectrum of already validated or potentially useful preventive agents, including SERM's (Selective Estrogens Receptors Modulators), AIs (aromatase inhibitors), retinoids, NSAID's (Non-steroidal antiinflammatory drugs), corticosteroids, statins, metformin, with particular attention in seeking the minimal active doses.
In line with improving subjects characterization we are also studying the Cytochrome P450 enzymes, CYP2-D6 and CYP2-C19 polymorphisms in particular, in order to stratify patients in different classes of tamoxifen metabolizers, with the ultimate goal of a more effective and less toxic prevention treatment. Moreover we are studying the polymorphisms of VDR and IGFBP3 (vitamin D receptor and Insulin like Growth Factor Binding Protein 3).
Increasing research and clinical assistance have been recently dedicated in our Division to the selection, surveillance, risk-reduction strategies in subjects at very high risk, being carriers of constitutional germline mutations (BRCA1 and 2, MLH1, MLH2, MSH6, APC, MYH, TP53, CDKN2A, PTEN and CDH1) in strict collaboration with the genetic lab at the IFOM-IEO Campus. We have in fact an established High Risk Clinic (HRC) run by our staff and involving a multidisciplinary group of specialists (radiologists, pathologists, statisticians, endoscopists, surgeons, plastic surgeons and basic researchers). Our HRC provides to the public the possibility of cancer risk assessment, genetic counseling and testing, tailored surveillance and prevention programs, psychological and counseling support, nutritional and physical activity guidelines, access to chemoprevention trials or off-trial personalized treatment, up to prophylactic surgery in highly selected subjects.

During the year 2013 we performed 4460 visits in our prevention outpatients clinic. In our HRC service we performed 478 first genetic counseling sessions. Within the BRCA1 and 2 genes we found 72 BRCA1 mutations, 76 BRCA2, one subjects with a double BRCA1 and 2 mutation, 271 wild-type and 58 true negative. Among the other genes tested: two APC one mutation and one WT; 13 CDH1 of which three mutation; Lynch syndrome was tested in 10 subjects with six mutations two WT and two true negative, two with Li-Fraumeni syndrome out of 35 tested, and one CDK4 mutation out of four subjects.
We coordinate various national research networks collaborating in multicenter phase III studies. We have also a long established research collaboration with international institutions, including: the Division of Cancer Prevention, US National Cancer Institute; the M.D. Anderson's Cancer Center Consortium for Chemoprevention Trials; Cancer Research UK; the International Breast Cancer Study Group (IBCSG); the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) and "Gruppo di studio ENIGMA" on Unknown Variant mutations for BRCA1/2 genes; the Consortium for the study of the MMR alleles and their modifiers (CONSAMM), and Study group MOMA-CONSAM on Unknown Variant mutations of MMR genes; the Department of Endocrinology, University of Bergen; In-TEF: Italian National Network for "Tumori Eredo-Familiari" coordinated by "Istituto Superiore di Sanità".
In 2013, our Division published 21 articles in International peer reviewed journals with a total Impact Factor of over 220.

Research activities

Our current research lines are focusing mostly on chemoprevention, pharmacogenomics and the effects of lifestyle changes in various cohorts of subjects at higher risk of developing cancer in order to validate the most effective strategies to reach a tailored prevention.

Scientific aims:
Validation of low dose tamoxifen as chemoprevention strategy in phase III clinical trial. We recently concluded the HOT Study: Hormone Replacement Therapy and low dose Tamoxifen. A phase III trial of primary breast cancer prevention with low dose tamoxifen in HRT users. An ongoing randomized, placebo controlled, phase III trial in women with surgically treated ER positive intraepithelial neoplasia of the breast.
Furthermore to improve dose tamoxifen tailoring we are conducting pharmacogenomics studies on single nucleotide polyporphisms (SNPs), particularly on CYP2D6 and CYP2C19.

The role of aromatase inhibitors in prevention, with an international multicenter study, the IBIS II. The primary prevention study, anastrozole vs placebo in postmenopausal women at increased risk of breast cancer, was recently published (see below). A second study was design for postmenopausal women with ER+ Ductal Carcinoma in Situ (DCIS), the randomization was tamoxifen vs anastrozole for 5 years, this trial is still ongoing.
We also studied exemestane in a phase II pre-surgical trial and the final results will be published soon.
Other agents we are studying through window of opportunity (pre-surgical) trials are metformin, raloxifene, very low dose tamoxifen and celecoxib, The primary endpoint is the KI67 modulation; several other secondary endpoints are enclosed.
Green tea and silybin are under WOP study with a pilot study to evaluate the breast tissue concentration of the agents.
We are studying the role of fenretinide (4-HPR) for primary and tertiary prevention of breast cancer in subjects with BRCA 1 or 2 mutations.
Another field we are covering is chemoprevention in subjects at higher risk for ER negative breast cancer, such as patients with endocrine non-responsive DIN, and BRCA mutation carriers. In particular, we are studying two classes of drugs: NSAIDs and Statins; the NSAIDs are tested in a phase II biomarkers trial.
Diet and physical activity to prevent recurrence after standard treatment in women with invasive breast canceris a further matter of investigation conducting the DIANA (DIet and ANdrogens)-5: randomized controlled trial to test the efficacy of dietary change and physical activity to prevent or delay the recurrences in breast cancer patients estimated to be at higher risk based on their metabolic milieu.
The role of vitamin D is yet another significant investigational part and we are doing that in a randomized placebo-controlled phase III clinical trial in melanoma patients, while we are planning also a phase II on colorectal cancer.
The role of an accurate process to select high risk subjects for genetic counseling and their psychological and emotional response is a further clinical study.

Other studies include:
Identification of biomarkers to risk estimate and surrogate biomarkers to drugs efficacy. In particular genotype, SNPs of different genes that may correlate with breast and other cancer risk: among them we are studying VDR, IGFBP3, MTHFR in a large spectrum of population. NAF (nipple aspirate fluid) as a risk assessment tool and source of new biomarkers studies.

Evolution of undetermined ld-CT detected lung nodules. Within a screening program we have conducted a first randomized phase II trial with budesonide, and now we are starting a new project with low-dose aspirin versus placebo in subjects at high risk for lung cancer.

Finally for the hereditary diffuse gastric cancer (HDGC) syndrome we have an ongoing collaborative project to better study and characterize the probands who result wild type for CDH1 mutation and to improve the screening and the surveillance of these subjects.

Major achievements

Given positive results of our previous research on low-dose tamoxifen and breast cancer biomarkers modulation, we analyzed a large cohort of DIN patients treated with low-dose tamoxifen or no treatment as per institutional guidelines.
Consecutive women operated in our Institute for estrogen receptor (ER)-positive DIN (474 treated with low-dose tamoxifen and 509 untreated patients) were followed up for a median of 7 years.
The results showed a significant 30% reduction in breast cancer risk in low-dose tamoxifen treated patients, with an adjusted hazard ratio (HR) = 0.70 [95% confidence interval (CI) 0.51–0.94], with a greater benefit in postmenopausal (HR = 0.57; 95% CI 0.34–0.94) than in premenopausal women (HR = 0.79; 95% CI 0.54–1.17). Treated patients with ER and progesterone receptor (PgR) <50% DIN had apparently no protective effect. Drug discontinuation resulted in a doubled risk of recurrence in premenopausal women only (HR = 1.95; 95% CI 0.98–3.89). No excess of endometrial cancer occurred.
We concluded that low-dose tamoxifen is a promising and safe strategy for highly endocrine responsive DIN. Treatment adherence is crucial in premenopausal women. A randomized phase III trial is ongoing.

A collaborative updated meta-analysis has been done on selective estrogen receptor modulators (SERMs) in breast cancer prevention trials. The primary aim was incidence of all breast cancer (including ductal carcinoma in situ) during a 10 year follow-up period. We analysed 83 399 women with a median follow-up of 65 months. We observed a 38% reduction in breast cancer incidence. The reduction was larger in the first 5 years of follow-up than in years 5–10 (42%, HR 0·58, 0·51–0·66; p<0·0001 vs 25%, 0·75, 0·61–0·93; p=0·007). Thromboembolic events were significantly increased with all SERMs (odds ratio 1·73, 95% CI 1·47–2·05; p<0·0001). We recorded a significant reduction of 34% in vertebral fractures (0·66, 0·59–0·73), but only a small effect for non-vertebral fractures (0·93, 0·87–0·99).
For all SERMs, incidence of invasive estrogen (ER)-positive breast cancer was reduced both during treatment and for at least 5 years after completion. Similar to other preventive interventions, careful consideration of risks and benefits is needed to identify women who are most likely to benefit from these drugs. Based on this publication a new guideline NICE were released in Great Britain to support the use of SERMs in prevention settings within the British National Health System.

In order to improve the acceptance and tolerability of chemopreventive treatment we have publish a phase III low dose tamoxifen versus placebo in HRT postmenopausal women. 1884 were randomly assigned to either tamoxifen, 5 mg/day, or placebo for 5 years. After 6.2 years mean follow-up, there were 24 breast cancers on placebo and 19 on tamoxifen (risk ratio,RR, 0.80; 95% CI 0.44–1.46). Tamoxifen showed favorable trends in luminal-A tumors (RR, 0.32; 95% CI 0.12–0.86), in HRT users <5 years (RR, 0.35; 95% CI 0.15–0.82) and in women completing at least 12 months of treatment (RR, 0.49; 95% CI 0.23–1.02). Serious adverse events did not differ between placebo and tamoxifen.
Our trial suggests that the addition of low-dose tamoxifen to HRT may reduce the risk of breast cancer. But this study has important limitations, including the limited statistical power and the marked heterogeneity of HRT types having different risks of breast cancer. For these reasons, reliable conclusions cannot be drawn.

To further elucidate the activity of metformin as chemopreventive agent, we analyzed the apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) after metformin treatment in a presurgical study.
In accordance with our previous data metformin activity is modified by insulin resistance (HOMA index).
In the 59 women without insulin resistance (HOMA index< 2.8), there was a higher level of TUNEL at surgery on metformin vs placebo (median difference on metformin +4%, IQR: 2–14 vs +2%, IQR: 0–7 on placebo), whereas an opposite trend was found in the 28 women with insulin resistance (median difference on metformin +2% (IQR: 0–6) vs +5% (IQR: 0–15) on placebo, P-interaction = 0.1).
Overall, there was no significant modulation of apoptosis by metformin, but similarly to Ki67 mefromin can exert a differential effect due to the subjects' insulin resistance status.

Our Division coordinates the Italian centers within the IBIS II international, double-blind, randomised trial. The prevention trial randomized high risk women (based on familial history or personal history). 1920 women to receive anastrozole and 1944 to placebo. After a median follow-up of 5·0 years, 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard ratio 0·47, 95% CI 0·32–0·68, p<0·0001). The predicted cumulative incidence of all breast cancers after 7 years was 5·6% in the placebo group and 2·8% in the anastrozole group.
Anastrozole effectively reduces incidence of breast cancer in high-risk postmenopausal women. This results support the use of this aromatase inhibitor in postmenopausal women to lower breast cancer risk and should be included, alongside the SERMs, within the NICE guideline.

Publications

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Division of Palliative Care

Bruno ANDREONI, MD
Director

STAFF Pain Treatment Unit Director: Vittorio Guardamagna
Fellow: Samuela Bozzoni
Nurses: Loredana Lunghi, Angela Cocquio, Roberta Boschetti, Romina Calò
Secretary: Nordiana Baruzzi

Activities 2013. The recently created Division of Palliative Care is directed by a University Professor as requested by the agreement between the European Institute of Oncology and the University of Milan. Its activities complete the care IEO gives cancer patients from prevention and diagnosis to advanced, incurable, end-of-life stages when "Care" can and must go on so that the patient and his/her family do not feel "abandoned".

Our Activities

Care:

- Out-patient Clinic for Palliative Care and Out-patient Clinic for Pain Treatment open to all IEO patients as well as to patients leaving in the area.
- Palliative and pain care visits for patients hospitalized in all IEO Divisions and Units.
- (Invasive) anesthesiology procedures for pain treatment organized as out-patient surgical procedures during the previous visit (this activity is carried out in collaboration with some IEO anesthetists).
- Continuing care service for early supported discharge in patients with psychic, physical or social needs.
- Home palliative care (STCP-Home care) by physicians and nurses expert in palliative care.
- Call Center to monitor discharged patients with psychic, physical or social needs.
- 24/7 service for home patients.
- Combined activities with Hospice Cascina Brandezzata, part of the Milano Palliative Care Network, in particular for its southern area.
- Collaboration with the "Centro Universitario Interdipartimentale per le Cure palliative di Cascina Brandezzata".

Education: 1st e 2nd level Masters in palliative cure

CME-accredited post-graduate and refresher courses in palliative care for physicians, nurses, psychologists, physical therapists, social workers, nursing assistants, home caretakers, volunteers. Courses, seminars and training for medical and nursing students.

Research

Research projects in palliative medicine promoted in collaboration with "Centro Universitario Interdipartimentale per le Cure palliative", headquartered at Cascina Brandezzata (a building opposite the European Institute of Oncology).

Events

- Thursday 13 March 2014, in the IEO Conference Room: opening ceremony for Masters and Postgraduate Courses in Palliative Care as wll as opening ceremony of the new Headquarters of "Centro Universitario Interdipartimentale per la Medicina palliativa".
- Monday 5 May 2014, in the IEO Conference Room: Meeting "Narrative Medicine for a better care of advanced-cancer patients".

The Pain Treatment Unit

The Pain Treatment Unit is part of the Division. Its head is Vittorio Guardamagna (an Anesthetist expert in palliative care e pain treatment) who, in collaboration with some anesthetist of the Anesthesiology Division, is going to develop an outpatient pain treatment program at IEO using also invasive procedures.

Clinical Experimentations

Previous clinical in palliative medicine were carried out or promoted by the "Centro Universitario Interdipartimentale per le Cure palliative" (see the Center page at www.fondazioneluvi.org). The following multi center studies are currently ongoing:

- GWCA1103 Study (international multicenter phase-III study evaluating the efficacy of oral-spray Sativex in the treatment of chronic pain in advanced cancer refractory to opiates according to WHO guidelines)
- IOPS-MS multicenter Study (Italian Multi Setting Oncologic Pain Survey on Break Through Cancer Pain)

Publications

Final report on the research project "Rete Cure palliative area sud di Milano" organized by the local health authorities (Direzione Generale Salute Regione Lombardia) and financed by teh Italian Ministry of Health: - June 2009.

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F. Zucco, V. Guardamagna "A Totally Computerized Home-Care Medical Record In Palliative Care: our experience". Atti 6th Research Congress of the European Association for Palliative Care, Glasgow, UK 10 - 12 June 2010

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Applied Research Unit for Cognitive and Psychological Science

Gabriella PRAVETTONI

Director

STAFF Researchers: Ilaria Cutica (Cognitive Psychologist), Florance Didier (Clinical Psychologist), Alessandra Gorini (Cognitive Psychologist), Claudio Lucchiari (Cognitive Psychologist), Marianna Masiero, Ketti Mazzocco (Psychologist-Psychotherapist), Silvia Riva (Psychologist), Serena Oliveri (Psychologist), Chiara Renzi (Psychologist)
Fellows: Beatrice Colombo (Psychologist-Psychotherapist -Division of Dermato-Oncology), Victoria Intra (Psychologist), Ivana Palminteri (Psychologist), Stefania Spina (Psychologist-Cosmos Project), Valeria Vadilonga (Psychologist Psychotherapist)
Visitor: Andrea Gragnano
Scientific Secretary: Deborah Console
Secretary: Alessia Maria Cattaneo

Activities 2013. The new IEO Psychology Unit is the fruit of many years of academic experience dedicated to the decision-making processes by a multidisciplinary team under the coordination of Professor Gabriella Pravettoni.
In particular, over time the research has focused on the study of decision making process in medicine in order to study the factors involved both from doctors' and patients' point of view, in conditions of uncertainty and risk, often characterized by an increased emotional burden. With this background, the Unit promotes a multidisciplinary perspective, aimed at developing a new psycho-cognitive approach for decision-making in medicine. In addition to strictly medical matters and biological data, by developing a personalized approach that takes into account the analysis and interpretation of the cognitive components (information needs, preferences, decision-making, beliefs and knowledge about the disease and health), the psychological components (level of stress, anxiety, depression) and the behavioural (lifestyle) components of each

patient, we aim to promote patient empowerment and increase participation in the process of care, compliance and overall satisfaction. Systematic screening programs on psychological distress, adaptation and evaluation of psychosocial needs have been implemented, following the Joint Commission standards and the NCCN guidelines.
When patients are admitted to the hospital (whether as an in or out-patient), they are asked to fill in a self-evaluation form focused on their emotional state. In non-functional emotional reactions, an interview with a psychologist is recommended. This is a time for in-depth awareness enabling them to shed light on their own reactions and needs. During the interview, the opportunity is explored to embark upon a process of psychological support. Support to the couple and to the family is also offered.

Counseling / The psychological support

Counseling with the psycho-oncologist is aimed at people who experience a feeling of emotional distress. The interview helps the patient to come to terms with and understand the normal reactions to stress. During the interview, the patient is assisted in the management of emotional distress and in the process of recovery in order to cope with the disease in an active and positive way.

Individual Psychotherapy

In the presence of specific psychological discomfort or symptoms which damage the patient's well-being in addition to the physical illness, and which hinder functioning in important areas of life (work, daily activities, relationships between couples and family members), individual psychotherapy helps the patient to learn and understand their condition and to identify ways of thinking and behavior in order to deal effectively with critical situations. A cognitive process that in addition to promoting greater self-awareness, allows the patient to strengthen self-esteem, rediscover and strengthen their own resources, redefine priorities and facilitate change.

Psychological support to family members

The Psycho-Oncology Unit helps family members to deal with the illness of their family member and with the consequences that may ensue in family relationships. This help aims to facilitate adaptation to the disease, in order to improve the quality of life of the members of the whole family.

Couple counseling

Cancer affects not only the patient, but sometimes also adversely affects the relationship with the partner. The purpose of couple counseling is to understand the thoughts and feelings of both partners in order to activate resources that allow the couple to manage the emotional and practical difficulties that arise.

Sexological counseling

The destabilizing impact of a cancer diagnosis, the stress and bodily changes caused by surgical and oncological treatment sometimes radically change the relationship, emotional communication and sexuality. Sexological counseling is a helping relationship aimed at the individual or the couple, and it aims to offer support to understand physical, psychological and relational difficulties, and to find out a solution to reduce discomfort.

Psychological counseling in the genetic field

Information on the personal risk of developing a tumor often involves a number of changes at a cognitive, emotional and behavioral level. Although the oncological risk does not mean that one currently has a tumor, it is often experienced as an anticipation of the disease. The perception that a woman may have of the invulnerability of her physical state, in fact, collapses, giving way to emotional reactions of insecurity, anxiety and fear that harm physical and mental well-being and change everyday behavior. The cognitive representation corresponding to the thought: "cancer is not there, but it will be" could become pervasive and affect the lifestyle of the woman, her family and social relationships and physical and psychological well-being.

Relaxation therapy and stress management (Biofeedback, relaxation imagery, conscious breathing)

Cancer treatments often interfere with the quality of life of patients, not only on the physical plane, but also on the psychological plane. The proposed techniques (individual or group) can help patients to increase their effectiveness in managing emotions and stress, promoting a better adaptation to their treatment pathway and the recovery of their physical and mental wellbeing.

Research Activities

P-medicine

Within the framework of the European project "P-medicine", our research team is working together with the medical oncologists to develop a set of tools designed to improve the doctor-patient interaction via a personalized approach to treatment. Such an approach aims to identify the profile of the individual patient so that the doctor can use a personalized interaction mechanism that will increase the empowerment of patients, enabling them to feel more involved in the process of care and in treatment decisions.

Effects of adjuvant endocrine therapy on cognitive performance in patients with breast cancer: a longitudinal study

Cancer patients often report memory and concentration difficulties. Several studies have indeed shown the presence of cognitive deficits in these patients, particularly in tasks of working memory, verbal and long-term. It is not entirely known what causes these deficits, but the most likely cause seems to be the chemotherapy treatment, and the endocrine dysfunction and alterations in the metabolism of stress hormones resulting both from the treatment and from the high emotional distress characterizing these patients. Cognitive deficits in patients with breast cancer have been found, unexpectedly, even before the administration of chemotherapy or hormonal treatments, thereby lending support to the hypothesis that psychological distress generated by the diagnosis contributes towards inducing a cognitive malfunction (Berndt et al., 2009). Based on these findings, the present study aims to analyze the possible presence of cognitive deficits, with an emphasis on executive function in a sample of women receiving adjuvant endocrine therapy.

Advantages of using tobacco-free devices in heavy smokers participating in a screening program for lung cancer: a randomized study

The aim of the experimental protocol is to analyze the role that electronic cigarettes can play in helping smokers to increase their well-being, reducing the harmful effects of traditional cigarette. Smoking cigarettes with tobacco, in fact, not only increases the risk of developing lung cancer, but also has negative effects on the health of the lungs, increasing the presence of cough, phlegm and other respiratory problems. Furthermore, the smoke is correlated with a wide range of cardiovascular and respiratory diseases and other cancers. Consequently, helping heavy smokers reduce the number of smoked cigarettes is an important goal that allows both the reduction of risk of serious diseases, and the enhancement of a general improvement in the quality of life.

Impact of the intervention system and adherence to long-term care of the patient

Even in a major disease such as cancer, in which suspending treatment puts lives at risk, some individuals decide to cease treatment or screening checks. A study on the evaluation of adherence to hormonal treatment with aromatase inhibitors has shown for example that, one year after the beginning of treatment, 23% of patients are no longer adhering to treatment. In order to improve the understanding and management of patient adherence a research protocol has been developed, whereby we can highlight what features of personality, cognitive, decision-making and beliefs induce patients with breast cancer not to adhere to the prescriptions, whether pharmacological or follow-up. A better understanding of the phenomenon will allow strategies of patient empowerment to be developed, which in the final analysis will translate into an increase in positive outcomes.

Breast reconstruction. Preferences and needs of patients and satisfaction of long-term choices

Mastectomy has consequences not only on the physical domain, but also on the psychological, social and relational domain, with a negative impact on the quality of life of women, both personally and socially. Breast reconstruction may offer the possibility to recover a good quality of life. But while there are few women who choose not to do the reconstruction, those who opt for reconstruction are faced with the decision-making dilemma "what kind of reconstruction". The choice now is between two possible types: a permanent prosthesis, or implants with the woman's own muscle tissue and/or skin. In this decision-making context, she must examine the benefits and potential risks in the short and long term, including changes in lifestyle (smokers, for example, have a higher risk of complications). The right choice depends not only on the clinical need but also on the needs and expectations of the patient. Within this research protocol, we investigate the factors that influence the perception of the variables involved and the decision-making style of each patient, in order to effectively support in understanding the information provided, the process of managing emotions, the perceived risk and the choice.

Publications

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Division of Anaesthesiology and Intensive Care

Marco VENTURINO, MD
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Activities 2013. In 2013 surgical activity at IEO has performed 14730 operations of whom 4236 (29%) in day surgery regimen. According to different kind of surgery and patients, techniques of either general or locoregional anaesthesia are used, with a large use of Monitored Anesthesia Care (MAC, a form of deep sedation) in day surgery operations. A computerized monitoring system is used in order to collect data from all devices connected to patients and to record the anaesthetic procedures.
An outpatient's department is activated for the preoperative assessment of patients that need surgical operations: in 2013 a large amount of patients submitted to surgical interventions (9278) has been checked in this department, with a new modern approach to chemical and instrumental examination requests.

In 2013 the robotic surgery program has been improved: we have performed 815 interventions with this technique with a very low incidence of complications, developing one of the largest experience in Europe in robotic surgery (more then 4300 from 2006).
Anaesthesiologists also support invasive radiological and endoscopic procedures often in very critical patients.
According to IEO project called "Pain-free Hospital", and to the italian law (38/2010) introducing a new perspective on pain management, specific attention is paid to treatment of postoperative pain and prevention of its chronicization.
The anesthesiologists are also involved in the safety management of operating room. They collect data about adverse events occurred in order to develop even more secure protocols, following the advanced rules of the "Helsinki Declaration on Patient Safety in Anaesthesiology" (2010) sponsored by ESA (European Society of Anesthesiology).
Our division is also active member of the ETN (European Trial Network), the research branch of ESA and is involved in the most important large european trials. One of these was published by The Lancet in 2012).
Moreover since 2011 our division has started a research collaboration with LABS (Laboratory of Biological Structure Mechanics Department of chemistry, materials and chemical engineering – CMIC - of Politecnico di Milano 2nd,– Milano Bicocca University) on development of a novel device for liquid ventilation.

The activity of the Intensive Care Unit is mainly devoted to post-surgical patients. In 2013 the ICU accepted 624 patients, 83% postoperative admissions. The mean ICU length of stay was 2.3 days and the mortality was very low (2.5%). The reported incidence of VAP (Ventilatory Acquired Pneumonia) was 0.5% while the CVC related bacteremia was 0.5.
The ICU is equipped with eight beds provided with complete invasive and non-invasive monitoring and with ventilators able to support different modalities of invasive and non invasive ventilation.
An isolated room is also available for patients affected by immunodeficiency.
Specific beds are also available to avoid decubitus problems.
In addition to usual invasive and non-invasive hemodynamic monitoring systems, new devices are available for monitoring hepatic and hemodynamic functions like PiCCO system and LiMON.
Continuous hemodiafiltration is used as part of treatment of patients with acute renal failure, and particularly in patients affected by sepsis. Clinical information about ICU patients is collected by a customized database. Our ICU is connected with the major Italian ICUs via the GiViTi network.
Special attention and studies are dedicated to new developments about the quality of life of ICU patients and their relatives, so our ICU is a pioneer in applying the "OPEN ICU" theory from many years. Particular care is taken on the functional recovery of critical patients treated by dedicated physiokinesitherapists".
The anesthesiological staff is trained to perform Transesophageal Echocardiography both in operating theatre and ICU as well. The staff is also trained to perform awake intubation with fiberoscopy and to safely manage difficult intubation.
In these years we have developed a special educational program for medical staff for vessels cannulation using echographic support. The medical staff also performs central venous catheterization for chemotherapy, plasmapheresis and total parenteral nutrition and also supports special procedure like HIFU, HILP, HIPEC and Liver Perfusion, developing innovative anesthesiological protocols.

Researches

In 2013 as member of ETN, our division became part of the european study "LAS VEGAS" (Local Assessment of Ventilatory Management During General Anesthesia for Surgery and effects on Postoperative Pulmonary Complications: a Prospective Observational International Multi-center Cohort Study). It is endorsed by the European Society of Anaesthesia (ESA), shared with 147 centres of 29 countries, stated as "the biggest observational study on current MV practice, with a very large ICU follow-up cohort!"

Publications

Pearse RM, Moreno RP et al. Mortality after surgery in Europe: a 7 day cohort study; The Lancet 2012;380;9847; 1059-65

Day Surgery Division

Giovanni Francesco MANFREDI, MD
Director

STAFF Head Nurse: Liliana Tadini
Ward Manager: Marianna Agnello
Registered Nurses: Monia Agostini, Marika Comensoli, Diana De Donno, Monica De Piano, Rachida Hazmi, Jelena Pavic, Anna Rita Tarantino.
Advanced Health Care Assistants: Marisa De Palmas, Antonella Paganoni, Monica Piscopo

Ambulatory Surgery
Ward Manager: Luca Benatti
Registered Nurses: Daniela Funetti, Alessandra Marras, Federica Macciola, Elena Occhetti, Aldina Pavan, Monica Scotti, Antonia Tarantino
Health Care Assistants: Lucrezia Piccolomo, Wubneh Meharit Berhe

Activities 2013. Established on May 2010, The Division of Day Surgery deals with all surgical, laparoscopic or endoscopic operations/procedures, both operative and diagnostic, performed either by local or locoregional, or under general anesthesia or sedation, where the patient is discharged on the same working day, without a night of hospitalisation.
Most people would rather recover from surgery in the comfort of own home, with relatives or friends, than in hospital.
Day surgery provides fast come back to family environment, relationships and professional activity. Thank to the short hospital stay we achieve clinical advantages too; in fact, there are low rates of complications, such as infections and thromboembolism.

Since the opening of the Centre, the rate of the activity has steadily grown and during year 2013 over than 4500 patients were admitted for surgical treatments or diagnostic procedures. Patients come from all of the surgical and diagnostic divisions of IEO. Only 3.5% of the patients need for unplanned admission.

We pay attention especially to guarantee both patient safety, comfort and satisfaction. Our main goals include the control of postoperative pain and quality improvement as well.

Very good performances results from customer's satisfaction charts among quality of care.

During 2014, we will try to transfer more patients into day-case setting.
Moreover, other 4500 operations/procedures were performed in the ambulatory setting.
Collaborative activity includes the membership in The Day Surgery Study Group of Italian Society of Anesthesia, Analgesia and Intensive Care (SIAARTI).

Robotic Surgery Research Program

Robot-assisted surgery is the latest evolution of minimally invasive surgery; it has been evolving from simple adjustable arms to support cameras in laparoscopic surgery through to the more sophisticated four-armed machines now available. The da Vinci™ operating robot is a telemanipulation system consisting of a surgical arm cart, a master console and a conventional monitor cart. It acts as remote extensions completely governed by the surgeon and thus are best described as master-slave manipulators. At IEO two of da Vinci™ operating robots (Surgical Intuitive, Inc., Mountain View, CA) are active, the first one since October 2006. To maximize utilization and reduce maintenance costs, they are jointly used by the departments of Urology, Gynecology, Abdominal-Pelvic, Thoracic, and Head and Neck Surgery.
The main technological advantages of this system are realistic 3-D imaging, motion-scaling and tremor filtration, facilitating more precise and accurate endoscopic surgery. It makes difficult and previously inaccessible body areas easier for surgeons to access and may lead to decreased morbidity for patients. Various surgical procedures have proved feasible and safe when performed with the da Vinci™ robot. The advantage of the system is best seen in tiny areas difficult of access and when dissecting delicate, vulnerable anatomical structures, like mesorectum, prostate, uterus, pulmonary lobes or larynx. In the light of our present experience, we regard prostatectomy, hysterectomy, pulmonary resection, oropharyngeal and supraglottic laryngectomy, adrenalectomy and total mesorectal excision deep in the pelvis as appropriate for a robotic approach, whereas, other operations such as thyroidectomy, pneumonectomy, splenectomy, pancreasectomy and liver resection need further evaluation. The steric vision and the intuitive use of the instruments are of great assistance, although the lack of most laparoscopic devices sometimes hamper full robotic performance.
The robotic approach is significantly more expensive than conventional minimally invasive surgery. This extra cost is due to longer operating times, as well as the high cost of the robot itself and higher costs for the robotic instruments, which are re-usable ten/twenty times only. The time delay has been explained by the learning curve. However, with increasing experience on the part of the entire team (surgeons, scrub nurses, and theatre attendants), the setup time has been markedly reduced in our Institution, and no longer involves any time loss. Cost-effectiveness is a major issue; 2 recent studies comparing robotic procedures with conventional operations showed that although the absolute cost for robotic operations was higher, the major part of the increased cost was attributed to the initial cost of purchasing the robot and yearly maintenance. Both factors are expected to decrease as robotic systems gain more widespread acceptance. Decreasing operative time and hospital stay will also contribute to the cost-effectiveness of robotic surgery. Other drawbacks to robotic surgery include the bulkiness of the robotic equipment currently in use. Lack of tactile and force feedback to the surgeon is another major problem, for which haptics (ie, systems that recreate the "feel" of tissues through force feedback) offers a promising, although as yet unrealized, solution. The patients' satisfaction following a robotic approach is high. Ready acceptance of the robotic approach may result from the satisfactory cosmetic and symptomatic results, but also from the patients' impression that they had taken part in the dawn of a new surgical era.
In the single Divisions' Chapters, a complete list of all ongoing studies is presented. Most IEO Divisions are currently runnnig clinical research projects supported by the Italian Ministry of Health, but all surgical Divisions are actively working in research applications of this new surgical tool.
IEO has actively participated as leader Italian Institution to the International multicenter randomized ROLARR trial, comparing robot-assisted vs conventional laparoscopic rectal resection for cancer. Patients' enrollment has been recently completed (> 400 pts.), and preliminary results are now expected.

Perspectives

Robotic surgery was originally developed to render possible a kind of telesurgery bridging thousands of kilometers or even continents. Although the feasibility of this aspect was proven and gained some media attention, it is not the future of robotic surgery. More probable opportunities for robots are image fusion and surgical training.

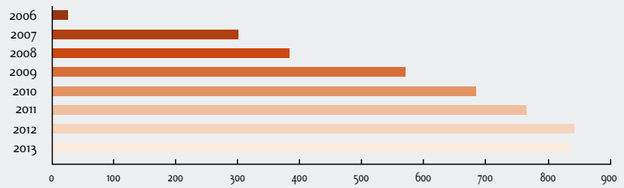

Figure 1
Robotic Surgery

At this stage the superposition of different radiologic imaging systems permits more precise and detailed surgical planning. The da Vinci™ system is able to implement this technique in the operating room itself by flashing a patient's scan images into the virtual three-dimensional view on the console. This will enable the surgeon to more easily detect and identify hidden anatomical structures, and in this way robotic surgery will help to make minimally invasive surgery safer. Another great potential for the da Vinci™ robot probably lies in its impact on surgical training. It is possible to carry out a particular patient's complete surgical procedure using his CT scans and robotic virtual-reality training programs. Thus, similar to a pilot on a flight simulator, surgeons in training will perform new operations only after performing them successfully in virtual reality.

Conclusions

With the da Vinci surgical robot surgery regains two fundamental tools of surgical procedures: intuitive control over the surgical instruments and steric perception of the operative field. Only several centers are currently using surgical robots and publishing data. There is an agreement in the effectiveness of robotic surgery in the treatment of malignant tumours of the pelvis (prostate, uterus, mainly in obese patients, and rectum), and the indication of this procedure together with the laparoscopic surgery is reported in several guidelines (NCNN, and guidelines of the Gynecological and urological societies).
In gastrointestinal, head and neck and thoracic oncology, robotic surgery is applied to a wide range of procedures, but is still in its infancy. Most studies reported that robotic surgery in these fields is feasible and safe, provides improved dexterity, better visualization, reduced fatigue and high levels of precision when compared to conventional laparoscopic, thoracoscopic and mini-invasive oropharyngeal surgery.
In a relatively short time, robotic procedures spanning the whole spectrum of surgery have been successfully executed. Initial results show that mortality, morbidity, and hospital stay compare favorably to conventional laparoscopic operations. Figure 1 shows the increasing use of robotic – assisted surgery at IEO. However, only a limited number of randomized, prospective studies that compare outcomes of robotic techniques with conventional methods exist. While current robotic systems have considerable advantages over conventional laparoscopic techniques, they are not without limitations. Robotics main drawbacks in surgical practice are the absence of force feedback and extremely high costs. Miniaturization of robotic components and systems is feasible and necessary to allow minimally invasive techniques to reach full potential. The ultimate extrapolation of this progress is the development of intracorporeal robotics, the feasibility of which has been demonstrated. At this moment there are no reports to clearly demonstrate the superiority of robotics over conventional laparoscopic, thoracoscopic and mini-invasive surgery. Further research and more prospective randomized trials are needed to better define the optimal application of this new technology in gastrointestinal oncologic surgery.
The challenge for today's robotic surgeons is to advance the system through clinical research in such a way that it becomes suitable and indispensable for future routine applications.

Division of Cardiology

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Cardioncology Unit Staff

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Activities 2013. Cardiology Division's activities involve pre- and post-operative and pre- and post-chemotherapy complete cardiovascular assessment, respiratory function evaluations, general internal medicine consultations, antismoking activities, extensive clinical monitoring and therapy for internal (also by means of telemetry multiparametric data controls) and external wards diagnostic and treatment of all the emergencies.
Starting from April 2013 Cardiology Division strongly supported the activities of a new activity, the EIO Check Up for Oncologic and Cardiovascular Prevention, that performed over 200 complete multidisciplinary evaluations.
The specific cardiological activity is strongly oriented to the diagnosis and therapy of cardiac disorders in order to detect and treat comorbidities (52% of EIO cancer patients present concomitant cardiovascular diseases!) as well as potential or evident consequences of oncologic treatments

(as cardiotoxicity related heart function reduction, mainly due to old and newer chemotherapeutic agents, as targeted therapies).
Cardiological evaluations, either clinical or instrumental, are present in over 160 scientific research protocols presently active in the Institute.
In 2013 the Unit performed:

a. cardiological assessment of 25150 internal and outpatients;
b. complete echocardiographic and doppler colour evaluations in 4150 patients;
c. respiratory physiopathology diagnostic and assistance (2232);
d. 75 antismoking protocols on the efficacy of electronic cigarettes without nicotine (official international trial reported on USA Government Research Agency);
e. clinical consultations and/or echocardiographic examinations for over 1765 patients enrolled in different Division's scientific chemo- or radio- therapeutics official protocols;
f. overall 62343 written clinical official cardiovascular / respiratory clinical reports.

During 2013 over 1200 patients were treated in urgency/emergency setting, 78% internal cases, 22% outpatients; the increasing number of treated cases will be one of the elements that will lead the Institute to the opportunity of opening in 2015 a new and original structure: a 24/24 hours ambulatory ward for continued oncologic assistance.

Cardioncology Unit

Cardioncology is a novel, interdisciplinary, rapidly evolving area of growing interest, based on a comprehensive approach for the management of cardiovascular problems of cancer patients, pre-existent or induced by anticancer therapy. The Cardioncology Unit of the EIO is the first created in Italy to deal with this need. The main clinical and research areas of the Unit are early diagnosis of cardiotoxicity, cardiac risk stratification, prevention, treatment and monitoring of cardiotoxicity during anticancer therapy, including both traditional and new biologic agents. As the current standard diagnostic methods allow to detect cardiotoxicity only when a function impairment has already occurred, precluding any chance of prevent its development, the Cardioncology Unit of the EIO has created specific internal procedures, based on our almost twenty-year-long clinical and research experience. They include the assessment of cardiac biomarkers (Troponin I and NT-proBNP), and an early preventive therapy with ACE-inhibitors, in selected high-risk patients, namely those showing myocardial injury during the oncologic treatment, revealed by the increase of Troponin I. This approach has proved to be able to prevent the development of cardiotoxicity in more than 3000 cancer patients, followed in EIO for more than 8 years.

Due to the increasing number of long-term cancer survivors, the ageing of the population, as well as the increased incidence and prevalence of oncologic and cardiovascular diseases, the number of patients presenting oncologic and cardiologic comorbidities are increasing. These patients are often excluded from intensive cardiologic treatment and/or interventions, and, on the other hand, often excluded from a first-line, aggressive – and therefore more effective – therapeutic oncologic strategy, because considered to be at too high a risk for cardiovascular complications. This behavior may lead to negative prognostic impact during the course of the two illnesses, whereas a integrated and multidisciplinary approach, involving both the cardiologist and the oncologist, may allow the patient to be effectively and safely treated. To achieve this aim, the EIO Cardioncology Unit has created a specific procedure for these "frail" patients, to allow them to receive an effective oncologic therapy as well. This internal procedure provides a very close cardiac surveillance – including the assessment of both cardiac biomarkers, Troponin I and NT-proBNP – and the sharing of all patients' information with the oncologist at each step of the way. At present more than 240 patients, with pre-existing cardiac disease, have been treated successfully, without the worsening of the underlying cardiac condition and the occurrence of adverse cardiac events. These procedures are available at our institution's web site.
In 2013 the out-patients clinic of the Unit (Ambulatorio di Cardioncologia – working from 2009) has performed more than 1400 cardioncologic evaluations, both for oncologic patients treated at EIO and in different Italian hospital, also creating active and effective teamwork/collaborations with both cardiologists and oncologists colleagues.
The Cardioncology Unit is strongly involved in several clinical and translational research projects, in collaboration with IFOM-EIO and the Laboratorio di Biologia Vascolare e Medicina Rigenerativa of the Centro Cardiologico Monzino of Milan, mainly focused on the evaluation of new, earlier, biomarkers of cardiotoxicity (i.e cytocromo C, cardiac mRNAs) and the role of angiotensin-converting enzyme inhibitors on cardioprotection against cardiotoxicity, both in animal and human populations. More recently, in collaboration with the Proteomic Unit and the Cardiac Magnetic Resonance Unit of the Centro Cardiologico Monzino, we have activated clinical research projects evaluating biochemical and imaging biomarkers of cardiac fibrosis and pulmonary toxicity in patients undergoing both traditional and novel oncologic therapy.

Specific Clinical and Research Activities

Diagnosis of cardiotoxicity.

Cardiotoxicity is a common complication of chemotherapy (CT). The clinical manifestation of cardiotoxicity can range from transient asymptomatic left ventricular dysfunction to cardiac death.

This is a growing problem in the setting of clinical oncology due to the tendency in using progressively higher doses of anthracyclines, as well as newer compounds, as thyroxin kinesis inhibitors, antiangiogenic drug, and monoclonal antibodies potentially deserve cardiotoxic implications. The clinical implications of cardiotoxicity are particularly relevant in those cancer patients in which onset of cardiac dysfunction, even asymptomatic, seriously limits their therapeutic opportunities and negatively impacts on clinical outcome. At present, oncologic guidelines recommend regular cardiac function assessment (generally by echocardiography or MUGA scan) to detect CT-induced cardiac damage in an early phase. The weak point of such an approach is that these techniques have low sensitivity and poor predictive value. Indeed, cardiotoxicity is usually detected when cardiac damage has already occurred. In our clinical practice we utilize different tools for the early identification of patients at increased risk of cardiotoxicity: biomarkers of myocardial damage, like Troponin I, and hemodynamic markers like NT-proBNP. For all of them, an accurate predictive value has been demonstrated by our investigations.

Cardiotoxicity prevention. The possibility to identify patients at higher risk of developing late myocardial dysfunction by cardiac biomarkers (Troponin I, NT-proBNP) provides a rationale for the development of prophylactic strategies directed against CT-induced cardiotoxicity. Considering the results of our published studies, a possible clinical application of these markers is the evaluation of pharmacological strategies in selected high-risk patients, with the aim to prevent acute cardiac damage, left ventricular dysfunction, and cardiac events. Two different therapeutic strategies could be implemented in order to reduce the clinical impact of cardiotoxicity: 1) use of specific cardiologic treatments given to cancer patients during CT in the attempt of preventing or blunting the rise of these markers; 2) use of cardiologic treatments given only to those selected cancer patients showing an increase in these markers after CT. This with the aim to interfere with the natural evolution of cardiac toxicity, and prevent the occurrence of left ventricular dysfunction and cardiac adverse events. In particular, the increase of Troponin I soon after CT is a strong predictor of left ventricular dysfunction and poor cardiologic outcome. We hypothesize that cardioprotective therapies that might limit or prevent the TNI rise after CT, as well as cardiologic treatments that interfere with Troponin I persistence, could improve cardiac prognosis of these patients. As activation of the renin-angiotensin system has been proved to be involved in the development and progression of cardiac dysfunction in several clinical settings, and has been suggested to have a role in the occurrence of CT-induced cardiotoxicity, we investigated with very positive results the role of treatment with an ACE-inhibitor, enalapril, in the prevention of left ventricular dysfunction in high-risk cancer patients (those with Troponin rise after CT). Our data confirm that prophylactic treatment with enalapril effectively prevents the occurrence of asymptomatic left ventricular dysfunction and overt heart failure in these patients. More recently, to assess whether enalapril started concurrently to anthracycline-containing treatments, can prevent cardiac toxicity more effectively than when enalapril is prescribed to selected patients showing a Troponin I increase during chemotherapy, we designed a randomized trial involving 20 Italian centers (ICOS-ONE). The trial is ongoing (158/268 patients have been randomized) and will end in 2015.

Cardiotoxicity treatment. CT-induced cardiotoxicity can result in a cardiomyopathy generally considered to be irreversible, and leading to congestive heart failure and cardiac death. Clinical manifestations of cardiotoxicity may appear months or even years after the end of CT, and are preceded, in most cases, by asymptomatic left ventricular dysfunction. In no monitored patients, symptoms of congestive heart failure usually represent the first manifestation of cardiotoxicity. In our recently published experience, most patients receiving early adequate treatment that included ACE-inhibitors and beta-blockers, showed a complete recovery of cardiac function in most cases, associated with relevant improvement in clinical status and a better cardiologic prognosis. For the optimization of cardiologic therapy we usually monitor NT-proBNP levels, which are related to the clinical and prognostic status of patients with congestive heart failure.

Diagnosis and management of neoplastic pericardial effusion. Pericardial disease and pericardial involvement are increasingly common complications of neoplastic diseases which can be life-threatening, not only in patients with unresponsive or aggressive terminal malignancies, but also in patients with otherwise favourable prognosis. Different methods may be used to treat malignant pericardial effusions, but the gold standard treatment in this subset of patients is yet to be defined. In particular, percutaneous pericardiocentesis (PC) is associated with a very high incidence of early pericardial effusion recurrences (up to 40%). In order to prevent recurrences, we started not to consider PC a mere palliative approach but we associate to the fluid withdrawn an intrapericardial "oncologic therapy" with both chemotherapeutic and "etiologic" properties. We started a prospective, controlled, interventional study in order to investigate short-term safety and effectiveness of PC followed by intrapericardial infusion of an active antiblastic, sclerosing agent, thiotepa, in patients with large malignant pericardial effusion. The results of our study have clearly showed that PC plus thiotepa is a low-cost, low-risk, and safe therapeutic approach, and should really be considered as a first choice procedure in approaching neoplastic pericardial effusions. At present, we are a referral centre for this kind of intrapericardial treatment in Italy, and we have treated more than 150 patients.

Chemotherapy induced ECG abnormalities and regulatory QT monitoring. The evaluation of ECG abnormalities in CT treated patients is routinely performed in our clinical practice. In addition to serial ECG evaluations, we settled an ECG telemetry system to continuously monitor high-risk patients and easily detect arrhythmias and conduction disturbances. Several distinct ECG changes have been described during or soon after the administration of chemotherapeutic drugs: ECG abnormalities may result in ST-segment and T-wave changes, decreased QRS voltage, and prolongation of the QT interval. CT-induced arrhythmias and conduction disturbances include ventricular, supraventricular and junctional tachycardias, and atrioventricular and bundle-branch blocks. In particular, a prolongation in QT interval is associated with onset of severe life-threatening ventricular arrhythmias, named "torsades de points". In order to more precisely identify a possible pro-arrhythmic substrate induced by CT drugs, we perform, in selected high-risk patients, also the evaluation of heart-rate variability.

International Cardioncology Society

ICOS, our International Cardioncology Society, was founded in 2009 in Milano. This Society has a European branch in Milan, an American branch in the US, and an Eastern European branch in Poland. Members of this society are made up of cardiologists, oncologists, as well as colleagues from other medical disciplines. The aim of the society is to study, in depth, every aspect of patients with both oncologic cardiologic (pre-existent, or developed after CT, or due to the oncologic situation) and oncologic problems, in order to develop an evidence-based integrated and skilled approach. In December 2013 with the strong cooperation of the CSRS (Cardiac Safety Research Council), FDA and the Vanderbilt University, Tennessee, we organized the fifth International Congress on Cardioncology that had a very big impact on the overall worldwide clinical and scientific development of Cardioncology and of the International Cardioncology Society (www.cardioncology.com).

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Roberto Latini, Laboratory of Cardiovascular Pharmacology, Istituto Mario Negri, Milano;
Marco Giorgio, IFOM-IEO Campus, Milano;
Cecilia Garlanda, Istituto Clinico Humanitas, Milano.

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Day Hospital Division

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Health Care Assistants: Gian Marco Prampolini, Claudia Salis, Claudia Blini

Activities 2013. The Outpatient Cancer Care represents an important part of the activity in oncology in addition to the inpatient approach. Cancer outpatients receive highly complex and technical procedures and treatments, avoiding their in-staying, resulting in an increase of efficiency and a more satisfying diagnostical-therapeutic process, helping patients fit their medical care into their lives instead of fitting their lives into their medical care. The Division of Day Hospital is an essential Department at European Institute of Oncology and provides a range of treatments that can safely be given on a day patient basis.
The Day Hospital of European Institute of Oncology is open five days a week, from 7:30 AM to 18:00 PM.

The Day Hospital has a mixture of beds and chairs for use during treatment, and in particular:

- Sixteen chairs or infusion stations in which patients can receive therapy in a light, open environment that allows for interaction with others patients. Every care setting includes accommodations for the patient's family or friends.
- Sixteen beds for patients receiving longer treatments or who need more complex support. In this area, chemotherapy patients who would normally need to be hospitalized will be able to receive their medical treatments during the day and then go home in the evening.

The Division of Day Hospital has the capability to treat up to 30 patients at a time.

All treatment areas are within view of the Nurses' Station to ensure a close monitoring of patients, and each infusion area is connected to a nurse call system for an extra measure of safety.

The examination rooms for the clinical evaluation of the patients before and during the treatment are located in the treatment area, designed appropriately to maximize efficiency. The Division of Day Hospital is composed of a team of a highly skilled oncology nursing. The nursing service is organized according to the model of primary nursing. The primary nurse is responsible for developing the patients' plan of care, continually assessing progress and outcomes, adjusting accordingly the plan. The primary nurse often provides care to the patient at each visit, and is responsible for directing the care.

The Division of Day Hospital will provide medical oncology care including consultation, evaluation and management of patients and the administration of chemotherapy, biotherapy and supportive therapies such as intravenous hydration, electrolyte replacement, blood/cellular product infusions.

Divisions and Units operating in Day Hospital: Medical Division of Breast Tumors, Division of Clinical Haemato-Oncology, Division of Early Drug Development for Innovative Therapies, Medical Division of Urogenital and Head & Neck Tumors, Medical Oncology Division of the Respiratory system, Medical Division of Gynecological Tumors, Medical Division of Gastro-Intestinal Tumors, Medical Division of Melanoma.

Adult oncology patients, including hematologic and solid tumor, during all phases of treatment including standard care regimens, cutting edge research and supportive care are treated in Day Hospital. Treatment includes progressive modes of therapy and symptom management.

Medical specialists working in Day Hospital belong to the individual Divisions and Units of medical oncology. Patients are considered for outpatient treatment after a multidisciplinary discussion and a clinical evaluation with a medical oncologist specialist, who establishes treatment program offering patients the possibility to participate to national or international clinical studies which evaluate the advantages that innovative treatments could provide as compared to standard treatments in specific tumor types.

During 2013 approximately 20,000 treatments were administered.

Translational Research

Drug Discovery Program

Saverio MINUCCI & Mario VARASI
Directors

Vision and Mission

The primary objective of the DDP is to translate basic research into drug discovery projects. The aims of the DDP are to: i) identify and validate new druggable targets and their role in specific diseases; ii) generate innovative biological and screening assays to understand their functional roles; iii) successfully bring these projects up to the identification of preclinical candidates, to ensure their development for maximum patient benefit and to exploit their potential for the growth of the DDP and IEO. Additional goals of the DDP are to create a network of collaborators committed to excellence in drug discovery and to contribute to the education and training of talented young people to develop future leaders in drug discovery and cancer research. The biology-inspired, chemistry-driven effort to identify innovative therapies against cancer is a team effort developed in strict collaboration with the Group Leaders, the Molecular Medicine for Care Program and the TTFactor.

Research activities

The DDP includes two Units: the Target Identification and Validation Unit (TIV) and the Drug Discovery Unit (DDU).

Target Identification and Validation Unit (TIV)

This part of the Program is based on the assumption that there is a fundamental biological heterogeneity among tumors, and these differences must be understood and exploited to identify cellular pathways governing the biology of the tumor within a specific patient, that can be targeted pharmacologically. In our view, rather than taking a "descriptive" approach to the anatomy of tumors, a "functional" strategy has better chances to lead to the identification of immediately validated targets. To this end we have generated an *in vivo* RNAi screening platform with the aim to screen a large cohort of patients' samples transplanted in immunocompromised animals (NSG mice) with lentiviral-based shRNA libraries of epigenetic and metabolic targets and kinases.

Drug Discovery Unit (DDU)

The DDU is the team devoted to the activities (medicinal chemistry/biology) required for the identification of small molecules with the desired activity/specificity against the defined targets. These small molecules are identified through an iterative process that is based on the design of an appropriate **screening funnel**, that is a combination of biochemical, cellular and *in vivo* assays used to rank and select the compounds, up to the identification of a **preclinical candidate**.

Target Identification and Validation Unit

Luisa LANFRANCONE
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Activities 2013. This part of the Program is based on the assumption that there is a fundamental biological heterogeneity among tumors, and these differences must be understood and exploited to identify cellular pathways governing the biology of the tumor within a specific patient, that can be targeted pharmacologically. In our view, rather than taking a "descriptive" approach to the anatomy of tumors, a "functional" strategy has better chances to lead to the identification of immediately validated targets. To this end we have generated an *in vivo* RNAi screening platform with the aim to screen a large cohort of patients' samples transplanted in immunocompromised animals (NSG mice) with lentiviral-based shRNA libraries of epigenetic and metabolic targets and kinases.

Research Projects

Our interest is focused on aggressive cancers for which patients have few effective treatment options, namely metastatic melanoma, metastatic breast carcinoma resistant to conventional therapy and adenocarcinoma of the pancreas. Freshly ex-vivo explanted human tumors are transplantated in NSG mice mainly orthotopically, according to well-established techniques.

Patient-derived xenografts (PDX) phenocopy the heterogeneity and the complexity of the tumor of origin. Moreover, an extensive immunophenotypic characterization of serial transplantation of the human tumors has shown a stably reproducible propagation of the original tumor. A panel of human tumor markers, as well as whole exome sequencing and epigenetic and proteomic profile of the tumors, are used to better characterize the human phenocopy in the mouse. Our aim is to stratify our cohort of PDXs according to: i) *in vivo* growth properties; ii) phenotypic markers; iii) genetic lesions; iv) characterization of intracellular signaling networks and v) epigenetic profile. At the end we might be able to generate a prognostic signature of the patient and the most suitable model for RNAi *in vivo* screenings.

To set up the *in vivo* RNAi screening in our model systems we are investigating the frequency of tumor initiating cells in the tumor samples and the interaction of the tumor cells with the microenvironment. We have set up the proper amplification and sequencing technique to evaluate hairpins' representation in the tumor and analyse and validate target genes and pathways.

Melanoma is an aggressive disease with high metastatic potential and resistance to cytotoxic agents. The molecular mechanisms involved in the progression of the malignancy and the genetic markers associated with metastatic melanoma dissemination and the acquisition of chemoresistance are only beginning to be defined. An understanding of the underlying molecular biology of melanoma provides a necessary basis to enable the generation of more effective therapeutic modalities. Our interest is to understand which are the molecular pathways involved in melanoma-genesis by an *in vivo* approach. In particular, we will pursue *in vivo* RNAi screens in metastatic melanoma PDXs to identify druggable genes that are essential for melanoma growth and progression.

Breast cancer is not a single disease. Deregulation of specific gene pathways is associated with different sensitivity to chemotherapy in various subtypes. Some clinically relevant molecular aberrations are identified in a subset of metastatic breast cancer patient population or also, due to tumor heterogeneity, within subclones of tumor metastases. Triple negative (TN), luminal B (LB) and HER2 positive (H+) breast cancer are characterized by high risk of relapse following adjuvant therapy, resulting in a rapidly fatal clinical course.

To identify genetic alterations and pathways involved in tumor resistance we will couple *in vivo* RNAi-based screening in a xeno-transplantation setting obtained from tumor metastases to exome sequencing on tumor samples from metastases, archival primary and xenograft.

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Drug Discovery Unit

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Fellows: Roberto Dal Zuffo, Elisa Zagarrì, Silvia Brambillasca

Activities 2013. The DDU is the team devoted to the activities (medicinal chemistry/biology) required for the identification of small molecules with the desired activity/specificity against the defined targets. These small molecules are identified through an iterative process that is based on the design of an appropriate screening funnel, which is a combination of biochemical, cellular and *in vivo* assays used to rank and select the compounds, up to the identification of a preclinical candidate (a molecule that is ready for the studies required to enter the clinical stage). The current pipeline includes targets in the field of cancer epigenetics. Exploratory activities are also developed, either internally or through external collaborations, to create a machinery ready to feed the running project pipeline.

Epigenetic targets

Chromatin is a key component of the machinery that regulates the dynamics of eukaryotic genomes and epigenetic mechanisms. Post-translational modifications found in the protruding "tails" of histones (the basic units of chromatin, together with genomic DNA) have been proposed to generate a "histone code", that dictates the accessibility of other factors to chromatin, imposing subsequent changes in nuclear functions. These modifications are carried out by macromolecular complexes containing components endowed with enzymatic activities. Emerging evidences suggest that epigenetic alterations are linked to oncogenesis and tumor progression, and that the enzymes responsible for histone modifications can be valid targets for drug discovery. Among these candidate targets the Lysine demethylase (KDM) family has been selected for the epigenetic platform in the DDU, based on the know-how of several basic research groups working in the Institute, and the important role proposed for this family in cancer. For one of the currently investigated targets, the screening funnel has been set-up. Novel, irreversible, inhibitors of this lysine demethylase have been designed, synthesized and evaluated: the new derivatives, besides having inhibitor potency in the nanomolar range, showed target-related gene modulation in cells and a cellular phenotype consistent with target inhibition.

Several compounds have been profiled for *in vitro* ADME and *in vivo* pharmacokinetic characteristics.
Selected compounds are currently being evaluated in *in vivo* tumor models. In addition, an alternative strategy to identify reversible inhibitors of the same lysine demethylase was established and a high throughput screening campaign utilizing a proprietary library of commercially available compounds was successfully conducted, leading to the identification of several interesting hits belonging to different chemical classes. For a second KDM target under investigation, a high throughput screening has been performed, which allowed the identification of low micromolar hits belonging to diverse chemical classes. Concurrently, a screening funnel intended to characterize both the biochemical and the cellular potencies has been set up and the relative assays developed and validated.

Exploratory activities

Among the exploratory activities, we are focusing on molecular pathways that regulate the activity of cancer stem cells, and in particular on Numb, based on the expertise of basic research groups in the Institute. Loss of Numb expression concomitantly results in two major effects: deregulation of a potent oncogene (the Notch receptor) and loss of function of a tumor suppressor (the p53 protein). The combined dysfunction of the Numb/Notch and Numb/p53 axes most likely accounts for the particularly aggressive phenotypes displayed by Numb-defective tumors (e.g breast and lung cancers). Numb expression in tumors is most likely determined at the post-transcriptional level where post-translational modifications (ubiquitination, phosphorylation) target the protein for degradation. Hence, there is an urgent need to identify these upstream mechanisms as their inhibition could restore Numb levels and counter the imbalance in both the Numb/ Notch and Numb/p53 axes. These potential Numb regulators represent ideal pharmacological targets for the stabilization of Numb levels and the restoration of its tumor suppressor activity. Two strategies have initially been considered to identify the "upstream regulators" of Numb: "target identification" by siRNA screening (forward strategy- ongoing); "phenotypic screening" against a library of small molecules (reverse strategy). The "forward" strategy has been implemented and candidates of different gene families have been identified and are currently undergoing validation.

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The Molecular Medicine Program

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Activities 2013. There is an impelling need to speed up the transfer of scientific results from the laboratory to the clinic: clinicians require it, society demands it, and scientists must respond. Each interest group depends on the other two to achieve it. This is why we established the Molecular Medicine for Care (MMC) program at IEO. Through the mutual collaboration of scientists, clinicians and patients, we are driving discoveries from our basic research programs into the clinical domain, through four scientific programs that focus on breast, lung and ovarian cancers. While these are being carried forward, we have brewing in the pipeline a number of other new discovery projects that will ultimately translate into the improved clinical management of breast, lung, ovarian and prostate cancer.

MMC Scientific Programs

To date, our biological knowledge of different cancers has had little impact on way they are managed in the clinic. Because of this, our research programs are designed to generate knowledge that will produce concrete clinical applications. The success of our scientific program rests, in no small part, on the expertise of scientists running the support infrastructures that were set up as part of MMC.

1. Stem cell markers for the diagnosis, prognosis and therapeutic stratification of breast, lung and ovarian cancer
   Stem cells are a rare population of cells necessary for tissue integrity and regeneration in case of injury. Their numbers within any normal tissue are very tightly controlled, but it is now widely accepted that these restraints can malfunction in cancer, leading to an inappropriate expansion of stem cell populations. We discovered that genes expressed in breast stem cells can be used as biomarkers to improve the stratification of breast tumors according to their pathological, molecular and clinical characteristics. However, the original stem cell signature contained more than 1,000 genes, too many to be of clinical use. Consequently, we are now developing a smaller stem cell signature based on 10-20 genes that retain the predictive features of the original 1,000-gene profile.

These can be analyzed more easily in a clinical setting using immunohistochemistry or quantitative PCR analysis. We are assessing the ability of these biomarkers to classify breast tumors according to aggressiveness, associated metastatic risk and therapeutic response to hormonal and/or chemo-/radio-therapy. Ultimately, we aim to develop a clinical test that will fine-tune the current diagnostic/prognostic ability of clinicians to improve the clinical management of breast cancer.

Using a similar approach to that pursued for breast, we are now trying to identify and isolate cells with stem properties in non-small cell lung cancer (NSCLC) and in ovarian cancer, for which stem cell identity remains poorly defined. The identification and characterization of the cells that initiate, sustain, and disseminate lung and ovarian tumors should create new opportunities for two of the current outstanding challenges in modern clinical oncology: early detection and improved treatment for these diseases.

2. Development of a blood test for the early diagnosis of lung cancer

The absence of national screening programs for lung cancer, and its lack of symptoms make the early detection of this disease difficult. The development of clinical tools for the early diagnosis of lung cancer is, therefore, a pressing clinical necessity, particularly for at-risk subjects (smokers or ex-smokers, aged 50 years or more). We have previously identified and validated in independent patient cohorts a circulating miRNA signature (based on 34 miRNA species) that can be used in a blood test to detect early stage lung cancer in asymptomatic patients. We now aim to to prove the clinical applicability of this test through its large-scale validation in a prospective trial that will recruit some 10,000 patients. This is an essential study, which will permit the transfer of our results to the clinic, should our initial results be confirmed. In collaboration with the Division of Thoracic Surgery and the Division of Radiology, we are currently assessing the clinical applicability of this test through its large-scale validation in a prospective multicenter trial launched by the Lung Cancer Early Detection Unit in September 2012 (COSMOS II). The trial has already recruited close to 6,000 of the planned 10,000 patients. If effective, this blood test will be significantly cheaper and easier to apply in national lung cancer screening programs than the only currently available clinical test, which is based on low dose computer assisted tomography screening.

3. Understanding breast cancer for early diagnosis

This scientific program is designed to investigate whether prognostic/diagnostic miRNA profiles exist for breast and ovarian cancers. Based on our experience in developing a blood test to detect early stage lung cancer, we are now collaborating with the Molecular Senology Unit of the Division of Senology, and the Gynaecologic Oncology Units in serum screening projects, involving breast and ovarian cancer patients, to identify diagnostic cancer-specific miRNA profiles. If we are successful, a small blood sample is all that will be necessary to determine if these miRNAs are present, and this could be sufficient to diagnose breast or ovarian cancers. Our work will lead to the development of a comparatively inexpensive first level diagnostic test for breast and ovarian cancers that can easily be implemented within national screening programs.
We have previously shown that more aggressive breast cancers tend to have a larger number of stem cells than less aggressive tumors. Within the context of this program, we are also analyzing the miRNA profile of breast stem cells. If these stem cell-specific miRNAs are also present within the sera of breast cancer patients, they might reflect the proportion of stem cells within a tumor. Though we are still a long way from our endpoint, we hope that testing for the presence of circulating stem-cell miRNAs in blood could form the basis for a prognostic test for breast cancer, which will complement the clinico-pathological parameters that currently used to assess the aggressiveness of the disease.

4. New discoveries to feed cancer research

Our translational medicine program would be short-lived if it were not continually fed by new discoveries in basic research which are improving our understanding of the molecular mechanisms that lie at the root of normal and cancer cell behavior. A number of these projects were born in the basic research laboratory of Pier Paolo Di Fiore, while others are fostered directly within the MMC scientific programs. Amongst these, we are studying the molecular mechanisms that regulate normal stem cell division and we are defining how these are subverted in breast cancer. We are also characterizing critical signaling/endocytic pathways involving Numb/Notch/p53 and factors that cause loss of Numb in cancer, with a view to developing targeted drugs for lung and breast cancer. Several members of the group are involved in high-resolution studies on individual markers that were identified in past genome-wide screening projects, and that potentially have significant clinical relevance as prognostic or therapeutic targets. Our ovarian cancer group is generating molecular tools for the identification and characterization of ovarian cancer stem cells, whose precise identity still remains uncertain today.
As well as these classical approaches to research, our group is using cutting edge next-generation sequencing technology to define the genetic determinants of lung cancer in smokers and in non-smokers, and to analyze the clonal origin of breast and lung cancers and their metastases.

MMC Laboratory Infrastructures

The following facilities provide critically important enabling conditions for the MMC scientific programs:

Tissue bank

The Tissue Bank (IEO Biobank and Biomolecular Resource Infrastructure - IBBRI) collects, catalogues and stores biological samples (surgically excised tissue samples non-essential for diagnosis, plasma/serum, total blood, DNA and RNA) from patients who provide informed consent for the use of their tissues for research purposes. We have established a direct pipeline with the operating theatres for the collection of tissue samples and these are stored according to specific protocols and standard operating procedures that ensure optimized and standardized treatment of all samples for research purposes.
We also store any primary cell cultures, stem cell preparations, and xenotransplanted tumors derived from collected samples, these being essential for testing new combination therapies or new drugs that will be developed in the future through MMC. All biobanked samples are managed and tracked through a software package that is fully integrated with the hospital medical records database, pathology database and central registry of patient demographic information. This ensures that each sample is linked to a full complement of anonymous or anonymized (according to patient choice) patient information that is accessible solely by authorized Biobank personnel. The high quality biospecimens we collect are used for biomarker and drug discovery experiments, both for basic research and for MMC translational research projects.

Molecular pathology laboratory

The IEO Molecular Pathology Laboratory works to identify novel putative cancer targets for drug discovery, diagnostic and/or prognostic applications through high-throughput Tissue Microarrays (TMAs) combined with *in situ* detection methods (*in situ* hybridization and immunohistochemistry). TMA technology allows gene expression analysis on thousands of patient tissues simultaneously, and is a powerful tool for determining the relevance of basic research findings to cancer. We collaborate closely with the Pathology Department at IEO, who maintain tissue archives dating back to 1994, when IEO was established. These are an invaluable source of material for the construction and continuous replenishment of our TMAs. Thanks to data stored by the IEO Tumor Registry, all arrayed tissues are linked to complete clinico-pathological and follow-up information. The Molecular Pathology Laboratory can therefore link the expression patterns of genes of interest to clinical evaluation and outcome, a necessary step for the validation of new diagnostic and prognostic markers.

Primary epithelial and stem cell culture/xenotransplant laboratory

The Primary Epithelial and Stem Cell Culture Laboratory derives bulk primary epithelial cells and stem cells from human biopsy specimens. Primary-derived cells are used for the establishment of either *in vitro* or *in vivo* (xenotransplant) model-systems that retain many features of their parental tissues. These models are therefore a valuable tool for studying the molecular features of naturally occurring human cancers. We have developed efficient protocols and SOPS for the processing of tissue biopsy specimens, for the preparation of bulk primary epithelial cell and stem cell cultures from breast, lung, ovary and prostate tissues, and for their xenotransplantation in immunocompromised murine hosts. Samples reach our laboratory via a continuous pipeline from the operating theatres, coordinated by the Tissue Bank.

Clinical biomarkers laboratory

The Clinical Biomarkers Laboratory performs screening, pre-clinical validation, and optimization of biomarker candidates to aid their translation into the clinical setting. As part of this service, we design cancer diagnostic assays and provide any necessary technological development (such as the implementation of novel technological platforms for the group). We also support collaborative study programs between biotech companies, researchers and clinicians for the co-development of biomarkers and novel therapies. The facility is also responsible for the optimization of protocols for the extraction of nucleic acids (including total RNA, DNA and miRNAs) from human tissues, such as blood, plasma, fresh tissue biopsies, paraffin-embedded tissue specimens. Finally, we select the appropriate patient cohorts and tissue samples for prospective and retrospective studies in collaboration with the Genomics and Bioinformatics Unit.

Genomics and bioinformatics laboratory

The Genomics and Bioinformatics Laboratory draws together the fields of genomics, biostatistics and applied bioinformatics. We apply “omics strategies” to identify novel cancer biomarkers and potential therapeutic targets and use computational biology and biostatistical approaches to prioritize cancer biomarkers. We are primarily involved in the screening for circulating miRNA biomarkers for the early diagnosis of lung, breast and ovarian cancer patients, and in the transcriptome analysis of primary tumors and cancer stem cells.
One of our key roles is to provide support to other MMC units. We are responsible for: i) coordinating, centralizing and managing clinical information associated with biological samples collected by the Tissue Bank; ii) designing and analyzing studies involving the screening, pre-clinical validation, and optimization of biomarker candidates, identified by the Clinical Biomarkers Laboratory.

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SmartFood: Program in Nutrition Science & Communication

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Technician: Mariangela Storto
Dietary intervention trials and communication coordinator: Lucilla Titta, PhD
Nutritionists: Krizia Ferrini, Francesca Ghelfi

Vision and Mission

SmartFood is the IEO program in Nutrition Science and Communication, the aim of the project is to develop nutritional improvement at different levels taking advantage of our already existing network. The potential goals of the project include:

- Identify bio-active compounds in foods that interact with longevity "genetic pathways" (smart food compounds)
- Evaluate the effects of "smart food compounds" and "smart foods" in disease prevention and cure, in model systems and humans
- Promote good health and primary prevention of nutrition related illness in the population through different communication skills (web, publishing and events)

Patient care

Lifestyle factors have increasingly been identified as potential means to impact cancer outcomes and improve quality of life in survivors. Obesity, inactivity, poor dietary quality, and continued smoking after cancer diagnosis have all been linked to increased risk of cancer recurrence and mortality in individuals with common cancers. Interventional studies have demonstrated that behavior change after cancer diagnosis is achievable, and individuals who are able to lose weight, exercise more, and improve their diets experience better quality of life and other benefits. In our research activity in the Smart Trial 1 we experimented dietary counselling with great results showing the relevant role of such activities in patient care.

Research Activities

The SmartFood program consists of two research lines:

1) Laboratory activities

The SmartFood basic research program is searching for plant food bioactives that induce longevity pathways and healthy aging. The final goal is to provide a rationale in selecting compounds, plant extracts and "smart" foods that prevent aging associated diseases such as diabetes, cardiovascular disease and cancer.
The molecular targets for this screening are the genetic pathways of mammalian longevity and response to caloric restriction that retards aging. Crude extracts and purified compounds are investigated trough an experimental pipeline including enzymatic assays, cellular systems and preclinical models.
Currently we are validating the protective effect of selective extracts and compounds on myocardial ischemia/ reperfusion damage and chemotherapy toxicity, glucose intolerance, diabetic retinopathy, cancer initiation and growth.

2) Dietary Intervention Trials

The endpoints of the SmartFood dietary intervention research area, are trials in humans to validate the findings obtained in cellular or animal models.
To investigate the effects of diets in humans many issues impacting on the feasibility of advancing clinical evaluation, such as food component selection, bioavailability, mechanistic and safety properties, are suitably explored in small and relatively short-term studies in either healthy volunteers, individuals with pre-malignancies or cancer patients.
SmartTrial 1 (Randomized cross-over intervention trial on the effect of a regular consumption of an anthocyanins rich orange juice on side effects of aromatase inhibitor treatment in postmenopausal patients with breast cancer) is the on-going dietary intervention trial in IEO in collaboration with Division of Early Drug Development for Innovative Therapies. This study is designed to determine whether a program of anthocyanins dietary consumption (500ml/ die Moro orange juice), provided for a 12 weeks period in

addition to defined adjuvant therapy with letrozolo, will effectively reduce cholesterol levels increasing HDL and decreasing LDL blood levels in post menopausal women with radically resected early breast cancer.

Educational Activities

The SmartFood project is also aimed at promoting a healthy lifestyle and providing practical tools for adapting the information obtained through scientific research to the daily dietary habits of the individual. By basing each selection upon the results of scientific research, the communication program is aimed at providing useful tools for making practical and well-informed dietary choices on a daily basis. All this in keeping with the philosophy that a healthy diet can also be varied, appetising, and well-suited to every age group and dietary requirement. Therefore, the program is spent in different area of communication: educational, editorial and web. Link to https://www.facebook.com/SmartFoodIEO

Publications

Scientific Pubblications

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Editorial Pubblication

Mondadori Editore (2013). “La dieta del digiuno” di Umberto Veronesi

Trenta Editore “Omega ME” (2013)

Division of Epidemiology and Biostatistics

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Activities 2013. The Division of Epidemiology and Biostatistics is conducting epidemiological research activity on a wide range of topics, focusing on patients with cancer or on patients at increased risk of developing the disease. It has continuously attempted to develop international collaborative research programmes and as a result, the majority of the research activities involve co-operation with scientists from a range of disciplines, both intra-mural and extra-mural.
The Division is involved in the establishment and management of clinical research databases at the hospital and has responsibility upon data quality control. The Division is running the IEO hospital-based tumour registry. The tumour registry was activated in 2006 and after 7 years of activity, by March 2013, data for 154,099 tumours were retrospectively coded and entered (out of 240,440 individuals presenting for the first time at the IEO over the period 2000-2008).

The tumour registry has proven to be a valuable source of data for both epidemiological and clinical research and has been the basis for many research projects.
The Division also provides consultation in a wide range of areas including the statistical design of experiments and clinical trials, including sample size calculations and randomisation schemes, protocol development, database management, analysis of data and interpretation of results, preparation of interim reports and manuscripts. In addition, staff in the Division has developed a strong expertise in the field of statistical modelling and in the conduct of meta-analyses, providing important information to public-health policy makers and clinicians.

Achievements 2013

The Division is maintaining large institutional clinical databases which have been, already in the past, the basis for numerous studies, particularly the IEO Breast Cancer database. During 2013 a major research focus was made on the treatment, outcome and clinical aspects of breast cancer subtypes defined either by their molecular or morphological characteristics. Specific projects focussed on the outcome of very young women with breast cancer and of women who became pregnant after breast cancer. Other research interests in breast cancer during 2013 included the prognosis of breast cancer patients who underwent plastic or reconstructive surgery, investigating for example outcome after immediate breast reconstruction, nipple-sparing mastectomy or fat grafting.
The Division contributed to the publication in 2013 of results from three major institutional randomised clinical trials: A randomised phase II pre-surgical trial of weekly low-dose tamoxifen versus raloxifene versus placebo in premenopausal women with oestrogen receptor positive breast cancer; a phase-III prevention trial of low-dose tamoxifen in postmenopausal hormone replacement therapy users: the HOT study; and a randomised controlled equivalence trial of Intraoperative radiotherapy versus external radiotherapy for early breast cancer: the ELIOT trial.
In summary, the statistical support activity of the Division led to the publication of 33 peer-review clinical research articles in various fields ranging from cancer screening, cancer chemoprevention, cancer treatment, cancer prognosis and cancer outcome. Most of this activity was related to cancer of the breast, lung, head and neck; to gynaecological, digestive or urogenital cancers; as well as haematological neoplasms.
The Division is also largely involved in epidemiological studies and in collaborative research with other Italian or international institutions: In 2013, in collaboration with the US Cystic Fibrosis Foundation, it published results from a large cohort study of patients with cystic Fibrosis confirming an increased risk of digestive tract cancer, particularly following transplantation. The Division is also part of the PANC4 consortium, which last year published results from large multicenter pooled analyses on the association between a history of allergies or ulcer and pancreatic cancer risk. The division also conducted several meta-analyses and reviews on the association between alcohol drinking and cancers, Vitamin D and overall mortality, use of vitamin supplements and cancer.
During 2013, the Division pursued its research activity on melanoma, through a varieties of studies ranging from the melanoma aetiology, screening, prevention, treatment and outcome. Specific research topics included: sun-bed use, self-examination, surgical treatment, sentinel node biopsy and whole-body diffusion-weighted imaging.
Another research area in which the division had a long-standing interest and reputation includes nutrition. In 2013, special research focus was made on the role of vitamin D, including vitamin D supplementation, on cancer and mortality risk. The Division also conducted a large-scale nutritional survey among heavy smokers enrolled in a lung cancer prevention study and reported on the association between nutrient intake, nutrient pattern, red meat consumption and adherence to the Mediterranean diet and lung cancer risk.
In total, in 2013 the division contributed to 76 articles published on peer-reviewed journals, with an overall impact factor of 373.

Specific Research Programs

Food Composition Database for Epidemiological Studies in Italy

Principal Investigator: Patrizia Gnagnarella

The Division is responsible for the Food Composition Database for Epidemiological Studies in Italy, which has become a major instrument for the conduction of National epidemiological nutritional studies. This database, available online since 2007 (http://www.ieo.it/bda) is continuously updated and amplified. The project was started because of the need of epidemiologists for a large database with information about the most important nutrients in the main food items consumed in our country.

Understanding how cancer stem cells drive breast cancer growth and how to exploit them as its Achilles' heel

Coordinated by Pier Paolo Di Fiore

Sub-task: Establishment of a task force for biometrics: Patrick Maisonneuve.
This research program is focused on understanding the mechanisms regulating normal and cancer stem cell asymmetric and symmetric division and how this impacts breast cancer prognosis and treatment. The task of the Division of Epidemiology and Biostatistics is to establish a task-force for biometrics to provide support for the design, analysis and reporting of translational studies on cancer biomarkers.
The full project is supported by a grant from the Italian Association for Cancer Research (AIRC 5 per 1000).

Melavid

Principal Investigator: Sara Gandini

This research project aims to assess whether vitamin D supplementation could improve prognosis of melanoma. This is an Italian multicentre trial in stage II resected melanoma patients, monitoring changes in 25(OH)D. In short term, we intend to study the biology of VDR and Vitamin D Binding Protein in relation to melanoma prognosis and on vitamin D metabolism, taking into account vitamin D intake. Findings from this study will be of large interest for a wide spectrum of cancers. This is a collaborative study carried out in collaboration with the Division of Melanoma and Muscolo-cutaneous Sarcoma and the Division of Prevention and genetics of IEO.
The project is supported by a grant form the Umberto Veronesi Foundation.

CoViDMicrobiome: Relationship between microbiota, Vitamin D and colorectal cancer

Principal Investigator: Sara Gandini

The principal aim is to compare microbiota profiles in patients with colorectal cancer and healthy subjects. Secondary aims are the comparisons of Vitamin D levels, gut flora and vitamin D genes polymorphisms with cancer stage and proliferation.
We designed a case-control study to evaluate differences of bacterial composition at baseline by disease status and in association with Vitamin D level. Colorectal cancer patients will be recruited before undergoing surgery. Healthy subjects will be match by age, sex, body mass index and season.
Faecal and serum samples will be collected and analysed by real time PCR and competitive immunochemiluminescent assay. Discovery of a microbiota composition, associated with colorectal cancer and modulated by Vitamin D, might allow identification of pathological mechanisms and definition of new preventive strategies.
The results might be applicable also for other health conditions since microbiota and Vitamin D are involved in several pathophysiological processes.
This is a collaborative study carried out in collaboration with the Department of experimental Oncology and the Division of Prevention and genetics of IEO.
The project is supported by a grant form the Umberto Veronesi Foundation.

M-SKIP

Principal Investigator: Sara Raimondi

The M-SKIP project It is an international pooled-analysis investigating the role of the pigmentation gene MC1R on skin cancer development, with a specific focus on melanoma. This collaborative project, leading by the Division of Epidemiology and Biostatistics, involves 31 international researchers, around 8000 melanoma, 3000 non-melanoma skin cancer cases and 15000 healthy subjects.
The main goal is to investigate the dependent and independent contribution of MC1R gene on skin carcinogenesis by phenotypic characteristics, taking into account the complex interactions between genetic, phenotypic and environmental factors, like sun exposure. To achieve this goal, appropriate statistical methods to assess for interaction, mediation and population heterogeneity have been investigating and applying. The identification of subjects with a markedly high MC1R-associated skin cancer risk will be of particular importance for assessing targeted preventive strategies in a screening setting.
The project is supported by a grant from the Italian Association for Cancer Research.

Publications

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Tumor Registry

The project

The Tumour Registry (TR) was activated in March 2006 with the aim to collect data on all those consulting at the European Institute of Oncology (IEO), at risk of developing or already presenting with a tumour. It has actually become a supporting tool for the current practice as well as for epidemiological/ basic research, guaranteeing a quick analysis of the IEO clinical activity and playing a key role in the production of scientific publications.

The purpose is also to provide global information on the activity of the hospital, to document the cancer burden borne by the hospital for specific periods of time, to provide background information useful for the design of clinical studies, and to encourage clinicians and researchers to enquire about data and run new projects on the population of our patients.

Eligible to enter the Registry are all those coming to the IEO for consultation since its opening, with unique identification number (patients' record) and at least one episode accessible from Institute's intranet. A minimum data set of variables was defined and data entry was divided in 4 forms.
Briefly, on the first form personal data (i.e., sex, address, date of birth) and information on follow-up (i.e., date of last contact, date of last visit, vital status, cause of death) are recorded.

Data Collected

The following types of record are assigned:

1. Visit: a healthy individual comes to IEO for either visit or genetic counselling.
2. Anamnesis: the patient, at the moment free of disease, reports on a tumor diagnosed in the past and already treated and cured.
3. Diagnosis: diagnosis of tumor is made at IEO. The patient decides to be treated elsewhere.
4. Second Opinion: the patient or the patient's parents come to IEO and ask for a second opinion on a diagnosis and/or a treatment proposed elsewhere.
5. Long: the patient receives at least one treatment at IEO.

Detailed information on patient's tumor(s) (i.e., date of diagnosis, morphology, topography, TNM staging) is recorded on the second form, together with some epidemiological information (i.e., familiarity, height and weight at diagnosis and smoking habits).
The third form is dedicated to the treatment strategy, where every therapy is classified as administered or proposed. The fourth is dedicated to the chronology of events, in order to better describe the history of the disease and to take note of the tissues preserved in the Biobank of IEO.

Sources of information for data collection are:

1. database of patients' administrative data (personal information is automatically downloaded);
2. files accessible on intranet;
3. online databases (surgery, laboratory medicine);
4. patients' clinical dossier digitalized and accessible on e-Paper.

The Registry was implemented using the interface software ArgosTM, based on Oracle TM database system. The implementation, completed in February 3 2006, was managed in the division of Epidemiology and Biostatistics, with the help of the ICT IEO/CCM division.
Although it was decided that data from the TR must not be directly accessible to researchers or clinicians, we have established a system to collect and answer requests. Data extrapolation and analysis are managed in the division of Epidemiology and Biostatistics on the advice of the Scientific Direction of IEO.

Confidentiality

All cancer case information included in the Tumour Registry is considered confidential. Data that identify patient-specific information are not included in the database. Use of the data has been authorised by the Institutional Ethics Committee and renewed on March 7th 2013.

First 7 years of activity

After a 6 months pilot period, from March to August 2006, which involved the training of the operators, ad hoc improvements to the structure of the registry, data quality control and editing of the user guide, from September 2006 the data entering has been running at top speed. We started entering individuals who came for the first time to IEO in the year 2000 (dossier number CC00) in a sequential fashion.
By September 2013, 256,959 individuals who visited IEO for the first time in the years 2000-2009 were entered in the Tumour Registry. Individuals' characteristics are reported in Table 1.

Table 1. Characteristics of individuals

	Classification	No. Patients (%)
Gender	Male	83,410 (32.5)
	Female	173,549 (67.5)
Age	< 20 years	3,824 (1.5)
	20-34 years	27,517 (10.7)
	35-49 years	76,825 (29.9)
	50-64 years	88,137 (34.3)
	65-79 years	55,103 (21.4)
	≥ 80 years	5,553 (2.2) 173
Place of residence	Northern Italy	165,518 (64.4)
	- Lombardy	134,743 (52.4)
	- Milan	48,188 (18.8)
	Central Italy	48,870 (19)
	Southern Italy	40,407 (15.7)
	Foreign countries	2,164 (0.8)
Type of record	Long	59,820 (23.3)
	Second Opinion	82,959 (32.3)
	Anamnesis	3,420 (1.3)
	Diagnosis	2,732 (1.1)
	Visit	108,028 (42)
Total		256,959 (100)

Table 2. Tumors by site[a]

Tumor site	Collected Overall[a]	Invasive tumors		
		Total	IEO diagnosis	IEO Surgery
Head and Neck	4,773	4,248	1,231	875
Lip	147	136	38	32
Tongue	860	829	359	324
Major salivary glands	840	448	154	104
Gum	59	55	26	25
Floor of mouth	144	139	37	35
Other and unspecified parts of mouth	748	704	203	156
Oropharynx	711	697	167	108
Nasopharynx	521	516	99	11
Hypopharynx	350	348	69	45
Other and other ill defined sites	393	376	79	35
Digestive organs and peritoneum[b]	25,672	25,193	4,120	2,499
Oesophagus	716	700	143	78
Stomach	4,368	4,332	797	587
Small intestine, including duodenum	484	472	111	34
Colon	9,190	8,964	1,416	998
Rectum, rectosigmoid junction and anus	3,942	3,876	832	630
Liver and intrahepatic bile ducts	1,858	1,833	228	60
Gallbladder and extrahepatic bile ducts	1,458	1,416	105	21
Pancreas	3,143	3,117	358	69
Retroperitoneum and peritoneum	208	196	63	19
Other and ill-defined sites	305	287	67	3
Respiratory and intrathoracic organs	21,251	20,399	5,062	3,265
Nasal cavities, middle ear and accessory sinuses	120	117	11	3
Larynx	2,174	1,949	636	576
Lung	17,676	17,142	4,092	2,550
Pleura	846	800	179	56
Thymus, heart and mediastinum	429	385	144	80
Other and ill-defined sites	6	6	0	0
Bone, connective tissue, skin and breast	67,264	56,484	28,732	19,497
Bone and articular cartilage	21	15	3	1
Connective and other soft tissue	3,582	3,441	1,168	498
Skin Melanoma	4,744	4,462	1,805	596
Skin Non Melanoma[c]	4,286	4,051	1,805	1,581
Breast	54,631	44,515	23,951	16,821
Genitourinary organs	32,982	27,084	7,105	4,980
Cervix uteri	5,772	2,175	798	565
Uterine corpus	2,541	2,316	752	547
Ovary and other uterine adnexa	5,070	4,668	1,518	901
Other and unspecified female genital organs	1,091	727	254	171
Prostate	9,690	9,509	2,139	1,548
Testis	1,108	1,055	306	189
Penis and other male genital organs	170	141	57	45
Bladder	3,725	2,888	545	418
Kidney and other and unspecified urinary organs	3,815	3,605	736	596
Other and unspecified sites	5,285	4,160	754	605
Eye	23	19	3	1
Brain	1,858	1,833	48	0
Other and unspecified parts of nervous system	56	52	2	0
Thyroid gland	3,126	2,100	674	592
Other endocrine glands and related structure	222	156	27	12
Lymphatic and haematopoietic tissue	5,562	5,528	1,574	99
Hodgkin lymphoma	1,024	1,024	275	12
Non-hodgkin lymphoma	2,918	2,918	1,062	83
Multiple mieloma	574	574	95	2
Leukemia	860	860	109	2
Other and unspecified	186	152	33	0
Non-skin melanoma	212	212	34	27
Malignant neoplasm without specification of site	2,489	2,424	613	77
Total	165,490	145,732	49,225	31,924

At that time, 165,490 tumours, out of 148,933 individuals presenting with 1 or more tumours, were entered (Table 2).

Developments

Eleven studies based on the data from the TR have been published so far.
Over 15 studies in collaboration with other divisions of the IEO are ongoing.
The TR will soon be linked with the Biobank, allowing new molecular features to be available.
The IEO TR has proven to be functional and reliable in monitoring the activity of the Hospital, allowing extraction of data from any subset of patients with characteristics of interest. This structured and centralized Registry represents an important tool for our research-oriented Institution.

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Carmen Criscitiello, Davide Disalvatore, Michele Santangelo, Nicole Rotmensz, Barbara Bazolli, Patrick Maisonneuve, Aron Goldhirsch, Giuseppe Curigliano No link between breast cancer and meningioma: results from a large monoinstitutional retrospecitive analysis Cancer Epidemiol Biomarkers Prev. 2014 Jan;23(1):215-7.

Notes to Table 2 (pag 172)
[a]Including all invasive and in-situ tumors. Benign neoplasia/negative histology after radical surgery in IEO are also collected.
[b]Polyps are not collected; [b]Benign nevi are not collected.

Basic Research

Department of Experimental Oncology

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Activities 2013. The Basic-Research activities of IEO are carried out at the Department of Experimental Oncology, which is located within a Campus also hosting the European School of Molecular Medicine (SEMM), the FIRC Institute of Molecular Oncology (IFOM), and the Center for Genomic Science of the Italian Institute of Technology (IIT). The Department of Experimental Oncology of IEO is composed of about 250 scientists, 17 Group Leaders and 2 Unit Directors. It also includes three Translational Programs: the Drug Discovery Program, the Molecular Medicine Program and the SmartFood Program. The Department has adopted an open-space lab-model that fosters communication, cooperation among researchers, and participation in the decision-making process of lab management. The Department employs highly qualified technical staff to work in Core Support Units (Cell Culture; Kitchen; Technical Services; Information Technology).

Scientific activities. They are mainly focused on molecular mechanisms of transformation (genomic instability, epigenomic alterations, cell-fate determination) and biological aspects of tumors (including tumor stem cells, tumor cell-heterogeneity, tumor microenvironment). Emphasis is given to the generation of tumor models (mouse-models, xenotransplants), applications of high-throughput technologies [proteomics, (epi) genomics, structural biology and screenings] and development of dedicated computational tools and approaches.

Post-graduate Education. We provide postgraduate education through the European School of Molecular Medicine (SEMM, www.semm.it). SEMM hosts three PhD programs (Molecular Oncology, Computational Biology, Foundations & Ethics of the Life Sciences) and an International postdoc program (SIPOD).

University of Milan. The Department actively collaborates with the University of Milan and several of our scientists are also University Professors.

Technological Services. The Department shares state-of-the-art technological platforms and facilities with IFOM and IIT, including: Genomics, Crystallography, Mass Spectrometry, Imaging, Mice, Protein Chemistry, PCR and other DNA services, Microarrays.
The DEO has implemented a mixed system to provide access to a broad spectrum of technological services. The DEO Technological Units are conceived as high-tech structures run by specialized technologists in coordination with DEO scientists in order to guarantee a constant technological update and flexibility to the needs of the groups. Standard services are provided by Cogentech (Consortium for Genomic Technologies, owned by IEO and IFOM), whose facilities are commercial and open to external users.
The Technological Units of the DEO include the Genomic Unit, the Crystallography Unit and the Mass Spectrometry Unit.

Genomic Unit: This unit is jointly run by IEO and the Center for Genomic Sciences of IIT and has set up protocols to cover the majority of applications requiring high-throughput sequencing (including ChIP-seq, RNA-seq, mutational analysis, methylation analysis).

Crystallization Unit: The three-dimensional structure of biological macromolecules and their complexes can significantly contribute to the understanding of the biological processes in which they are involved. This unit has established an automated platform for high-throughput protein crystallization in order to maximize the success rate of initial crystallization trials with minimal amounts of sample.

Mass Spectrometry Unit: The Protein Analysis Unit aims to provide assistance in the design of experiments and in data interpretation, as well as scientific and technical knowledge in proteomics by supplying tools for protein isolation, identification and characterization using mass spectrometry.

The Cogentech facilities include the Mouse facilities, the Protein Chemistry facility, the DNA Sequencing and quantitative-PCR facility and the Microarray facility.

Mouse facilities: Two facilities currently allow researchers to carry out experiments in mouse models: i) the Mouse Genetics facility (Director: Gobbi A.), which deals with mice housing and caring and colony maintenance and expansion; ii) the Transgenic facility (Director: Allievi E.), which provides support for the generation of transgenic and knock-out mice. Activities in both facilities are carried out in compliance with the ethical rules imposed by the European Commission and adopted by the Italian Laws, under the supervision of professional veterinarians (Dr. Manuela Capillo and Dr. A. Gobbi).

Protein Chemistry facility: This facility offers integrated services for the production and characterization of recombinant proteins, maintains a collection of vectors, strains and protocols, and helps users generate monoclonal and polyclonal antibodies.

Microarray facility: This facility routinely performs complete microarray analysis for internal and external users, using both Affymetrix and Nimblegen technologies.

DNA Services: This facility offers DNA sequencing, human cDNA Library Colony Picking and Real Time PCR technologies.

Functional Genomics

Myriam ALCALAY, MD, PhD
Director

STAFF Post-doctoral Fellows: Angela De Laurentiis, Alicja Gruszka, Marco Saia, Elisa Barbieri

Activities 2013. High-throughput technologies have become essential for the discovery and analysis of genetic networks underlying cancer. Recent technological advancements, in particular next-generation sequencing, allow for a more comprehensive analysis of complex molecular interactions that accompany neoplastic transformation and tumor progression. The concerted use of these approaches to discover and characterize genetic and epigenetic events that are relevant to oncogenesis is one of the current challenges in the field of functional genomics applied to cancer research. We are using an integrated genomic approach to study the molecular basis of acute leukemias. In particular:

- we are performing detailed analyses of transcriptional networks underlying normal hematopoietic differentiation and their subversion in the pathogenesis of acute leukemias caused by chromosomal translocations involving the AML1 gene. Our approach includes the generation of cell lines expressing recurrent AML1-fusion proteins (AML1/ETO, TEL/AML1, AML1/MDS1, AML1/PRDM16), analysis of their DNA binding patterns and associated chromatin status, the study of their capacity to interfere with the binding profiles of other regulators of hematopoiesis such as CEBPα and PU.1, and of their effects on nuclear architecture and regulation of mRNA and miRNA expression.
- we are studying the activation of stem-cell signalling pathways in acute myeloid leukemia (AML) bearing mutations of the nucleophosmin (NPM1) through the analysis of the hematopoietic compartment in developing zebrafish that express mutant NPM1.
- we are investigating the molecular basis of chemoresistance in AML through mutational analysis of matched tumor samples from patients at diagnosis and relapse. Our results will be integrated in a database of genomic data from AML that is being compiled in our laboratory

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Oncogenes, Chromatin and Cell Cycle Control

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Activities 2013. Oncogenic signals induce cell cycle progression and malignant transformation, but concomitantly elicit tumor-suppressive mechanisms (including apoptosis, senescence, and/or DNA Damage Responses), which must be bypassed in order to allow tumor progression, and which constitute the main selective pressure for mutation and/or silencing of tumor suppressor genes. Apoptosis and senescence also determine the therapeutic efficacy of genotoxic treatments (whether chemo- or radio-therapy). Hence, the same genetic lesions and/or epigenetic alterations that allow tumor progression also influence therapeutic responses.

Our group has a long-standing interest in the c-myc oncogene and its product, the Myc protein. Under physiological circumstances, Myc is a central regulator of the cellular responses to extracellular stimuli.

When its expression become uncontrolled, however, Myc acquires potent oncogenic properties. Myc is a transcription factor: it functions as a heterodimer with a unique partner, Max. The Myc/Max dimer directly or indirectly binds a multitude of target genes, and can either activate or repress transcription.

In general terms, our research aims at explaining the oncogenic activity of Myc, its action on the genome, its effects on cell cycle progression, cell death and differentiation, the tumor suppressor pathways that antagonize it, and their impact on tumor progression and maintenance.

We also use Myc as a paradigm to study the epigenetic organization and regulation of the genome. In particular, we are interested in understanding how specific chromatin environments – or epigenetic states – determine recognition by Myc of its binding sites in the human and mouse genomes, and how Myc further modifies chromatin to regulate gene expression. These studies rely on advanced protocols based on next-generation DNA sequencing technology (ChIP-seq, RNA-seq and others).

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Nuclear Proteomics to investigate multi-layered gene expression regulation

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Activities 2013.

Dynamic analysis of global-protein methylation by Mass Spectrometry and its impact in microRNA biogenesis (MS).

Protein methylation is an enzymatically-mediated post-translational modification (PTM). Its reversible nature and roles in a diverse range of pathways make accurate global identification and quantification of methylated sites an important goal.
Results in 2013: We were among the first studies to define a large-scale human methylome (Bremang et al., 2013). To date, we have identified 635 distinct lysine and arginine methylations, on 159 unique proteins. We have profiled methylation changes upon PRMT5 depletion, experimentally validating a number of symmetrically-dimethylated peptides (Collaborator: E. Guccione, IMCB).
On-going activity:

- Extending the detection capability of our approach, based on heavy methyl stable isotope labelling by aminoacids in cell culture (hmSILAC), through optimisation of analytical methods, extensions to our computational pipeline and application of new mass spectrometry techniques
- Elucidating the impact of distinct protein-arginine methyltransferases (PRMTs) on global protein-methylation upon siRNA-mediated depletion
- Dissecting the methylation state of the Large Drosha Complex (LDC), crucial for miRNA biogenesis, by means of a combination of hmSILAC, affinity enrichment and high-resolution MS
- Investigating the impact of different PRMTs on LDC methylation and on microRNA biogenesis

Systematic investigation of global-regulatory networks between transcription factors and microRNAs in cancer.

Although the synergism between the miR-17-92 cluster and MYC has been elucidated during tumor initiation, the role of these miRNAs is largely unknown in established malignancies. In this project we investigate the functional interplay between the cluster and MYC in full-blown B-cell lymphomas.
Results in 2013: Changes in mRNA 3' UTR lengths during tumor development leads to the rewiring of the regulatory circuits governed by miR-17-92, MYC and their shared targets. In addition, miR-17-92 reduces MYC synthesis through the modulation of the Chek2-dependent HuR/RISC axis. Accordingly, subtle increases in miR-17-92 levels interfere with tumor growth *in vitro* and *in vivo*. We developed a model where miR-17-92 adjusts MYC expression and functions in established tumors, to ensure tumor homeostasis.
On-going activity:

- miR-17-92 depletion in human Burkitt lymphoma cells to confirm the role of the cluster in tumor homeostasis
- Proteomic analysis of MYC 3'URT interactome to identify the factors determining its differential translation upon miR17-92 induction

MS- analysis of hPTMs patterns in breast cancer as biomarkers for personalized epigenetic therapy.

Abnormalities in hPTM patterns are frequently implicated in the development of cancers and could represent biomarkers for drug response and disease detection and classification. We undertook a study to identify the epigenetic biomarkers that determine cellular responses to a set of known and novel histone deacetylase (HDAC) inhibitors in breast cancer.
Results: we identified panels of breast cancer cell lines that are either sensitive or resistant to these compounds and profiled differences in hPTMs among them, through MS-proteomics. This approach involves a SILAC set up where a mix of heavy-labelled breast cancer cells serves as spike-in reference for comparative analysis with samples from unlabelled cells.
On-going activity:

- Profiling hPTMs in the presence and absence of the compounds, to pinpoint the modifications affected by HDAC inhibitors with different specificities
- Applying this method to the analysis of primary samples, including formalin-fixed-paraffin embedded breast biopsies
- Profiling the acetylation status of sensitive/resistant cell lines beyond histones

Dynamic profiling of chromatin proteome at enhancers of inflammatory genes.

Inflammatory stimulus drives a fine rearrangement of cell-specific chromatin determinants at cis-regulatory regions of inflammatory genes. A complete picture of the enhancers' molecular determinants -at basal conditions and during inflammation- remains elusive. We applied the recently published ChroP approach (Soldi and Bonaldi, 2013) in Raw 264.7 cells, using H3K4me1 and Pu.1 as baits to dissect the enhancers' proteome.
Results in 2013: We identified a set of potential novel enhancers' determinants at basal state. Time-course ChroP enable to profile nuclear factors that are specifically recruited/evicted at these regulatory regions during inflammation.
On-going activity:

- Functional validation of novel proteins, candidates as enhancers' determinants, at both basal and inflammatory state
- Analysis of the hPTMs associated

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Biomedical Humanities

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Activities 2013. Recent advances in understanding the molecular bases of (oncological) diseases, at the level of genetic predisposition as well as of its interaction with individual lifestyles and environments, are drastically changing our perceptions of diagnosis and therapy.

Given this scientific scenario, innovative foundational, ethical, and sociological analyses are needed, and these could be provided inside the BIOMEDICAL HUMANITIES framework. It is a humanistic approach addressing that chain which finishes with the care of patients in clinical practice and which commences with the basic and translational researches on the molecular roots of diseases, on how to detect them, and on how to cope with them by taking into account individual patients' genetic makeups, lifestyles and aspirations.

The research group in BIOMEDICAL HUMANITIES at the Department of Experimental Oncology of the IEO focuses on cancer research and cure and consists of three research units (RU):

- RU1: Foundational questions
- RU2: Individual and public ethical questions
- RU3: Societal questions

RU1: Foundational questions

There are at least two ways of addressing biomedicine and clinical practice from a philosophical perspective: one is more attentive to the philosophical side and one more attentive to the scientific side. Concerning the former, we are interested in the conceptual analysis both of terms belonging to biomedical research or clinical practice (gene, susceptibility, disease, therapy, cancer, stem cell, model organism, etc.) and of terms that may be explicated by means of biomedical knowledge (life, death, individuality, organism, etc.). Regarding the latter, we propose a philosophy that has a real impact on science, both at research and at clinical level. For example, i) we are developing a formal language that should permit to write intra- and infra-cellular processes as computable theorems; ii) we are working on bio-ontologies, which, in these years, have a great relevance relatively to the elaboration, storage and retrieval of the enormous bulk of data coming from the lab and from the clinical research.

RU2: Individual and public ethical questions

Each step of the chain from the scientist's lab bench to the patient's bedside raises a host of ethical issues, both at the individual level and at the collective level. Our research focuses on some of these, for example those raised by biobanks, consent, clinical trials, human embryonic stem cells, patient stratification, and so on. Our aim is to improve the quality of the public discussion on these important issues as well as to promote responsible individual choices and effective public policies (we touch issues such as democratic legitimation of public policy concerning health matter, responsible and active citizenship in the health domain, freedom of choice and expression in relation to research and treatment, etc.). Our research is characterized, i) at public level, by an emphasis on deliberative practices to improve collective choices on ethical issues concerning biomedicine and clinical practice; ii) at individual level, on the establishment of a good ethical counseling to really empower patients in front of any diagnostic or therapeutic action needing an ethical decision.

RU3: Societal questions

In our Science and Technology Studies (STS) approach we focus on the mutual shaping of epistemic and normative orders that arise at the interface of biomedicine and society. The momentous developments of molecular biomedicine are unfolding in a space of experimentation that is not only technical and epistemic but also, and importantly, social. In its steep acceleration the production of biomedical knowledge is also being redistributed to a host of new sites that extend well beyond academia, and all the while the public space is itself changing rapidly, evolving new institutions and accommodating new relationships among citizens along with new distributions of power. From cells to sequences, from regulatory agencies to patent offices, we pay attention on the objects and sites of contemporary biopolitics, and harness STS to trace their implications for health care policy.

Pubblications

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Viral Control of Cellular Pathways and Biology of Tumorigenesis

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Activities 2013. Viruses are hijackers of the host's cellular machinery: several viral proteins are known to utilize, interfere, and/or augment cellular proteins and signaling pathways in order to replicate and/or enter latency in cells. We have been studying how viral proteins interfere with the regulation of the SUMO (Small Ubiquitin-related Modifier) pathway, a post-translational modification system enzymatically analogous but functionally diverse from the classical ubiquitin system (Ub). As a model system we have been using a peculiar adenoviral protein called Gam1 and demonstrated indeed how a viral protein can degrade SUMO enzymes by recruiting endogenous cellular components of ubiquitin E3 ligases. Protein post-translational modification by ubiquitin and SUMO regulate pathways that contribute to numerous biological processes. An ongoing research theme in our lab is to understand how viral proteins and oncoproteins impact tumorigenesis by post-translational modification of proteins.

In particular, we had previously shown that Histone Deacetylase 1 (HDAC1) is post-translationally modified by SUMO and recently also published that cancer cells differ from normal cells in the SUMOylation state of HDAC1.
Mammalian histone deacetylases (HDACs) are composed of ubiquitously expressed class I, tissue specific class II, and NAD-dependent class III enzymes. Human HDACs are targets for cancer therapy. In fact, therapeutic efforts with HDAC inhibitors for the treatment of cancer are being pursued and the role of individual HDACs in tumorigenesis is starting to emerge. HDAC1 can also be phosphorylated, ubiquitinated and acetylated. Therefore, we are assessing how different interdependent modifications modulate the biological function of HDAC1.
Our laboratory is therefore pursuing two major projects:

a. The biology of HDAC1 (and HDAC2) and how its post-translational modifications cross-talk and control its activity, also in light of its potential significance as a target for cancer therapy.
b. The regulation of the SUMO pathway by oncoviral proteins.

Research Projects.

Biology of Histone Deacetylase 1, HDAC1 (and HDAC2):
HDAC1 and HDAC2 are deregulated in many cancers and are emerging as the main deacetylases involved in neoplastic transformation. In fact chemical inhibitors of HDACs are a relatively new class of drugs with anticancer potential.
HDACS are not only protein-modifiers, but are in turn regulated by post-translational modifications (PTMs): phosphorylation, acetylation, ubiquitination, SUMOylation, nitrosylation and carbonylation, creating a rational "code" for a differential, context-related regulation.
We have been attempting to decipher a part of the PTM code of HDAC1 and HDAC2: we now know that HDAC1 and HDAC2 are hyperphosphorylated specifically in mitosis in a variety of different cell types and are currently rounding up its biological significance. Concurrently, we have recently observed an HDAC1 serum and growth factor dependent phosphorylation.
Furthermore, we have recently uncovered that conjugation to the two main SUMO paralogues (SUMO1 and SUMO2) has a different outcome on HDAC1 stability and protein turnover in tumorigenic vs non-tumorigenic cells.
Finally, in a collaborative project (with Saverio Minucci and the Pathology Division at IEO hospital), we have been trying to understand why subsets of breast cancers respond differently to HDAC inhibitors.

Viral interplay with key cellular proteins involved in carcinogenesis: the Gam1 adenoviral protein has been an exceptional tool to reveal novel and peculiar viral strategies to bypass host cellular defenses. Recently, our studies have highlighted Gam1 as a model for viral BC-box domain containing proteins, such as Human Papilloma Virus (HPV) oncoproteins, and uncovered a new viral mechanism to degrade host tumor suppressors.
Furthermore, our interest on viral exploitation of the SUMO system continues: we have been focusing on other oncogenic viral proteins interaction with SUMO enzymes, in collaboration with Dr. Chiara Casadio and Dr. Mario Sideri, in one study and Dr. Mohssen Ansarin, Dr. Fausto Chiesa and Dr. Fausto Maffini in another study (HPV-AHEAD: http://hpv-ahead.iarc.fr).
Much scientific evidence is indeed suggesting that pathogen modulation of the host SUMO pathway is quite a common mechanism.

Pubblications

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Bioinformatics and Evolutionary Genomics of Cancer

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PhD. Students: Omer An, Vera Pendino, Shruti Sihna
Visitors: Marco Gentilini, Emanuele Ratti

Activities 2013. Our group studies the effects of genomic instability in the development of human cancer. We tackle this issue using a combination of experimental and computational methods, with the aim of:

1. tracing the progressive acquisition of mutations during cancer development;
2. identifying systems-level properties of cancer genes;

1. Measure of somatic and constitutional genomic instability

In addition to searching for cancer-specific mutations, we exploit deep next generation sequencing (NGS) to re-sequence several thousands single DNA filaments in parallel and unravel different aspects of cancer progression. For example, we developed a procedure for the quantification of somatic and constitutional genomic instability that is based on the detection of random mutations.

We performed an ultradeep screening to identify random modifications that occur in a tiny fraction of cells, even prior to the establishment of the tumoral clone. To account for the occurrence of sequencing errors, we developed a statistical framework that relies on the ultraconserved elements of the human genome as error normalization. Using this method we were able to measure the constitutional genomic instability in individuals with heterozygous mutations in MMR genes, thus suggesting a predisposition of these individuals to acquire the second hit needed for tumor initiation. Our study constitutes the proof of principle for the development of a more sensitive molecular assay of genomic instability.
We further used this feature of NGS to rebuild the proliferative tree of cancer clonal expansion. Mutation frequency indeed reflects the proportion of cells that bear each individual mutation while the number of somatic mutations is informative of the relative occurrence of cell death, cell proliferation, and cell quiescence during the clone formation. Following this idea, we reconstructed the proliferation trees of four colorectal tumors using their mutation profiles. We showed that the majority of the tumor mass in all four tumors is formed of a dominant subclone that started to prevail very early, although its establishment varied over time between and within tumors and seemed to be correlated with tumor genetics and clinical aggressiveness.

2- Systems biology of cancer genes

We undertook a systematic study of the properties of cancer genes in the attempt of rationalizing the genetic heterogeneity of human cancer. We set out to analyze the relationship between the propensity of cancer genes to duplicate (i.e. gene duplicability) and the network properties of the encoded proteins, because connectivity and duplicability are usually indicative of gene fragility towards perturbations. We showed that cancer genes are mostly singletons and tend to encode central hubs at the crossroads of multiple biological processes. Although these properties are rare within the human gene repertoire, they are recurrent within known cancer genes, thus confirming the existence of systems-level properties –not detectable from the individual gene function– that explain the role of these genes in tumor development in terms of systems perturbation. We also discovered that most cancer genes appeared at two time points in evolution: caretakers and tumour suppressors are ancient genes that have orthologs also in prokaryotes, while gatekeepers and oncogenes were acquired with metazoans. These two time points correspond to two main transitions in evolution that led to an increase in complexity of the whole protein interaction network.

Web Servers and Public Databases

a) Network of Cancer Genes: a web resource to analyze duplicability, orthology and network properties of cancer genes (http://bio.ieo.eu/ncg/)

This public resource collects and integrates data on systems-level properties of cancer genes. It provides information on duplicability, orthology, evolutionary appearance and topological properties of the encoded protein in a comprehensive version of the human protein-protein interaction network. NCG also stores information on all primary interactors of cancer proteins, thus providing a complete overview of 5357 proteins that constitute direct and indirect determinants of human cancer.

b) FancyGene: dynamic visualization of gene structures and protein domain architectures on genomic loci http://bio.ieo.eu/fancygene/)

FancyGene is a web-based interactive tool for producing representations of one or more genes directly on the corresponding genomic loci. It is extremely flexible and allows the user to change the resulting image dynamically, to modify colors and shapes and to add and/or to remove objects. FancyGene is a useful tool to draw scientific pictures for scientific publications and presentations.

Publications

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Studying the regulation of chromosome segregation at centromeres, kinetochores and rDNA

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Activities 2013. Our lab studies how replicated chromosomes segregate from the dividing mother cell into its two daughters. As most solid tumors contain abnormal chromosome numbers it has long been hypothesized that chromosome missegregation contributes to cancer initiation and/or progression. By identifying, studying and understanding the proteins involved in chromosome segregation we will be able to convert them into novel cancer biomarkers and new anticancer drug targets.

As the chromosome segregation process is highly conserved from yeast to humans we study it in yeast (Saccharomyces cerevisiae), a model organism that is highly amenable to imaging, genetic, biochemical and cell division (cell cycle) research. Findings made with this species can then be translated to the human cell system.
Segregation of the replicated chromosomes during mitosis depends on the timely activity at two genomic regions: the centromeres and rDNA. Kinetochores, large complexes containing >100 proteins, assemble on the centromeres of each replicated chromosome pair (sister chromatids) to bind (align) the sister chromatids to the microtubules of the mitotic spindle. After the cohesion rings that hold the sister chromatids together are cleaved, the kinetochores move the chromatids along the spindle into the daughter cells. Importantly, one of the last regions of the genome to segregate is the ribosomal DNA (rDNA) array, which is actively transcribed to generate rRNA, ribosomes and ultimately proteins, required to sustain cell growth. Only at the end of mitosis does rDNA transcription become temporarily downregulated, allowing for the condensation and segregation of this region, which completes the chromosome transmission process.

One focus of our lab lies on kinetochore protein Cnn1. Cnn1 (CENP-T in humans) is a centromere-binding protein that inhibits in a cell cycle-dependent manner the interaction between the kinetochore Ndc80 and Mtw1 complexes, which establish the contact between kinetochores and the spindle. We have shown that Cnn1 concentrations at centromeres change through the cell cycle, as directed by phosphorylation via a set of conserved kinases. Cnn1 becomes enriched at centromeres during anaphase (mitotic stage during which chromosomes segregation initiates) resulting in a less compact kinetochore, which allows for an efficient transduction of forces required to move the separated chromosomes. In myriad tumors, CENP-T is overexpressed. Our work with yeast indicates that this pathology disturbs kinetochore structure and function resulting in chromosome missegregation, which may help to drive the cancer transformation process. Using yeast, we have identified a novel and conserved ubiquitin-mediated response pathway that antagonises high levels of Cnn1/CENP-T thereby preventing cells from producing daughters with abnormal chromosome numbers.

We also identified the Rio1 kinase (RioK1-3 in humans) as a novel kinetochore kinase that also regulates rDNA segregation in late anaphase. Rio1 activity represses DNA polymerase I at anaphase onset to halt rDNA transcription and permit condensin recruitment to the region. This promotes the condensation and segregation of the rDNA array into the daughter cells. We have also shown that Rio1 acts similarly at centromeres; a timely inhibition of local transcription by RNA polymerase II allows for kinetochore assembly and condensin recruitment, resulting in a timely attachment of the sister chromatids to the spindle and their subsequent segregation at the metaphase-anaphase transition. By studying how Rio1 directs chromosome segregation we will gain new insight into how this essential kinase underlies chromosome transmission, both in healthy and cancer cells, in which Rio1 is often misexpressed or mutated.

Publications

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Molecular Carcinogenesis and Stem Cell Biology Research

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Activities 2013. Understanding the molecular mechanisms that govern tumor initiation and progression is crucial to improve current cancer treatments. In recent years, increasing evidence supporting the involvement of stem cells in the tumorigenic process has emerged. According to the cancer stem cell (CSC) model, tumor growth is fueled by a small subpopulation of cells with stem cell-like properties, including self-renewal and the ability to produce differentiated progeny. However, these CSCs lack control mechanisms of normal stem cell function and, thus, show unpredictable behavior and uncontrolled growth. Our research is focused on investigating the molecular mechanisms involved in the maintenance of the normal stem cell compartment and how these mechanisms are altered in cancer, in particular, in breast and lung.

We believe that a high-resolution picture of the normal stem cell compartment will allow us to develop new diagnostic, prognostic and patient stratification tools.

We have previously identified a normal breast stem cell molecular signature that is predictive of the biological, molecular and pathological features of human breast cancers. Indeed, we showed that breast cancers can be CSC-rich or CSC-poor, with poor-prognosis (high tumor grade, G3) tumors tending to be enriched in CSC compared to more favorable prognosis (low tumor grade, G1) tumors. By doing so, we have demonstrated that an expansion of the stem cell compartment occurs in breast tumors.

Currently, we are following two separate lines of research, designed to gain a deeper understanding of the molecular mechanisms involved in the maintenance of the stem cell compartment and in tumor progression.

Role of Numb in tumorigenesis

Numb is a well-known regulator of the stem cell compartment. Recently, we have also established that Numb acts as a tumor suppressor in human breast and lung tumors. Our results show that Numb is degraded in ~50% of breast tumors and ~30% of lung tumors. In addition, Numb-deficiency is associated with clinico-pathological parameters of biological aggressiveness and, at least in breast cancer, with poor prognosis. This has led us to hypothesize the existence of a mechanism, caused by the absence of Numb, which subverts normal stem cell homeostasis thus contributing to tumorigenesis. We aim to unravel the role of this protein in tumorigenesis by:

1) Analysing the involvement of Numb in the regulation of the mammary gland stem cell compartment. We have developed an *in vitro* model based on the ablation of Numb expression in mouse mammary stem cells using a lentiviral vector expressing short-hairpin RNAs and an *in vivo* mouse model (K5-Cre/Numbflox/flox), in which Numb expression has been ablated specifically within the basal/ myoepithelial layer of the breast parenchyma, where breast stem cells reside. We are investigating how changes in Numb expression and in its downstream targets (Notch and p53) affect the mammary stem cell compartment.

2) Identifying molecular players causing Numb degradation in human cancers. Aberrant Numb degradation occurs as a consequence of enhanced ubiquitination of the Numb protein. Thus, are examining how the deregulation of specific components of the ubiquitination machinery, in particular E3-ubiquitin ligases that catalyze the transfer of ubiquitin to the protein substrates, are involved in the loss of Numb expression in Numb-deficient tumors. Through a high-throughput RNA interference-based screening approach, we have identified several candidate ligases, the silencing of which affects Numb expression. These negative and positive candidate regulators of Numb expression are currently being validated through high-resolution studies in Numb-defective tumor cells. We aim to identify novel molecular targets for the development of new strategies to treat Numb-deficient cancers.

3) Characterizing the Numb-p53-HDM2 tricomplex. We have shown that Numb can regulate the activity of the tumor suppressor p53. Numb forms a complex with p53 and the E3-ubiquitin ligase HDM2 (also known as MDM2). In the context of the Numb-HDM2-p53 tricomplex, Numb prevents HDM2-mediated ubiquitination and degradation of p53, which translates into increased p53 protein levels and activity. Understanding the interaction between Numb-p53-HDM2 will allow us to design new molecules that can restore p53 function in cancer cells through inhibition of HDM2 activity.

Mechanisms driving tumor progression and metastasis formation.

Most cancer-related deaths occur as a consequence of metastasis formation, a process that is still incompletely understood, and that we remain powerless to control. For example, our ability to completely cure breast cancer depends mainly on early diagnosis and the absence of secondary tumors. Our findings demonstrate that more aggressive tumors are characterized by an expansion of the CSC compartment, arguing for a supportive role of CSCs in tumor progression. However, the origin and identity of the molecular/genetic alterations driving this process are still unknown. We are currently focused on tracing the origin of the genetic lesions responsible for tumor expansion and metastasis formation by i) identifying cancer driver mutations and ii) verifying if these genetic lesions are harbored within CSC compartment.

Our experimental approach combines high-throughput genomics with a technological platform to study CSC biology. Our goal is to determine whether cancer driver mutations present in breast tumors and in their matched metastases are also found within CSCs. Through this approach, we expect to determine whether the metastatic potential of tumors stochastically arises from individual cell clones within the bulk tumor population or whether its origins lie within the stem cell compartment specifically. Any metastasis driver mutations we identify will be analysed for their potential applicability as prognostic markers in the clinic.

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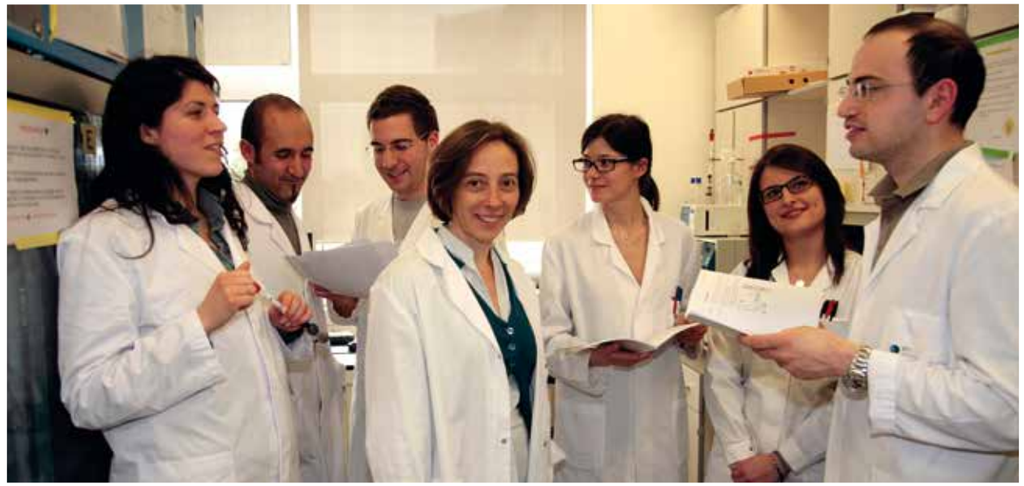
Structural and Functional Studies of the Mitotic Spindle Orientation during Asymmetric Cell Divisions

Marina MAPELLI, PhD

Director



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PhD Students: Manuel Carminati, Sara Gallini
Temporary fellow: Valentina Palmerini

Activities 2013. We are interested in the molecular mechanisms governing asymmetric stem cell divisions, with emphasis on the role of mitotic spindle orientation in determining daughter cells' fate.
The proper execution of asymmetric divisions is crucial in generating tissue diversity during development, and for tissue homeostasis and regeneration of adult organisms. An increasing body of literature supports the notion that certain human cancers arise from abnormalities in adult stem cells asymmetric divisions, altering cell fate and leading to over-proliferation (the so called cancer stem cell hypothesis). It is known that failures in asymmetric divisions occur when pathways controlling the spindle orientation, and hence the position of the cytokinesis plane, are compromised.

To make a cell division asymmetric, the position of the mitotic spindle has to be tightly coordinated to the cortical polarity, so that daughter cells will be properly positioned within the tissue, inherit unequal sets of fate determinants and follow differential fates. This observation sets the stage for our studies, aimed at gaining insight into the structural and functional organization of the molecular machines responsible for spindle coupling to polarity cues during stem cells asymmetric divisions. To address this biological problem, we use a combination of high-resolution X-ray crystallography, biochemical analyses on reconstituted protein complexes and stem cell biology. Using the detailed molecular information delivered by our structural studies, we formulate precise models of how intrinsic properties of individual protein relate to the behavior of the mitotic spindle during asymmetric cell divisions, that we challenge in living cells. An emerging concept in the cancer field is that cancer stem cells may be responsible for relapse and resistance to anticancer therapies. In this view, a clear molecular description of processes underlying asymmetric cell divisions will be instrumental in identifying new stem-cell specific drug targets for therapeutical intervention.

Our activity is organized in three main research lines:

1. Structural and functional characterization of cortical force generators.

   Cortical force generators are molecular motors orchestrating the correct placement of the mitotic spindle within the cell. To achieve this result, they accomplish different tasks: a) they organize contacts with specialized cortical domains; b) they coordinate in space and time pulling forces acting on astral microtubules; c) they transduce cytosolic and extracellular stimuli instructing the spindle orientation. The core components of force generators and the non-canonical G-protein signaling pathway involved in their regulation are evolutionary conserved from nematode to mammals. Their central module consist of heterotrimeric NuMA/LGN/Gαi complexes, assembled on GDP-loaded Gαi species. From a topological point of view, LGN has been depicted as the molecular link between Gαi subunits anchored at the plasma membrane and the microtubule associated protein NuMA. Recently, LGN has also been shown to associate with the actin-binding protein Afadin, hinting at an active role of the acto-myosin cytoskeleton in stabilizing spindle placement in mitosis. We are interested in understanding the molecular events triggering the LGN conformational transition required to assemble and maintain NuMA/LGN/Gαi complexes at the cell cortex.

2. Molecular characterization of the interplay between polarity and cell division plane.

   Our second research line deals with the issue of how force generators are specifically recruited at sites of polarization. In several model systems, cortical polarization is established by the asymmetrical distribution of Par3/Par6/aPKC complexes, which in turn defines the asymmetrical localization of fate determinants. In fly neuroblasts and vertebrate skin progenitors, Par3/Par6/aPKC localize at the apical site, and recruit force generators via an adaptor named Inscuteable (Insc). We have recently solved the crystallographic structure of the LGN/Insc complex, and discovered that Inscuteable and NuMA are mutually exclusive partners of LGN. This unexpected finding challenges the established model of force generators assembly, which we are revising based on the newly discovered properties of the intervening components. An emerging concept is that several cues contribute to define the position of the cytokinesis plane in asymmetric divisions and oriented divisions of epithelial cells. Based on this evidence, to unveil the molecular network coupling force generators to cellular polarity in different environments, we are also pursuing the identification of new tissue specific interactors of NuMA, LGN and Inscuteable.

3. Implications of the mitotic spindle orientation pathway in stem cell asymmetric divisions.

   The genetic pathways affecting the interplay between spindle position and asymmetric divisions have been first discovered in Drosophila neuroblasts, and later documented in skin and neural progenitors. Recent reports highlighted the involvement of oriented divisions in progenitor differentiation during mammary gland morphogenesis. However, very little is known to about the molecular mechanisms sustaining asymmetric divisions in this system, and how they are deregulated in cancers. We started investigating how cortical polarity and spindle alignment pathways affect the asymmetric outcome of mammary stem cell divisions in mice. We also study the relevance of these pathways on the stem cells regenerative potential and proliferation, which we believe will ultimately pertain to breast cancer progression.

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Chromatin Alterations in Tumorigenesis

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Activities 2013.

Cancer cells show global changes in chromatin structure (DNA methylation and histone post-translational modifications), that lead to stable alterations in gene expression and potentially other nuclear functions (such as DNA replication and repair). Unlike genetic lesions, those alterations are reversible since the underlying DNA sequence is unchanged: this fundamental difference between genetic and epigenetic alterations makes the epigenome much more amenable to the development of therapeutic strategies. Indeed, small molecules with the capacity to interfere with chromatin modifying enzymes have antitumor activity. The concept of epigenetic therapy has been clinically validated with the approval by regulatory authorities of a small number of drugs for use in selected forms of cancer. In our view, however, drugs interfering with epigenetic enzymes (such as DNA methyl-transferases and histone deacetylases, the most advanced targets in the epigenetic arena) have been used in the vast majority of cases rather aspecifically, without taking into account the context of chromatin alterations occurring in cancer cells. We surmise therefore that one of the major goals of both basic and applied research in this area should be the search of a set of epigenetic alterations in tumor cells, that dictate sensitivity or resistance to epigenetic drugs.
We have focused therefore our activities on the study of deregulation of chromatin structure/function in cancer with the goals of:

- Identifying sistematically epigenetic alterations in cancer cells;
- To exploit this knowledge to optimize epigenetic therapies towards a more targeted approach.

To fulfill these goals, we have adopted a combination of experimental strategies:

- *Mechanistical analysis of chromatin alterations in cancer*. We have developed new technologies for the study of epigenetic alterations in cancer patients, to reduce the amounts of material required, and to allow access to paraffin-embedded pathology samples: NASeq, and PAT-ChIP. Thanks to these new approaches, we are studying acute myeloid leukemias and breast cancer (where mechanistical insights on how epigenetic deregulation takes place are partially available) as a paradigm of the cancer epigenome.
- *Functional dissection of the role of chromatin modifiers in leukemogenesis*. In parallel, we are undertaking the systematic dissection of the role of individual chromatin modifiers in tumorigesis in murine models of acute myeloid leukemia. By the use of knock-down and conditional knock-out approaches, we are studying the role of histone deacetylases, Polycomb complexes, histone demethylases in both tumor initiation and tumor maintenance.
- *Epigenetic therapy of cancer*. In the same disease model, we are studying the biological and mechanistical effects of epigenetic drugs (histone deacetylase and demethylase inhibitors, DNA demethylating agents). In particular, we have developed new assays for the study of the contribution of different subpopulations of tumor cells to cancer growth, focusing on the role of leukemic stem cells.
- Optimization of anticancer therapies. The know-how and results gained above are being increasingly useful in other settings, to try to exploit the epigenome and its manipulation for the optimization of anticancer therapies. With this goal, we are:
  - Using yeast as a model system (in collaboration with M. Foiani, Project "TYM") studying systematically the synthetic lethal interactions of anticancer and epigenetic drugs, and subsequently validating them in mammals;
  - By quantitative chemical proteomics (in collaboration with T. Bonaldi, Project "TIP"), identifying systematically the cell interactors of anticancer and epigenetic drugs;
  - In collaboration with the Drug Discovery Program of the IEO (TIV), conducting *in vivo* screenings to identify and validate epigenetic targets in leukemias (in collaboration with PG Pelicci), and analyzing the effect of novel epigenetic drugs being developed against chromatin-associated proteins.

Thus, there is an extremely appealing opportunity to perform a mechanistically oriented analysis ("to understand how things happen") that can immediately be applied to better treat the patients ("to try to change things, when they have gone bad"). The ultimate goal: to go towards a group that considers Man as the primary model system.

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Transcriptional Control in Inflammation and Cancer

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Activities 2013. The main objective of the lab is to understand mechanisms that control the expression of inflammatory genes.

Inflammation is a basic response to environmental and endogenous danger signals (such as microbes and cell debris, respectively) that serves an essential homeostatic and therefore beneficial role. At the same time, excessive or unresolved inflammation promotes the development of many disorders, ranging from autoimmune diseases to cancer.

Inflammation entails the induction (and repression) of hundreds of genes whose products contribute to different aspects of the response, such as the recruitment of leukocytes, changes in vascular permeability, the activation of anti-bacterial responses, and eventually the induction of a repair response leading to reconstitution of tissue integrity. An in-depth understanding of such mechanisms may provide the molecular basis for therapeutic targeting of selected transcriptional events. To achieve these objectives, standard biochemical approaches to transcription are integrated with genomics, computational approaches, physics and *in vivo* studies.

Most of the research tackled by the laboratory relates to one of the most important cell types involved in inflammation, namely macrophages. Macrophages are highly specialized cells widely distributed in tissues and active both as immune effectors and as housekeeping phagocytes responsible for maintenance of tissue integrity. Macrophages display a striking heterogeneity that reflects a complex interplay between different micro-environmental signals provided by various tissues (as well as by microbial and endogenous stress signals), and a robust differentiation program that determines macrophage identity. The main objective of the research activity in this unit is to understand how macrophage identity, functional specialization and plasticity are controlled by their specialized genomic organization, which is encoded in mammalian genomes, enforced by specific transcription factors, and modulated by the microenvironment. Within this area we provided the first genome-wide characterization of the genomic regulatory elements (enhancers) controlling inflammatory gene expression in macrophages. We determined a general organizational principle of these enhancers, which consists in the combination of binding sites for ubiquitous, stimulus-responsive transcription factors and binding sites for constitutive cell type-restricted and lineage-determining transcription factors. Specifically, we have found that in macrophages genomic regulatory elements that control inflammatory gene expression contain two minimal elements, namely a binding site for one or more of the transcription factors activated in response to stimulation (such as NF-kB and AP-1), and a binding site for the major transcription factor controlling macrophage specification, Pu.1. This combination allows creating a cell type-specific context within which transcription of inflammatory genes is regulated, thus explaining variability among cell types in the inflammatory gene expression program induced by identical stimuli. Interestingly, part of the enhancers controlling inflammatory gene expression were found to undergo transcription, which may be instrumental to the maintenance of an open chromatin configuration and/or to the production of non-coding RNAs that signal downstream transcriptional events.

Ongoing research in the lab is mainly focused on the characterization of the impact of different environmental stimuli on the functional organization of macrophage genome using both *in vitro* models and ex-vivo analyses on macrophages obtained from tissues and primary tumors.

As part of this effort we are characterizing the role of a panel of chromatin modifying enzymes, which represent potential drug targets, in the control of inflammatory responses. In this area we have reported a few years ago the first description of a histone demethylase involved in inflammatory gene expression. More recent work allowed us to identify a required role of specific histone methyltransferases and histone deacetylases in the control of macrophage responsiveness to inflammatory stimuli.

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Epigenetic mechanisms in stem cell differentiation and oncogenesis

Diego PASINI, PhD
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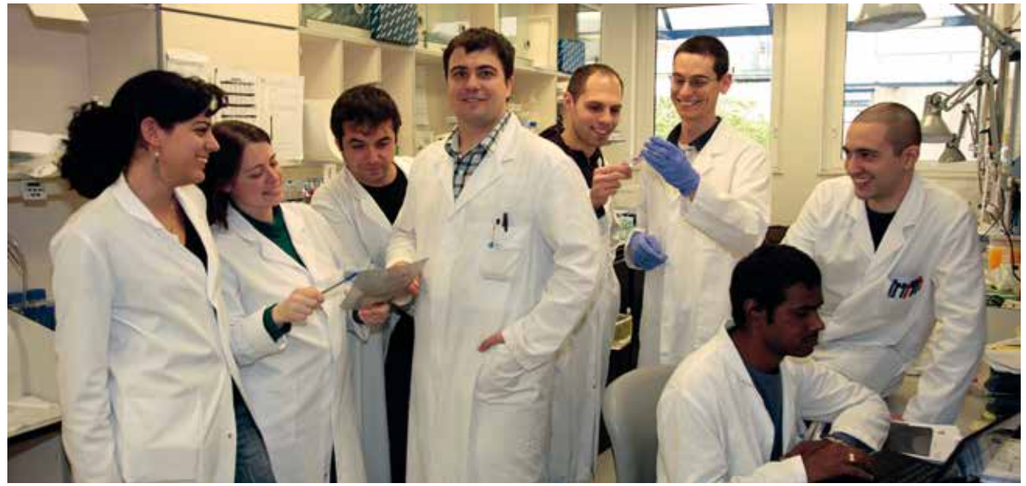

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Undergradueate Student: Cecilia Toscani

Activities 2013. The loss of cellular identity is a common feature of all human cancers. Indeed, the mechanisms that regulate the normal differentiation of cells often play a critical role in the development of cancer. Organisms' development and tissues homeostasis is achieved by a precise control of the fate of differentiating cells. Such regulation is influenced by several cell autonomous and non-autonomous stimuli that are translated by the establishment of specific transcription programs that allows a correct fate determination. In the cells, the DNA is packed in a condense structure celled chromatin that regulates all its activities (i.e transcription, splicing, replication, chromosome segregation, etc. etc.).

Such level of regulation, which is an additional layer above the genetic sequence an therefore is defined as "epigenetic", is controlled by a plethora of enzymes and adaptor proteins that modify the local chromatin environment regulating the establishment of specific transcription outcomes or by regulating specific nuclear activities. Importantly, these proteins are frequent target of genomic alterations in many different cancer types (i.e. mutations, deletions, translocations and amplifications), which point at a selective pressure that alter the epigenetic state of normal cells during cancer development.

The work of our laboratory aims to characterize of the molecular mechanisms behind the activity of chromatin remodellers in normal and pathological contexts as well as to study their role in different neoplastic environments. To achieve this, we use cell culture and *in vivo* approaches that takes advantage of mouse genetics to elucidate the role of chromatin modifiers in the development of tumours and their potential use as therapeutic targets. In addition, to better comprehend the molecular basis of cancer development, maintenance and evolution, we combine the biochemical characterization of multiprotein complexes with transcription and location high-throughput sequencing analysis to understand how histone and DNA modifications control transcription and genomic integrity in normal and pathological conditions, defining new molecular circuits that are relevant in oncogenesis.

Publications

Piunti, A., Rossi, A., Cerutti, A., Albert, M., Jammula, S., Scelfo, A., Cedrone, L., Fragola, G., Olsson, L., Koseki, H., Testa, G., Casola, S., Helin, K., d'Adda di Fagagna, F. and Pasini, D. (2014) Polycomb proteins control proliferation and transformation independently of cell cycle checkpoints by regulating DNA replication. Nature Communications. in press

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Biology and Signal Transduction of Normal and Cancer Neural Stem Cells

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Technician: Daniela Osti

Activities 2013. Our research is focused on two major specific areas of neuro-oncology, glioblastoma (GBM) and brain metastases.
Malignant gliomas and metastatic cancer with central nervous system involvement are the most common forms of adult brain cancer with a high recurrence rate such that more than 90% of individuals die within two years of diagnosis. Emerging evidences in tumor biology validate the hierarchical organization of tumors as abnormal tissues originating from and maintained by a subset of cells, termed cancer stem cells (CSC) due to their "stem cell-like" nature.

The demonstration of GBM CSC existence dates back more than 10 years ago; however, no marker or pattern of markers is still sufficiently robust to definitively identify them. With respect to brain metastasis, the existence of metastasis-initiating cells (MICs) has not yet been proved, although some evidences suggest that these cells might be found within subpopulations of CSCs.
To understand the molecular biology underlying the development of these type of brain cancers, our projects aim to: i) identify novel molecular determinants involved in GBM generation and progression, that could be used in clinical applications; ii) identify specific molecular alterations in brain metastases; iii) study of the relevance of the blood-brain barrier and/or the specific niche in brain metastases formation.

Current research projects

1. CLIC1 (Chloride intracellular channel 1) function in human GBM

   Recently, the laboratory has been focusing on the role of chloride intracellular channel-1 (CLIC1) in human GBMs. We have demonstrated that CLIC1 is over-expressed in GBMs, it clusters within GBM mesenchymal subtype and its expression inversely associates with patient survival. We have shown that CLIC1 silencing in CSCs isolated from human GBM patients negatively influences both proliferative capacity and self-renewal properties *in vitro* and impairs their *in vivo* tumorigenic potential. We are now evaluating how CLIC1 can exert its function.

2. Biological function of CLIC1 secreted protein in human GBM

   In addition to the increasingly recognized role of CLIC1 as a potential tissue marker for different tumor types, including GBMs, CLIC1 has been identified as a secreted protein and detected in exosomes released from different cell types. CLIC1-containing exosomes have been isolated and characterized also from biological fluids, such as human plasma and human urine. Two recent studies defined an important role for CLIC1 as a potential tumor marker: CLIC1 plasma levels are considerably higher in nasopharyngeal and ovarian carcinoma patients compared to samples from healthy controls. Our laboratory has already established a protocol for exosome purification. We aim to understand if and how exosomes secreted by GBM cells express CLIC1 and the biological functions exerted by CLIC1-expressing exosomes.

3. CLIC1 and microRNAs

   Basing on our recent findings of CLIC1 as novel regulator of GBM progression, promoting CSCs proliferation, we are performing large-scale analysis of CSCs isolated from human GBM patients to identify CLIC1 downstream effectors, among which we found microRNAs already known to be involved in GBM progression and aggressiveness.
   Our aim is to identify a signature of GBM drivers that could help to develop new therapeutic strategies, more effective and less dangerous for the patient.

4. Brain Metastasis

   The metastasis-initiating cells have not been identified yet, as well as the mechanisms through which those metastatic cells disseminate. What is clear is that among the tumor population there are "brain-seeking" clones endowed with the ability to leave the site of the primary tumor, to cross the blood-brain barrier and then colonize the brain.
   We aim to isolate human MICs first setting up an *in vitro* model consisting of immortalized brain endothelial cell line (bEnd5) that create a monolayer resembling the tight blood-brain barrier. Next we will select for clones that have the capacity to pass through the BBB to be distinguished from those that are not reaching the brain.

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Setti M, Savalli N, Osti D, Richichi C, Angelini M, Brescia P, Fornasari L, Carro MS, Mazzanti M, Pelicci G. Functional Role of CLIC1 Ion Channel in Glioblastoma-Derived Stem/Progenitor Cells. J Natl Cancer Inst. 2013 Nov 6;105(21):1644-55.

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Molecular mechanisms of cancer and aging

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Activities 2013. One of the challenges for the next decade is to understand how distinct, simple molecular functions may be part of complex pathways and systems, how multiple systems may come together to control complicated cellular behaviours, and how alteration of this composite molecular machinery may ultimately lead to cancer. Our laboratory is studying these molecular mechanisms/interactions with research into the regulation of cell division and proliferation, the control of DNA transcription and replication, the role of tumour-associated oncogenes and suppressors in tumour development and progression, and the links between cancer, metabolism and aging.
Accumulating evidence suggests that only rare cancer cells endowed with self-renewal properties, the cancer stem cells (CSCs), have the capacity to maintain tumour growth; thus, genetic targeting of relevant CSC-specific molecular pathways maybe the way forward to defeat cancer, as their disruption could lead to both the unambiguous demonstration of the existence of CSCs and their role in tumorigenesis. However, the relevant biological properties of CSCs and the underlying primary molecular mechanisms are still little known, thus a large part of our efforts is specifically devoted to the characterization of normal and cancer stem cells (SCs), and to study whether common mechanisms are controlling the growth and maintenance of both these types of cells across different normal and cancer tissues. To this end, we have generated accurate models of carcinogenesis in mammals, creating, in these model systems, mutations that mimic those that occur spontaneously in human cancers (especially leukaemia and breast). These model systems are used in combination with primary patient derived samples to identify biological markers of disease and to develop innovative strategies to target CSCs in a clinical setting.
Our studies are supported by state of the art technologies and an experienced bio-computational team.

In the course of 2013 we have investigated:

1. Biological and molecular mechanisms underlying the behaviour of normal and cancer SCs. Our experimental approach is based on the purification of normal and cancer SCs from the same tissues and on the biological and molecular analysis of self-renewal mitotic divisions.
2. Role of quiescence, DNA damage repair, and reprogramming in tumour progression and relapse. The tumour suppressor p53, the cell cycle inhibitor p21 and the oncogene Myc have been shown by our group to have a key and specific role in these events, in both breast and haematopoietic SCs. SC unique mechanisms of DNA damage repair appears to depend on the up-regulation of the cell-cycle inhibitor p21, which in turn leads to inhibition of apoptosis and symmetric SC division as a consequence of the down-regulation of p53. Reprogramming of more differentiated cells into SCs appears to depend on the deregulation of Myc expression. Both phenomena seem to rely on loss/inhibition of p53 activity. We are now further investigating these molecules and their interdependence in CSCs, as well as ways to target them for therapy.
3. The molecular basis of chemoresistance in acute myeloid leukaemia (AML) through next generation sequencing. We are testing the hypothesis that relapse acquired chemoresistance is due to the selection of rare tumour cell populations harbouring specific genetic and/or epigenetic mutations. Functional comparison between primary and recurrent tumours may allow the identification of markers predictive of therapy response.
4. Role of cooperative events that lead to the development of cancer. Often, oncogene expression *per se* cannot initiate or sustain cancer development and progression; it may require the accumulation, inside a cell, of other genetic and epigenetic changes, each conferring a selective advantage to the cell at a specific stage of tumorigenesis. Cytogenetically normal AMLs (50% of all cases) are a heterogeneous group whose treatment prognosis depends on the mutation status of different genes, in particular FLT3 (Fms-related Tyrosine Kinase 3) and NPM (Nucleophosmin). Mutations in these genes are frequently associated; patients with both mutations have a poorer prognosis than those only bearing the mutated NPM (NPMmut) and a better prognosis than those with the FLT3 (FLT3-ITD) mutation alone. We generated a novel transgenic mouse model of NPMmut-dependent leukaemia to study the effects of the combination of the two mutations on leukaemia development. Our data show that NPM and FLT3 mutations efficiently cooperate in inducing AMLs in mice and that, combined, are sufficient to initiate and promote leukaemogenesis. Next-generation sequencing (NSG) is also a powerful tool for the discovery of genetic alterations at high resolution. To identify gene mutations that might cooperate with PML-RARA in the process leading to acute promyelocytic leukaemia (APL, a distinct AML subtype), we have performed whole-exome sequencing of 5 leukaemias that developed in PML-RARA transgenic mice and of 11 patients' PML-RARA expressing leukaemias. Our results suggest that different myeloid leukaemias, including APLs, share the same subset of cooperating mutations and that specific initiating mutations may interact with a common pool of highly heterogeneous, yet phenotypically equivalent, cooperating mutations. Sequencing of additional AMLs is needed to completely define the pool of cooperating mutations in AMLs.
5. Replication origins and replication stress in cancer. A correct execution of the DNA replication program is crucial for cell division and for limiting cancer risk by preserving genome integrity.
Human DNA replication depends on the activation of thousands of origins; we found evidence that suggests that their distribution/timing varies between specific cell types or cell states, and that oncogenes induce alterations of the replication program, triggering replicative stress and DNA damage.
6. Longevity and cancer. Aging is associated with a number of events at the molecular, cellular and physiological levels that might influence carcinogenesis; indeed, cancer and aging can be regarded as two different manifestations of SC specific handling of DNA damage without undergoing apoptosis or senescence: both processes are the effects of a specific tumour suppression mechanism that limits SC lifespan but results in accumulation of cellular damage. Understanding these events can help cancer prediction and treatment.
7. Metabolism and cancer. There is growing awareness that diet and environmental factors have a profound effect in the initiation, promotion, and progression of cancer;

our group is examining these factors in animal models and human samples. In the course of last year, we have investigated whether being overweight or obese affects breast cancer outcomes. Specifically, we assessed the prognostic role of increased body mass index (BMI) on a consecutive series of non-metastatic HER2+ patients treated at our institution before the introduction of adjuvant Trastuzumab, separately analysing oestrogen receptor-positive (ER+) and negative (ER-) HER2+ cases. We found that obesity significantly correlates with worse overall survival and cumulative incidence of distant metastases in ER-/HER2+ breast cancer. Our results suggest that the biology of breast tumours may determine individual susceptibility to obesity and should be taken into account in the design of dietary intervention trials in breast cancer.

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Immunobiology of Dendritic Cells and Immunotherapy

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Activities 2013. Dendritic cells (DC) comprise a family of professional antigen presenting cells unique in their capacity to modulate T cell responses. DC play a primary role in pathogen protection, in central and peripheral tolerance and in anticancer immune responses. Understanding basic mechanisms governing DC function in biology and pathology can be instrumental to unravel how an immune response is initiated and to shape new protocols for immune intervention. In our unit we study the interaction of DC with bacteria both *in vitro* and *in vivo* with the aim to study the interaction between the host and the intestinal flora (microbiota) and to establish new protocols for cancer immunotherapy.

It is becoming increasingly clear that the interaction with the microbiota can control several essential functions of our body, such as the development of the immune system, the digestion of complex macromolecules, the control of intestinal homeostasis and the detoxification of carcinogens. Hence, understanding how our mucosal immune system copes with the millions of microorganisms that inhabit our gut is fundamental to unravel important physiological functions of our body and how deregulations can lead to tumor development.

In the laboratory we have two major lines of research, one is aimed at studying how microorganisms influence tumor development and how we can exploit them for the generation of new immunotherapy approaches of cancer. The other line of research deals in understanding basic mechanisms of host-microbiota interactions with particular focus on inflammatory bowel disease.
Within cancer, we try to use bacteria to fool the immune system and to target specifically tumor cells with vectors that have not induced immune evasion mechanisms. For instance, we have generated recombinant bacteria that express on their cell surface antibodies that target the bacteria specifically to tumor cells, in this case lymphoma cells. These bacteria also carry payloads of enzymes important for the catabolization of prodrugs into drugs for the local delivery of active antitumor compounds. These bacteria have lost the ability to enter cells that are not expressing the targeting antigen, thus generating a bullet that will target only tumor cells. Once inside the cells these bacteria express the prodrug converting enzyme (herpes simplex virus thymidine kinase) and in the presence of the drug (gancyclovir) generates the active compound that kills only the cells expressing the prodrug converting enzyme. With this technique we achieved complete regression of tumors also in immunodeficient mice.
In the second line of research, as a dysregulation in bacterial handling has been associated with the development of inflammatory bowel disease, we want to understand the basis of bacterial handling in the gut. We found that even though dendritic cells encounter bacteria in the gut they are inhibited in their inflammatory potential.
This characteristic is conferred by the local microenvironment and in particular by epithelial cells. We also studied the molecular factors involved and identified TGF-b, retinoic acid and TSLP as important mediators. Interestingly all of these factors are highly reduced in epithelial cells isolated from inflammatory bowel disease patients. We then analysed the microbiota in patients with metabolic diseases and found that obese patients can be divided according to the richness of their microbiota in two categories. One of the two is more prone to develop metabolic disorders, indicating that the microbiota composition is important to predict susceptibility to disease in prone individuals.

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Stem Cell Epigenetics

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Computational PhD student: Vivek Das

Activities 2013.

Our lab pursues the following lines of research:

- Modeling disease through cell reprogramming. We harness the unprecedented potential of cell reprogramming to develop physiopathologically meaningful models of both neurodevelopmental disorders and cancer.
- Epigenetic regulation of neural fate. We study the role of two major pathways of chromatin regulation, methylation of histone H3 on lysine tails 4 and 27, on the acquisition of neuronal fate, with a special focus on corticogenesis.
- Aberrant genome programming in brain cancer. Consistent with the role of Polycomb-mediated H3K27 methylation in lineage choices, this line of research investigates the onco-genic counterpart of the acquisition of neural fate, focusing on malignant gliomas, combining advanced murine models with the analysis of human tumors.

- Epigenetics of cell fate reprogramming. Finally, consistent with the role of the Trithorax and Polycomb families in cell fate transitions, we study their contribution to cell fate reassignment, both for induced pluripotency and direct transdifferentiation.

1. Modeling disease through cell reprogramming

One of the most tangible outputs of somatic cell reprogramming has been a paradigm shift in our ability to model human diseases, for which fundamental limitations have been so far: i) the scarce availability of primary diseased tissues, which is particularly salient for disorders of the nervous system; and ii) the difficulty of reconstructing disease history, which is salient also for cancer pathogenesis.
We are thus harnessing the unprecedented potential of cell reprogramming to develop physiopathologically meaningful models of both neurodevelopmental disorders and cancer, thereby aiming at the dissection of the genomic versus epigenomic components of their pathogenesis.
Specifically, within neurodevelopmental disorders we focus on a unique range of intellectual disability syndromes (including autism spectrum disorders) caused by mutations or dosage alterations in epigenetic regulators and transcription factors.
As far as cancer is concerned, we focus on ovarian cancer, a critical example of unmet medical need due to the lack of relevant cellular models and the very limited understanding of the developmental aberrations that underlie its pathogenesis.

2. Epigenetic regulation of neural fate

The methylations of histone H3 on lysine tails 4 and 27 (H3K4me and H3K27me), respectively mediated by the Trithorax (Trx) and Polycomb (PcG) protein families, are central regulators of the establishment and maintenance of differentiated cell states. In particular, the central nervous system has become a paradigm-setting model to define the functional relevance of H3K27me for cell fate transitions, with the realization that this mark is dynamically regulated throughout neuronal differentiation by the interplay of methyltransferases and demethylases.
Following the identification of JMJD3 as the first enzyme that antagonizes Polycomb silencing by demethylating H3K27 (De Santa et al. Cell 2007), our key contributions include the characterization of its essential role for the early neural commitment of embryonic stem cells (Burgold et al. PLoS One, 2008), and the discovery that aberrations in H3K27 methylation caused by JMJD3 loss in neural precursors impact the late maturation and function of neuronal circuits (Burgold et al. Cell Reports 2012). We are now using conditional approaches to study the role that H3K27me and H3K4me play in the expansion of neural stem cells and the sequential acquisition of neuronal fate during murine corticogenesis (Testa Bioessays 2011).

3. Aberrant genome programming in brain cancer

Consistent with the role of Polycomb in lineage choices, alterations in H3K27me figure prominently among the epigenetic aberrations of cancer. Furthermore, the majority of genes that are CpG hypermethylated in cancer are pre-marked by H3K27me3 in embryonic stem cells, suggesting that the Polycomb-dependent gene expression program that orchestrates development in normal cells is hijacked in cancer cells as the main template for cancer DNA methylation.
Hence, this line of research in the lab investigates the oncogenic counterpart of the acquisition of neural fate, focusing on malignant gliomas with the aim of elucidating the epigenetic basis of the lineage aberrations that characterize this disease. Specifically, we test the proposition that loss of the physiologic regulation centered around H3K27me3 is important for the initiation and/or maintenance of gliomas, combining the conditional modulation of this epigenetic axis in advanced murine models of glioblastoma with its functional dissection in primary cells isolated from both primary and recurrent human high grade gliomas.

4. Epigenetics of cell fate reprogramming

Consistent with the role of the Trithorax and Polycomb families in cell fate transitions, widespread changes in H3K4 and H3K27 methylation have been shown to accompany transcription factor-induced cell fate reassignment.
Our objective is to dissect functionally their relative contribution to cell fate reassignment, using both experimental paradigms of induced pluripotency - where fibroblasts are reprogrammed to induced pluripotent stem cells (iPSC) – and direct transdifferentiation, where fibroblasts are reprogrammed to induced neuronal cells (iNCs). Our recent contribution includes the discovery that in iPSC generation, Polycomb-mediated H3K27 trimethylation is required on a highly selective core of Polycomb targets, setting stage for defining the functional relevance of this core gene subset in other physiopathological paradigms of cell reprogramming, including cancer (Fragola et al. PLoS Genetics 2013).

Publications

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Mechanisms Controlling Chromosome Segregation

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Activities 2013. My laboratory is interested in understanding the molecular mechanisms that control cell division, the process by which a cell generates two genetically identical daughter cells. For this to occur, cells need to replicate their chromosomes and faithfully distribute each copy into the daughter cells. To ensure that each cell receives only one copy of each chromosome, cell cycle events need to be coordinated in time and space. If these mechanisms fail then genomic integrity is lost, which can lead to cell death or the acquisition of proliferation abnormalities. In particular, we focus on mitosis, the phase of the cell cycle during which replicated genomes are separated and packaged into daughter nuclei. We study chromosome segregation to better understand how errors made during this process contribute to the transformation of a healthy cell into a cancerous one.

Mitosis

Mitosis is comprised of a highly choreographed sequence of events that lead to dramatic cellular reorganization. Although it is a continuous process, cytological changes allow it to be arbitrarily divided into sub-phases including prophase, prometaphase, metaphase, anaphase and telophase. Three major transitions take place during mitosis: 1) the G2/M transition, where entry into mitosis is controlled; 2) the metaphase-anaphase transition, at which sister chromatid separation is triggered; and 3) the M/G1 transition, at which cells reverse the processes that led to mitotic entry and reset the conditions for a new round of cell division. In higher and lower eukaryotes transitions 2) and 3) define mitotic exit. These are the focus of our laboratory.

Metaphase-anaphase transition: Chromosome segregation

To ensure the correct transmission of chromosomes during cell division, replicated chromosomes (sister chromatids) must first be separated and then segregated between the daughter cells. Sister chromatid segregation occurs in anaphase and is triggered by the dissolution of the cohesin complexes that hold the sister chromatids together. Cohesin is cleaved by separase whose activity is restrained by securin. Securin, in turn, is controlled by a surveillance mechanism, the spindle assembly checkpoint (SAC). The SAC is a signaling pathway that delays sister chromatid separation until all sister chromatids have correctly attached to the microtubules of the mitotic spindle. When the SAC is satisfied cells can proceed into anaphase. Progression through anaphase is mediated by mitotic spindle activities. A focus of the lab is to obtain a molecular understanding of the regulatory networks that control sister chromatid separation and spindle dynamics. We recently found a budding yeast mutant that cannot proceed through anaphase regardless of having degraded securin and cleaved cohesin. Elucidating the molecular defects characterizing our double mutant will allow us to define a novel pathway that is essential for sister chromatid segregation.

M-G1 transition: Mitotic exit

Mitotic exit initiates with the down-regulation of cyclin-dependent kinase (CDK) activity, a family of kinases whose activity controls cell cycle progression. Next, the phosphate groups that CDKs added to their targets to allow cells to enter mitosis must be removed so that the cells can exit mitosis. During my postdoctoral work in Dr. Amon's laboratory I found that in budding yeast, the Cdc14 phosphatase is important for both CDK down-regulation and the reversal of mitosis-promoting phosphorylation events. We also showed that Cdc14 activity is controlled by changes in its subcellular localization. The phosphatase is sequestered in the nucleolus by its inhibitor Cfi1/Net1 for much of the cell cycle. At anaphase, two regulatory networks; the Cdc Fourteen Early Anaphase Release network (FEAR) and the Mitotic Exit Network (MEN) sequentially release Cdc14 from Cfi1. This sequential activation of Cdc14 triggers, in a wave-like manner, the dephosphorylation of distinct populations of CDK substrates and thus mitotic events at different stages of anaphase. Indeed the FEAR and MEN networks coordinate mitotic exit with different cell cycle events. When I started with my own laboratory I continued to work in this area of research because critically important questions regarding the control of exit from mitosis have remained unanswered. In particular, I wished to (1) Determine how Cdc14 becomes inactivated after completion of mitotic exit, and (2) Understand how the Cdc14-Cfi1 interaction is regulated.

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Educational Programs

IEO Education

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Daniele PIACENTINI
Management Coordinator

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Executive Committee: Annalisa Ariesi, Francesco Bertolini, Roberto Biffi, Bernardo Bonanni, Fausto Chiesa, Marco Colleoni, Giuseppe Curigliano, Pier Paolo Di Fiore, Luisa Lanfrancone, Angelo Maggioni, Giorgio Magon, Oliviero Rinaldi, Giulia Veronesi, Giuseppe Viale
Internal Education and Training Activities: Elena Mazzoleni, Ombretta David, Ferdinando Pastrello
External Education and Training Activities: Lucia Zigliani, Anna Brandovardi, Luisa Bordoni (since January 2014)

Scientific Committee for Italian CME Accreditation: Fausto Chiesa (coordinator), Danuta Lichosik, Rita Passerini, Mario Sideri, Giuseppe Testa

The year 2012 saw the implementation of several activities of IEO Education, which was set up to coordinate all IEO educational and training activities related to patient management and clinical research, integrate them in an innovative manner, and thereby promote, both internally and externally the Institute's knowledge.
The main areas of actions are a) Clinical Science Seminars in Oncology with at least one meeting per month with renowned speakers to visit IEO both for the training of young doctors and for networking; b) the revision of the Grand Round created by Professor Veronesi in order to encourage the participation of all the healthcare staff; c) the design of online surgery courses (e.g. the Esagon Biennial Course), providing education and training courses online and on demand with a considerable scientific impact; d) the monthly publication of the IEO Edu newsletter designed to circulate and promote the main scientific and training events, e) the launch of the new catalogue of IEO Web Education with seven courses on: Early Glottic Cancer, Management of Clinical Studies, Counseling in Medicine, Clinical Risk Management, Breast Reconstructive Surgery, Patients Radioprotection, Primary Nursing, two of them are in English. The English version of the Italian courses will be available by the end of 2013. Other three online courses (on urology, gynaecology, and pain treatment) will be released by June 2013.

An ad hoc scientific committee for the Italian CME accreditation was established. The following experts serve on this committee: Fausto Chiesa (coordinator), Danuta Lichosik, Rita Passerini, Mario Sideri, and Giuseppe Testa. This is a committee directly referring to the IEO legal representative and to the Italian Ministry of Health. It has the task to evaluate CME requirements as well as to monitor IEO events with CME accreditation.

IEO Education has divided its internal and external activities into ad hoc scientific programs handled by especially appointed program coordinators.

Internal education and training activities

The hospital education and training activities in 2013 were:
- 59 accredited CME courses.
- 39 non-accredited CME courses.
- 11 behavioral courses linked to needs arising from career development plans, during the annual staff evaluation.

The accredited courses produced a total of 1617 CME credits (1473 credits in 2012).
The number of participants totalled 1128 for scientific courses and 206 for behavioral courses.
Regarding participation in scientific congresses, a total of 425 participants were registered, of whom 190 as listener, 133 as speaker, 102 as intern/fellow.

External education and training activities

In 2013, 46 educational activities (courses, meetings, and congresses) were organized by the European Institute of Oncology. Of these:
- 15 events had Italian CME accreditation,
- 31 events had no CME accreditation

The total number of hours invested in external educational activities was 705. The total number of attendees (i.e., general practitioners, specialists, and other health care professionals/providers) amounted to 1937 with over 90% coming from national and international institutions. Based on evaluation questionnaires, the satisfaction rate was 88,14%.
Participants in IEO education and training activities gained 4190 Italian CME credits.

Following are the main educational activities organized in 2013:
- Milan Breast Cancer Conference
- Breast Cancer: Oncologic and Reconstructive Surgery. Interactive course with live surgery - 3D during live surgery as technological innovation.
- Esagon Biennial Course: a 2-week residential and online course with live surgery and theory sessions.

Esagon educational programmes were slightly modified and the following two different types of courses were set up:
- Program 1 focusing on ovarian cancer management, including 6 weeks in the OR with the surgical team of the Divisions of Gynaecology and Abdomino-pelvic and minimally invasive surgery and 1 week with theory and live surgery sessions;
- Program 2 focusing on gynaecologic oncology surgery, comprising 4 weeks in the OR with the Division of Gynaecology.

The IEO School of Robotic Surgery organized 7 courses in 2013, i.e. five basic courses on thoracic, abdomino-pelvic and minimally invasive, H&N, and gynaecologic oncology robot-assisted surgery, two advanced courses in urology (on robot-assisted prostatectomy and nephrectomy), and one for OR nurses.

SEMM - European School of Molecular Medicine

Pier Giuseppe PELICCI MD, PhD
Scientific Director

Domenico TRIARICO
Administrative Director

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Graduate Office: Francesca Fiore (coordinator), Veronica Viscardi (Students' administrator)
Events coordinator: Sabrina Frata

The European School of Molecular Medicine

The mission of the European School of Molecular Medicine (SEMM) is to promote the training and research of young scientists in the emerging sectors of biomedicine with a special focus on Molecular Oncology and Human Genetics.
SEMM collaborates with two Italian Universities, University of Milan and University of Naples Federico II, to create its training programmes and operates within research centers of excellence bridging together higher education and front-line research training.

SEMM is currently running five PhD programs: Molecular Oncology, Human Genetics, Computational Biology, Medical Nanotechnology, Foundations of Life Sciences and Their Ethical Consequences, and a post doc program.
The faculty of the school includes 34 scientists, eight of which are also professors at the University of Milan.

PhD programs: the characterizing traits of the PhD programs are their strong interdisciplinary traits, the international dimension and the training platform.
Training includes intensive laboratory work for the development of technical skills and attendance to specifically designed courses for the acquisition of new theoretical tools.
Currently, 153 are the students enrolled at the PhD programs 32 of them are foreigners coming from 16 different countries from Europe (Albania, Austria, Bulgaria, Georgia, Germany, Greece, Lithuania, Poland, Serbia), and other countries (Canada, China, Kenya, India, Iran, Nigeria, Turkey). Since SEMM started its activity, 197 students got graduated and 90% of them found a new position within one year from the graduation. The vast majority of them (75%) continued their scientific career with a post doc position.

Post doc program: the program is a project co-funded by the European Commission under the FP7-Marie Curie Actions – People program, which aims to support "International Mobility for non-resident Italians and foreigners". It is designed to boost the career of post-docs and to encourage them to become successful and independent scientists.

The project lasts 5 years (2009-2014) during which SEMM enrolled 32 post docs, 20 of them were foreigners coming from Egypt, France, Germany, India, Japan, Netherland, Russia, Spain, Turkey, USA. Currently all enrolled post docs under this project concluded the program. We are now starting the recruitment for the same program under a new EU funding.

Training courses and seminars

During 2013 27 training courses and 64 scientific seminars were organized. The SEMM faculty, with the support of 10 visiting professors, held the training courses for PhD students. Courses covered both basic knowledge, such as Scientific Methodology, Molecular Oncology, Biochemistry, and specialized/advanced courses specific per each educational program.

Seminars are held by internationally recognized scientists from around the world and cover a wide range of topics related to the subjects of the educational programs, such as Molecular Oncology, Immunology, Structural Biology, Genomics & Proteomics, Network Biology, Bioinformatics, Nanotechnology, Bioethics.

TTFactor and IEO Foundation

TTFactor Srl, the Technology Transfer Company

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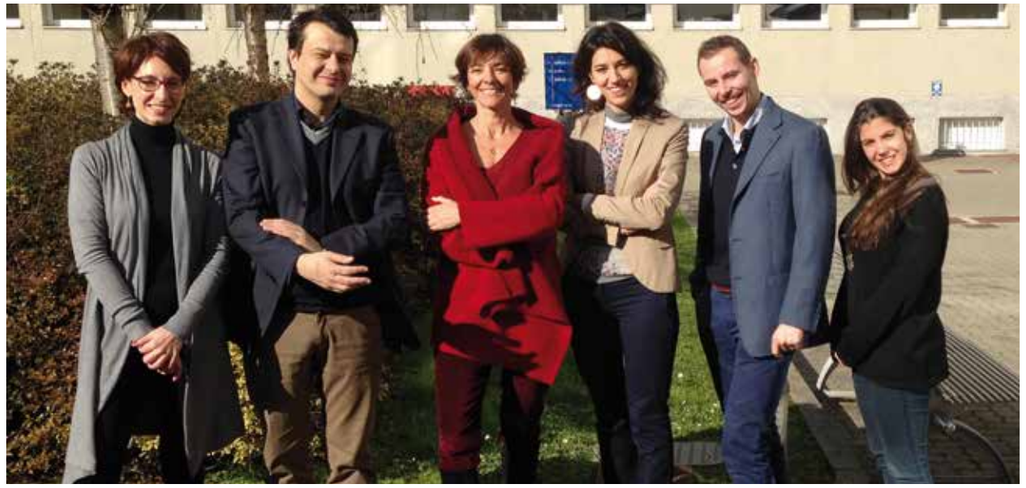
TTFactor is the technology transfer company of the European Institute of Oncology (IEO) and the FIRC Institute for Molecular Oncology (IFOM). Its mission is to support researchers and clinicians in evaluating the commercial potential of their research and promoting relationships with industry to foster further application and development of their research results and inventions. Typical TTF activities include technology scouting, patents filing and management, licensing, sponsored research and spin off creation.
The Company is composed by a team of professionals with qualified technical/economic/legal background (PhD, MBA, LLM) as well as industry experience (pharma & biotech); a Board of Directors composed by the representatives of IFOM and IEO, together with highly reputed international industry and technology transfer professionals, as well as a Business Development Advisory Board chaired by the Director of Applied Cancer Science at MD Anderson Cancer Center.
This team of experts has been created to serve scientists and ensure both Institutes that their intellectual properties are valued in accordance with fair principles, that means on the basis of their impact on patient's care and their ability to become commercial products attractive for the industry.

Activities 2013.

During our fourth year of operations, we intensified internal service to faculty, increasing invention disclosures, patenting and signing numerous contracts for information and material exchange with top companies worldwide.

In 2013 we successfully negotiated and closed important deals with two large investors, who committed themselves to incubate some of our patented products. If the incubation phase is successful we will finalize licenses and a spin off company may be created to carry the projects forward with potential significant return for IEO.



We have built a healthy and technologically wide patent portfolio that forms the basis for future license and spin offs transactions through internally scouting the best patentable ideas from scientists:

- 20 new invention disclosures received this year,
- 3 new patents filed,
- 8 extended and
- 1 abandoned.

Now the portfolio includes: 16 patent families and two trademarks (Smartfood and International CardiOncology Society).

We continued supporting the scientific excellence of IEO by collaborating with for profit counterparts benefiting internal researchers:

- 4 new sponsored research agreements with pharmaceutical and food industry partners and 1 co-development agreement with an Italian academic spin-off in the probiotic field,
- 5 material transfer agreements,
- 16 non-disclosure agreements and
- 6 research tools licensing deals and 1 out-licensing agreement of cell lines.

Consulting to Centro Cardiologico Monzino on all aspects of intellectual property and business development also yields important progress on applicative research outcomes.

The technology transfer model adopted by IEO has become a unique example in Italy attracting much attention and invitations in several events or seminars at Assobiotec biotech week, Filarete Healthy Start-up week, Recordati "R&D Day", Alma Graduate School in Bologna, Future Camp, Meeting Ambrosetti, Bocconi University and University of Milan. Furthermore we have been a technology transfer case study for the EU financed FinKT project (Financing Knowledge Transfer in Europe) led by University of Bologna.

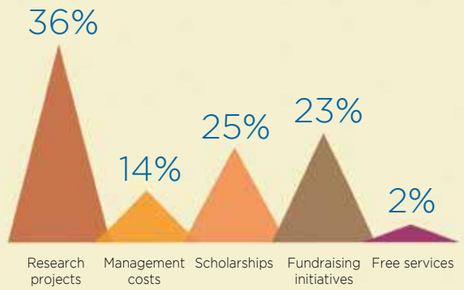
Starting from November 2013, we host a stageur from Bocconi University who started an internship period as part of her university study course in Innovation Management before graduation.

IEO Foundation

Support research. Help fight cancer. Make a donation.

IEO Foundation was established in 1992 to support the European Institute of Oncology in the development of clinical and experimental research and training to researchers, through several activities: Special Events; Direct Marketing; Major Donors and legacies; Charity Shops.

In 2013 we raised
2.965.287 euro
thanks to our donors



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Publications, Clinical Trials, Ongoing Grants and Seminars

Full Papers 2013

ALADOWICZ E., FERRO L., VITALI G. C., VENDITTI E., FORNASARI L., LANFRANCONE L. M.	Molecular networks in melanoma invasion and metastasis.	FUTURE ONCOL	9	713 - 726	3.202
ALMEIDA G. L., MUSI G., MAZZOLENI F., MATEI D. V., BRESCIA A., DETTI S., DE COBELLI O.	Intraoperative Frozen Pathology During Robot-Assisted Laparoscopic Radical Prostatectomy: Can ALEXIS® Trocar Make it Easy and Fast?	J ENDOUROL	27	1213 - 1217	2,074
ALONGI F., DE BARI B., CAMPOSTRINI F., ARCANGELI S., MATEI D. V., LOPCI E., PETRALIA G., BELLOMI M., CHITI A., MAGRINI S. M., SCORSETTI M., ORECCHIA R., JERECZEK FOSSA B. A.	Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review.	CRIT REV ONCOL HEMAT	88	550 - 563	4.637
ALONGI F., DE BARI B., FRANCO P., CIAMMELLA P., CHEKRINE T., LIVI L., JERECZEK FOSSA B. A., FILIPPI A. R, AIRO YOUNG AND AIRO PROSTATE CANCER WORKING GROUP	The PROCAINA (PROstate CAncer INdication Attitudes) Project (Part I): a survey among Italian radiation oncologists on postoperative radiotherapy in prostate cancer.	RADIOL MED	118	660 - 678	1,461
ALTERIO D., ANSARIN M., JERECZEK B. A., ZORZI S. F., SANTORO L., ZERINI D., MASSARO M. A., RONDI E., FERRARIO S., PIPERNO G., COSSU ROCCA M., GRISERI M., PREDA L., CHIESA F. G., ORECCHIA R.	What is the price of functional surgical organ preservation in local-regionally advanced supraglottic cancer? Long-term outcome for partial laryngectomy followed by radiotherapy in 32 patients.	TUMORI	99	667 - 675	0,922
ALTOMONTE M., DI GIACOMO A., QUEIROLO P., ASCIERTO P., SPAGNOLO F., BAJETTA E., CALABRO L., DANIELLI R., DE ROSA F., MAUR M., CHIARION-SILENI V., FERRUCCI P. F., GIANNARELLI D., TESTORI A., RIDOLFI R., MAIO M.	Clinical experience with ipilimumab 10 mg/kg in patients with melanoma treated at Italian centres as part of a Euxropean expanded access programme.	J EXP CLIN CANC RES	32	82 - 82	3,066
AMSON R., PECE S., MARINE J. C., DI FIORE P. P., TELERMAN A.	TPT1/ TCTP-regulated pathways in phenotypic reprogramming.	TRENDS CELL BIOL	23	37 - 46	11,721
ANDRE F., DIECI M. V., DUBSKY P., SOTIRIOU C., CURIGLIANO G., DENKERT C., LOI S.	Molecular Pathways: Involvement of Immune Pathways in the Therapeutic Response and Outcome in Breast Cancer.	CLIN CANCER RES	19	28 - 33	7.837
ANDREOLA G., BABIC A., PERSEGHIN P., CROVETTI G., MARSON P., SAVIGNANO C., IPSEVICH F., LANTI A., LASZLO' D.	Extracorporeal photochemotherapy: an Italian panel perspective on indications, ethodologies and clinical results	DRUDS CELL THER	1	122 - 132	0
ANDREOZZI P., MARTINELLI C., CARNEY R. P., CARNEY T. M., STELLACCI F.	Erythrocyte Incubation as a Method for Free-Dye Presence Determination in Fluorescently Labeled Nanoparticles.	MOL PHARMACEUT	10	875 - 882	4.57
ANNONI M. A.	Highlights from the 2013 Science of Placebo thematic workshop.	ECANCERMEDICAL-SCIENCE	7	346 - 346	0
AURILIO G., MONFARDINI L., RIZZO S., SCIANDIVASCI A. S., PREDA L., BAGNARDI V., DISALVATORE D., PRUNERI G., MUNZONE E., DELLA VIGNA P., RENNE G., BELLOMI M., CURIGLIANO G., GOLDHIRSCH A., NOLÈ F.	Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer.	ACTA ONCOL	52	1649 - 1656	2,867
AVERBOOK B. J., LEE S. J., DELMAN K. A., GOW K. W., ZAGER J. S., SONDAK V. K., MESSINA J., SABEL M., PITTELKOW M., ECKER P. M., MARKOVIC S. N., SWETTER S. M., LEACHMAN S. A., TESTORI A., CURIEL-LEWANDROWSKI C., GO R. S., JUKIC D. M., KIRKWOOD J. M.	Pediatric melanoma: Analysis of an international registry.	CANCER-AM CANCER SOC	119	4012 - 4019	5,201
AWADELKARIM K. D., ARIZZI C., ELAMIN E. O., OSMAN I., MEKKI S. O., BIUNNO I., BARBERIS M., MARIANI-COSTANTINI R.	Tissue microarray (TMA) versus whole section immunohistochemistry in the assessment of ER/PR and Her-2/neu status in a breast cancer series from Sudan.	BREAST J	19	446 - 447	1,831
AZIM H. A., KROMAN N., PAESMANS M., GELBER S., ROTMENSZ N., AMEYE L., DE MATTOS-ARRUDA L., PISTILLI B., PINTO A., JENSEN M. B., CORDOBA O., DE AZAMBUJA E., GOLDHIRSCH A., PICCART M. J., PECCATORI F. A.	Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study.	J CLIN ONCOL	31	73 - 79	18,038

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BAGNARDI V., BOTTERI E., ROTA M., PELUCCHI C., CORRAO G., REHM J., BOFFETTA P., LA VECCHIA C.	Re: light drinking has positive public health consequences.	ANN ONCOL	24	1421 - 1422	7,384
BAGNARDI V., ROTA M., BOTTERI E., TRAMACERE I., ISLAMI F., FEDIRKO V., SCOTTI L., JENAB M., TURATI F., PASQUALI E., PELUCCHI C., BELLOCCO R., NEGRI E., CORRAO G., REHM J., BOFFETTA P., LA VECCHIA C.	Light alcohol drinking and cancer: a meta-analysis.	ANN ONCOL	24	301 - 308	7,384
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BELTRAMI E., RUGGIERO A., BUSUTTIL R., MIGLIACCIO E., PELICCI P. G., VIJG J., GIORGIO M.	Deletion of p66Shc in mice increases the frequency of size-change mutations in the lacZ transgene.	AGING CELL	12	177 - 183	5,705
BELTRAMI E., VALTORTA S., MORESCO R., MARCU R., BELLOLI S., FASSINA A., FAZIO F., PELICCI P. G., GIORGIO M.	The p53-p66Shc apoptotic pathway is dispensable for tumor suppression whereas the p66Shc-generated oxidative stress initiates tumorigenesis.	CURR PHARM DESIGN	19	2708 - 2714	3,311
BERNIAKOVICH I., GIORGIO M.	Low oxygen tension maintains multipotency, whereas normoxia increases differentiation of mouse bone marrow stromal cells.	INT J MOL SCI	14	2119 - 2134	2.464
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BERTOLINI F.	Contribution of endothelial precursors of adipose tissue to breast cancer: progression-link with fat graft for reconstructive surgery.	ANN ENDOCRINOL-PARIS	74	106 - 107	1,022
BERTOLINI F.	Adipose tissue and breast cancer progression: A link between metabolism and cancer.	BREAST	22S2	S48 - S49	1,967
BERTOLINI F., SHAKED Y., MANCUSO P.	On the clinical relevance of circulating endothelial cells and platelets in prostate cancer.	BRIT J CANCER	108	1387 - 1387	5,082
BIANCHI P. P., LUCA F., PETZ W. L., VALVO M., CENCIARELLI S., ZUCCARO M., BIFFI R.	The role of the robotic technique in minimally invasive surgery in rectal cancer.	ECANCERMEDICAL-SCIENCE	7	357 - 357	0
BIANCHI S., BENDINELLI B., CASTELLANO I., PIUBELLO Q., RENNE G., CATTANI M. G, DI STEFANO D., CARRILLO G., LAURINO L., BERSIGA A.	Morphological parameters of lobular in situ neoplasia in stereotactic 11-gauge vacuum-assisted needle core biopsy do not predict the presence of malignancy on subsequent surgical excision.	HISTOPATHOLOGY	63	83 - 95	2,857
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BIFFI R., BOTTERI E., BERTANI E., ZAMPINO M. G., CENCIARELLI S., LUCA F., POZZI S., COSSU M. L., CHIAPPA A., ROTMENSZ N., BAZOLLI B., MAGNI E., SONZOGNI A., ANDREONI B.	Factors predicting worse prognosis in patients affected by pT3 No colon cancer. Long-term results of a monocentric series of 137 radically resected patients in a 5-year period.	INT J COLORECTAL DIS	28	207 - 215	2,238
BLASIMME A., MAUGERI P. M., GERMAIN P.	What mechanisms can't do: explanatory frameworks and the function of the p53 gene in molecular oncology.	Stud Hist Philos Biol Biomed Sci.	44	374 - 384	0
BLASIMME A., SCHMIETOW B., TESTA G.	Reprogramming potentiality: the co-production of stem cell policy and democracy.	AM J BIOETHICS	13	30 - 32	3,597
BOCK F., SHAHZAD K., WANG H., STOYANOV S., WOLTER J., DONG W., PELICCI P. G., KASHIF M., RANJAN S., SCHMIDT S., RITZEL R., SCHWENGER V., REYMANN K. G., ESMON C. T., MADHUSUDHAN T., NAWROTH P. P., ISERMANN B.	Activated protein C ameliorates diabetic nephropathy by epigenetically inhibiting the redox enzyme p66Shc.	P NATL ACAD SCI USA	110	648 - 653	9,737
BOELAERT K., MAISONNEUVE P., TORLINSKA B., FRANKLYN J. A.	Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine.	J CLIN ENDOCR METAB	98	1869 - 1882	6,43
BOEM F., GAUSSOU C., CHUK E., QUATTRI F., RATTI E., SANFILIPPO M. E., SOJIC A.	Diverse perspectives on ontology: A joint report on the First IAOA Interdisciplinary Summer School on Ontological Analysis	APPL ONTOL	8	59 - 71	1,08

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BONANNI B., LAZZERONI M.	Acceptability of chemoprevention trials in high-risk subjects.	ANN ONCOL	24 Suppl 8	viii42 - viii46	7,384
BONIOLO G.	Is an account of identity necessary for bioethics? What post-genomic biomedicine can teach us.	Studies in History and Philosophy of Science	44	401 - 411	0
BONIOLO G., D'AGOSTINO M., PIAZZA M., PULCINI G.	A logic of non-monotonic interactions	J APPL LOGIC	11	52 - 62	0,419
BOSETTI C., LUCENTEFORTE E., BRACCI P. M, NEGRI E., NEALE R. E, RISCH H. A, OLSON S. H, GALLINGER S., MILLER A. B, BUENO DE MESQUITA H. B, TALAMINI R., POLESEL J., GHADIRIAN P., BAGHURST P. A, ZATONSKI W., FONTHAM E., HOLLY E. A, GAO Y. T, YU H., KURTZ R. C, COTTERCHIO M., MAISONNEUVE P., ZEEGERS M. P, DUELL E. J, BOFFETTA P., LA VECCHIA C.	Ulcer, gastric surgery and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4).	ANN ONCOL	24	2903 - 2910	7,384
BOTTA F., CREMONESI M., FERRARI M. E., AMATO E., GUERRIERO F., VAVASSORI A., SARNELLI A., SEVERI S., PEDROLI G., PAGANELLI G.	Investigation of (90)Y-avidin for prostate cancer brachytherapy: a dosimetric model for a phase I-II clinical study.	EUR J NUCL MED MOL I	40	1047 - 1056	5,114
BOTTA F., MAIRANI A., HOBBS R. F., VERGARA GIL A., PACILIO M., PARODI K., CREMONESI M., PEREZ M. A., DI DIA G. A., FERRARI M. E., GUERRIERO F., BATTISTONI G., PEDROLI G., PAGANELLI G., AROCHE L. A., SGOUROS G.	Use of the FLUKA Monte Carlo code for 3D patient-specific dosimetry on PET-CT and SPECT-CT images.	PHYS MED BIOL	58	8099 - 8120	2,701
BOTTERI E., MUNZONE E., INTRA M., BAGNARDI V., ROTMENSZ N., BAZOLLI B., MONTANARI B. M., AURILIO G., SCIANDIVASCI A. S., ESPOSITO A., PAGANI G., ADAMOLI L., VIALE G., NOLE' F., GOLDHIRSCH A.	Role of breast surgery in T1-3 breast cancer patients with synchronous bone metastases.	BREAST CANCER RES TR	138	303 - 310	4.469
BOTTERI E., MUNZONE E., ROTMENSZ N., CIPOLLA C., DE GIORGI V., SANTILLO B., ZANELOTTI A., ADAMOLI L., COLLEONI M. A., VIALE G., GOLDHIRSCH A., GANDINI S.	Therapeutic effect of β-blockers in triple-negative breast cancer postmenopausal women.	BREAST CANCER RES TR	140	567 - 575	4.469
BOUSSIOS S., HAN S. N., FRUSCIO R., HALASKA M. J., OTTEVANGER P. B., PECCATORI F. A., KOUBKOVA L., PAVLIDIS N., AMANT F.	Lung cancer in pregnancy: report of nine cases from an international collaborative study.	LUNG CANCER	82	499 - 505	3.392
BOZZINI G., PICOZZI S., GADDA F., COLOMBO R., DE COBELLI O., PALOU J., COLPI G., CARMIGNANI L.	Long-term follow-up using testicle-sparing surgery for Leydig cell tumor.	CLIN GENITOURIN CANC	11	321 - 324	1.429
BREMANG M., CUOMO A., AGRESTA A. M., STUGIEWICZ M. M., SPADOTTO V., BONALDI T.	Mass spectrometry-based identification and characterisation of lysine and arginine methylation in the human proteome.	MOL BIOSYST	9	2231 - 2247	3.35
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BROLLO J., KNEUBIL M. C., BOTTERI E., ROTMENSZ N., DUSO B. A., FUMAGALLI L., LOCATELLI M. A., CRISCITIELLO C., LOHSIRIWAT V., GOLDHIRSCH A., LEONARDI M. C., ORECCHIA R., CURIGLIANO G.	Locoregional recurrence in patients with HER2 positive breast cancer.	BREAST	22	856 - 862	1,967
BROOKMAN-MAY S. D., MAY M., SHARIAT S. F., NOVARA G., ZIGEUNER R., CINDOLO L., DE COBELLI O., DE NUNZIO C., PAHERNIK S., WIRTH M. P., LONGO N., SIMONATO A., SERNI S., SIRACUSANO S., VOLPE A., MORGIA G., BERTINI R., DALPIAZ O., STIEF C., FICARRA V., MEMBERS OF THE CORONA-PROJECT, THE SATURN-PROJECT, AND THE YOUNG ACADEMIC UROLOGISTS RENAL CANCER GROUP	Time to recurrence is a significant predictor of cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma - results from a comprehensive multi-centre database (CORONA/SATURN-Project).	BJU INT	112	909 - 916	3,046
BROOKMAN-MAY S., MAY M., SHARIAT S. F., XYLINAS E., STIEF C., ZIGEUNER R., CHROMECKI T., BURGER M., WIELAND W. F., CINDOLO L., SCHIPS L., DE COBELLI O., ROCCO B., DE NUNZIO C., FECICHE B., TRUSS M., GILFRICH C., PAHERNIK S., HOHENFELLNER M., ZASTROW S., WIRTH M. P., NOVARA G., CARINI M., MINERVINI A., SIMEONE C., ANTONELLI A., MIRONE V., LONGO N., SIMONATO A., CARMIGNANI G., FICARRA V., MEMBERS OF THE CORONA PROJECT AND THE SATURN PROJECT	Features associated with recurrence beyond 5 years after nephrectomy and nephron-sparing surgery for renal cell carcinoma: development and internal validation of a risk model (PRELANE score) to predict late recurrence based on a large multicenter dat.	EUR UROL	64	472 - 477	10.476

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BROZZI A., URBANELLI L., GERMAIN P., MAGINI A., EMILIANI C.	hLGDB: a database of human lysosomal genes and their regulation.	DATABASE-OXFORD	2013	bat024 - bat024	4.2
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BRYCE J., PASSONI C.	Nursing management of patients with metastatic melanoma receiving ipilimumab.	ONCOL NURS FORUM	40	215 - 218	2.393
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BUONOMO B., D'ONOFRIO A.	Modelling the influence of public's memory on the corruption-popularity dilemma in politics.	J OPTIMIZ THEORY APP	158	554 - 575	1,423
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CANCELLO G., MAISONNEUVE P., ROTMENSZ N., VIALE G., MASTROPASQUA M. G., PRUNERI G., MONTAGNA E., IORFIDA M., MAZZA M., BALDUZZI A., VERONESI P., LUINI A., INTRA M., GOLDHIRSCH A., COLLEONI M. A.	Progesterone receptor loss identifies Luminal B breast cancer subgroups at higher risk of relapse.	ANN ONCOL	24	661 - 668	7.384
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CARAVAGNA G., D'ONOFRIO A., MAURI G.	NoisySIM: exact simulation of stochastic chemically reacting systems with extrinsic noises.	SIMULATION SERIES	45	84 - 89	0
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Clinical Trials in progress during 2013

Title	Principal Investigator	Patients enrolled in 2013	Total patients enrolled
Breast			
Randomized phase III trial of Herceptin followed by Taxol plus Herceptin versus the combination of Herceptin and Taxol as first-line chemotherapy in patients with HER2-overexpressing advanced breast cancer. SAKK 22/99	Goldhirsch	0	45
The HOT Study: Hormone replacement therapy opposed by low dose tamoxifen. A phase III trial of breast cancer prevention with low dose tamoxifen in HRT users.	Bonanni	0	479
Efficacy of intraoperative radiotherapy compared to conventional external radiotherapy to prevent local relapse of breast carcinoma after breast conserving surgery.	Veronesi U	0	1306
Adjuvant therapy for patients with breast cancer whose tumors are judged to require cytotoxic therapy (ER-negative and PgR-negative). Low-dose cytotoxics as "anti-angiogenesis treatment" following induction chemotherapy.	Goldhirsch	0	343
A randomized trial of axillary dissection versus no axillary dissection for patients with clinically node negative breast cancer and micrometastases in the sentinel node.	Goldhirsch	0	583
HERA: A randomised three-arm multi-centre comparison of 1 year and 2 years of Herceptin versus no Herceptin in women with HER2-positive primary breast cancer who have completed adjuvant chemotherapy. BIG01-01/BO16348D	Goldhirsch	0	25
An international multi-centre study of tamoxifen vs anastrozole in postmenopausal women with Ductal Carcinoma in Situ (DCIS). IBIS II	Bonanni	0	117
An international multi-centre study of anastrozole vs placebo in postmenopausal women at increased risk o breast cancer (Prevention). IBIS II	Bonanni	0	40
Suppression of Ovarian Function Trial (SOFT) A phase III trial evaluating the role of ovarian function suppression and the role of Exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer tamoxifen versus ovarian function suppression + tamoxifen versus ovarian function suppression + exemestan (IBCSG 24-02).	Goldhirsch	0	1
Tamoxifen and Exemestane Trial (TEXT) A phase III trial evaluating the role of Exemestane plus GnRH analogue as adjuvant therapy for premenopausal women with endocrine responsive breast cancer ovarian function suppression + tamoxifen versus ovarian function suppression + exemestane (IBCSG 25-02).	Goldhirsch	0	335
A randomized phase II prevention trial in subjects at high risk for hormone non-responsive breast cancer.	Bonanni	0	137
A randomised phase III trial of exemestane vs anastrozole in post menopausal women with receptor positive primary breast cancer.	Goldhirsch	0	122
Role of PET in the prediction of patients candidates to sentinel node biopsy after primary treatment for breast cancer.	Paganelli	0	120
A phase II study of Lapatinib for brain metastases in subjects with ErbB2-positive breast cancer following Trastuzumab-based systemic therapy and cranial radiotherapy.	Nolè	0	4
A phase II study to evaluate efficacy and tolerability of concomitant or sequential administration of Bevacizumab with oral vinorelbine and capecitabine in the treatment of advanced breast cancer.	Goldhirsch	0	66
New frontiers of breast diagnostic: optical mammography.	Cassano	21	220

A clinical trial for the evaluation of the tolerability of hypofractionated accelerated radiotherapy compared to the conventional scheme in the adjuvant treatment of breast cancer after breast conserving surgery.	Orecchia	0	250
Study of intermittent letrozole as adjuvant endocrine therapy.	Balduzzi	0	176
ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study. A randomized multicentre open-label phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer.	Colleoni	0	36
An observational study of cardiac events in patients with HER2 positive early breast cancer treated with Herceptin.	Goldhirsch	0	30
A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer. Sole	Colleoni	0	141
A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine combined with bevacizumab and erlotinib (BEXE), plus trastuzumab in HER2/neu positive tumours (BEXET) in advanced breast cancer.	Colleoni	0	32
Preoperative endocrine treatment with Letrozole ± Triptorelin in patients with ER and PgR positive locally advanced breast cancer.	Mazza	3	54
A randomised, multicentre, open-label, phase III study of neoadjuvant lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2/ErbB2 positive primary breast cancer. EGF106903/BIG 1-06 NEO ALTO	Colleoni	0	4
Evaluation of acquired overexpression of HER2/neu on circulating tumor cells in patients with advanced breast cancer during chemotherapy and assesment of activity of Trastuzumab-based therapy: a phase II trial.	Nolè	1	80
Phase II study of Exemestane dose intensification (150 mg/die) in postmenopausal patients with advanced breast cancer progressing under standard dose exemestane (25 mg/die) given as adjuvant or palliative therapy.	Goldhirsch	2	7
A phase II randomized study evaluating the role of 8 courses of primary chemotherapy versus 4 courses of primary chemotherapy in combination with endocrine therapy in locally advanced breast cancer.	Colleoni	2	30
A two-arm randomised open label phase II study of cp-751,871 in combination with exemestane vs exemestane alone as first line treatment for post-menopausal patients with hormone receptor positive advanced breast cancer.	Goldhirsch	0	3
Metronomic Capecitabine plus Docetaxel as first line treatment for metastatic breast cancer patients: a phase II trial.	Nolè	3	27
Breast Cancer prevention with fenretinide in young women at genetic and familial risk. A phase III randomized trial.	Bonanni	8	37
Randomized trial of diet, physical activity and breast cancer recurrences DIANA 5 study.	Bonanni	0	290
GIM8 (OVER): A randomized trial with factorial design comparing Fulvestrant ± Lapatinib ± Aromatase inhibitors in metastatic breast cancer progressing after aromatase inhibitor therapy.	Nolè	0	17
Role of HLA-G in the resistance mechanisms to trastuzumab in advanced breast cancer patients with HER-2 amplified and /or over expressed.	Goldhirsch	0	30
Randomized placebo controlled phase III trial with low dose tamoxifen in women with intraepithelial breast neoplasm. TAM-01	Bonanni	28	97
Phase II study with epirubicin, cisplatin and infusional fluorouracil (ECF) followed by weekly paclitaxel plus metronomic cyclophosphamide ± trastuzumab as preoperative treatment of locally advanced ER e PgR negative breast cancer.	Colleoni	25	81
Efficacy of telephone psychological support in reducing post-traumatic stress syndrome symptoms in women diagnosed with breast cancer awaiting surgery: information strategies compared.	Didier	0	150
Blood test for breast cancer associated auto antibodies.	Sandri	0	150
Phase II study of preoperative bavacizumab plus weekly paclitaxel, carboplatin and metronomic cyclophosphamide + - trastuzumab and endocrine therapy for inflammatory breast cancer.	Dellapasqua	7	34
Helping ourselves, helping others: the young women's breast cancer study.	Locatelli	2	64
18F-Fluorohyimidine positron emission tomography as an early predictor of response to neoadjuvant therapy in patients with locally advanced breast carcinoma.	De Cicco	0	13
Report on the dose to the foetus from intraoperative electron treatment of breast cancer on a pregnant patient.	Orecchia	0	6

A Phase II study of cisplatin plus cyclophospamide for patients with previously treated, advanced, triple receptor negative breast cancer.	Locatelli	9	24
A randomized multicenter phase III open label study of the efficacy and safety of Trastuzumab - MCC-DM1 vs Capecitabine + Lapatinib, in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior Trastuzumab based therapy. BO21977	Curigliano	0	4
A randomized 3 arms multicentre phase III study to evaluate the efficacy and safety of T-DM1 combined with pertuzumab or T-DM1 combined with pertuzumab-placebo (blinded for pertuzumab), vs the combination of trastuzumab plus taxane as first line treatment in HER2-positive progressive or recurrent locally advanced or metastatic breast cancer. BO22589	Curigliano	0	10
Sentinel node identification in breast cancer by fluorescence lymphography using indocyanine green dye (ICG):pilot study.	Veronesi P	8	176
Phase II study of metronomic oral Vinorelbine (Navelbine) plus Bevacizumab (Avastin) as first line treatment for metastatic breast cancer patients.	Nolè	0	24
A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients.	Esposito	20	42
A phase II study of low-dose vaginal estrogens in pre and postmenopausal breast cancer patients with urogenital atrophy.	Mazza	4	10
Role of CTCs in neoadjuvant setting in patients with triple negative and HER2 positive breast cancer.	Sandri	46	58
New frontiers in breast imaging: contrast enhanced digital mammography. - Clinical performance of contrast-enhanced spectral mammography (CESM - SenoBright) in pre-surgical evaluation of extent of malignancy in a population of women with breast cancer.	Cassano	92	94
Exploratory study to determine the efficacy and safety of the use of high intensity focused ultrasound (HIFU), as thermo-ablation method, in patients with small unifocal breast cancer.	Arnone	8	8
A randomized trial comparing sentinel lymphonode biopsy vs no axillary surgical staging in patients with small breast cancer and a negative preoparative axillary assessment.	Gentilini	154	268
MIRA-SOLE trial. MultIcentric RAndomized Study of cOnventionaL and hypofractionatEd RT in adjuvant breast cancer setting.	Orecchia	18	41
A randomized multicenter cross over study to evalutate patients preference and health care professional (HCP) satisfaction with subcutaneous (SC) di administration of trastuzumab in HER2-positive early breast cancer. MO22982	Colleoni	0	2
A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (APHINITY).	Colleoni	8	28
A prospective, exploratory observational study evaluating specific biomarkers in primary invasive breast cancer and their modulation by standard neoadjuvant therapy. 115400 ONCO RD-017	Colleoni	0	1
Cognitive funcitions: impact of presurgery treatments of breast cancer patients.	Montagna	7	15
Green tea and silybin for breast cancer. A pilot presurgical study.	Bonanni	12	20
A phase II, double blind placebo controlled randomized study of GDC-0941 or GDC-0980 with FULVESTRANT versus FULVESTRANT in advanced or metastatic breast cancer in patients resistant to aromatase inhibitor therapy. GDC49509 FERGI	Curigliano	1	2
Study of intermittent letrozole plus transdermal estradiol gel therapy for 3 months as adjuvant endocrine therapy (SOLETRE).	Balduzzi	6	6
An open-label, multi-center, expanded access study for postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane. CRAD001YIC04	Nolé	22	22
A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer.	Curigliano	6	6
Genome remodeling in Luminal B, HER2 positivo and ductal triple-negative breast cancer metastasis and xenograft: exome sequencing analysis for identification of driver pathways to overcome resistance.	Curigliano	10	18
Randomized, Open-Label Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone With or Without Exemestane in Postmenopausal Women With ER+ Metastatic Breast Cancer Progressing After Letrozole or Anastrozole Therapy.	Curigliano	4	4

SMART — Supplementation of anthocyanins from blood orange juice in post-menopausal women on adjuvant non steroidal aromatase inhibitors treatment.	Curigliano	31	72
A phase III randomized, double blind placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative locally advanced or metastatic breast cancer which progressed on or after aromatase inhibitor treatment. CBKM120F2302	Nolè	4	4
A multicenter, single arm study of trastuzumab emtasine (T-DM1) in HER2-positive locally advanced or metastatic breast cancer patients who have received prior anti-HER2 and chemotherapy-based treatment.	Curigliano	3	3
A case-control study to determine the effect of previous treatments and tumor characteristics on pregnancy outcome in women with a history of breast cancer.	Peccatori	33	33
A phase III randomized, double blind, placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative AI treated, locally advanced or metastatic breast cancer who progressed on or after mTOR inhibitor based treatment.	Nolè	1	1
A randomized, double-blind, placebo controlled, phase II study of BKM120 plus paclitaxel in patients with HER2 negative inoperable locally advanced or metastatic breast cancer, with or without PI3K pathway activation.	Munzone	2	2
EUROHOPE study: quality of life and satisfaction in patients with breast cancer trial.	Luini	0	0
A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer.	Colleoni	0	0
A randomized phase II study evaluating different schedules of nab-Paclitaxel in metastatic breast cancer (SNAP).	Colleoni	6	6
A randomized, multicenter, open-label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy (KATHERINE).	Colleoni	0	0
Lung			
Validation of low-dose spiral CT for early diagnosis of lung cancer in a high risk population.	Bellomi	0	6238
Cromogranine A as a marker for the diagnosis and follow-up of NET. The CROMaNET observational study.	Fazio	0	33
A phase I/II study to assess the safety and immunogenicity of recMAGE-A3+AS15 cancer immunotherapeutic given as adjuvant therapy, with or without adjuvant chemo(-radio) therapy, to patients with MAGE-A3-positive Non Small Cell Lung cancer (stage IB, II or III). Prot. 107240 (MAGE3-AS15-NSC-001)	De Pas	0	15
A double blind, randomised placebo controlled phase III study to assess the efficacy of recMAGE-A3 + AS15 antigen specific cancer immunotherapeutic ad adjuvant therapy in patients with resectable MAGE-A3 positive non small cell lung cancer. MAGRIT109493	De Pas	0	46
Analysis of the expression of a specific set of genes and tumor antigens in patients with non-small cell lung cancer and melanoma. ONCO RD-001 Prot 109752	De Pas, Testori	0	23
Evaluation of the accuracy of a serological biomarker (proGRP) in the differential diagnosis in the monitoring of small cell lung cancer.	Sandri	0	708
Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of PF-02341066 Versus Standard Of Care Chemotherapy (Pemetrexed Or Docetaxel) In Patients With Advanced Nonsmall Cell Lung Cancer (NSCLC) Harboring A Translocation Or Inversion Event Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus. A8081007	De Pas	0	11
Phase II open label single arm study of the efficacy and safety of PF-02341066 in patients with advanced non small cell lung cancer (NSCLC) harboring a translocation or inversion involving the anaplastic lymphoma kinase (ALK) gene locus. A8081005	De Pas	0	22
A phase III randomized study to compare Erlotinib and II line chemotherapy in patients with lung non small cell lung carcinoma stratified according to the proteomic profile.	De Pas	0	14
An open label phase I dose escalation study to assess the safety and immunogenicity of recPRAME+AS15 antigen specific cancer immunotherapeutic as adjuvant therapy in patients with resectable PRAME-positive NSCLC. 113174	De Pas	0	11
NGR014: Randomized phase II study of NGR-hTNF in combination with standard chemotherapy versus standard chemotherapy alone in previously untreated patients with advanced non-small cell lung cancer.	De Pas	0	22
Randomized double-blind placebo controlled phase III trial to assess the efficacy and safety of acetil-Lcarnitine in combination with cisplatin-containing chemotherapy as first line treatment of advanced or metastatic non small cell lung cancer.	De Pas	0	15

Phase II, open-label study of erlotinib (TaRceva®) treatment In patients with locally advanced or metastatic non-small-cell lunG cancer who present activatinG mutations in the tyrosine kinase domain of the Epidermal growth factor Receptor (EGFR) – TRIGGER.	De Pas	0	20
An open label two-stage study of orally administered BKM120 in patients with metastatic non-small cell lung cancer with activated PI3K pathway. CBKM120D2201	De Pas	0	3
MEK 114653. A Phase II, Open-label, Multicenter, Randomized Study to Assess the Efficacy and Safety of GSK1120212 Compared with Docetaxel in 2nd Line Subjects with Targeted Mutations (KRAS, NRAS, BRAF, MEK1) in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC Stage IIIBwet-IV).	De Pas	0	6
Phase III randomized study of standard lobectomy vs sublobar resection in patients with small, stage IA non small cell lung cancer.	Spaggiari	6	10
A Phase IIb/III randomized, double-blind, placebo-controlled study comparing first-line therapy with or without TG4010 immunotherapy product in patients with stage IV non-small cell lung cancer (NSCLC).	De Marinis	2	2
Early detection of lung cancer in asymptomatic high risk population by low dose CT Scan and molecular markers.	Veronesi G	1445	2886
Phase III, randomized, open label study of the efficacy and safety of Crizotinib vs Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in previously untreated patients with NSCL harbouring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus. A8081014	De Pas	3	5
Breath Test in lung cancer patients.	Spaggiari	94	94
A randomized, phase III, multicenter, double-blind, placebo-controlled study evaluating the efficacy and safety of MetMab in combination with Tarceva (erlotinib) in patients with met diagnostic positive non small cell lung cancer (nsclc) who have received standard chemotherapy for advanced or metastatic disease.	De Pas	7	7
LUME-Lung 3: A Phase I/II study of continous oral treatment with BIBF 1120 added to standard gemcitabine/cisplatin therapy in first line NSCLC patients with squamous cell histology.	De Pas	3	3
A multicenter, open-label, randomized phase II study to evaluate the efficacy of AUY922 vs pemetrexed or docetaxel in NSCLC patients with EGFR mutations who have progressed on prior EGFR TKI treatment.	De Marinis	0	0
A multicenter, randomized, double-blind, placebo-controlled Phase IIb Efficacy Study of Vx-001, a peptide-based cancer vaccine aimed to maintain disease control after first line treatment in HLA-A*0201 positive patients with TERT positive NSCLC (stage IV or recurrent stage I-III).	De Marinis	2	2
A Phase II study of the selective BRAF kinase inhibitor GSK2118436 in subjects with advanced non-small cell lung cancer and BRAF mutations.	De Marinis	2	2
A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib.	De Pas	6	6
A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer.	De Pas	1	1
An open-label, non-randomized, multicenter phaseI/II trial of RO5424802 given orally to non-small cell lung cancer patients who have alk mutation and failed crizotinib treatment.	De Pas	1	1
An open-label, randomized, phase 2 study comparing TAS-102 versus Topotecan or amrubicin in patients requiring second-line Chemotherapy for small cell lung cancer that is refractory or Sensitive to first-line platinum-based chemotherapy topotecan or amrubicin in patients requiring second-line chemotherapy for small cell lung cancer that is refractory or sensitive to first-line platinum-based chemotherapy.	De Marinis	0	0
An open label trial of afatinib in treatment naive (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non small cell lung cancer (NSCLC) harboring EGFR mutation(s).	De Marinis	1	1
A randomized, open label, phase 3 efficacy and safety study of dacomitinib (PF-00299804) versus Gefitinib for the first-line treatment of locally advanced or metastatic, NSCLC in subjects with EFGR activating mutation(s). ARCHER 150	De Marinis	0	0
Colorectal & Gastric Carcinoma			
A phase III trial of preoperative vs postoperative chemotherapy with Taxotere-Cisplatin-5FU (TCF) in patients with locally advanced operable gastric carcinoma.	Fazio	0	45
A phase II open label study of PTK787/ZK222584 in the treatment of metastatic gastrointestinal stromal tumors (GISTs) resistant to Imatinib mesylate.	De Pas	0	13
Open label randomised multicentre phase III study of adjuvant chemotherapy in radically resected adenocarcinoma of the stomach or gastroesophageal junction: comparison of a sequential treatment (CPT-11+5-FU/LV - TXT+CDDP) versus 5-FU/LV regimen.	Fazio	0	16

Identification and possible prognostic role of circulating tumor cells (CTC) in peripheric venous blood of patients with locally advanced rectal cancer diagnosed through traditional clinical workout and treated with radical surgical approach (open surgery or mini invasive laparoscopy).	Sandri	0	90
A randomised trial investigating the role of FOLFOX-4 regimen duration (3 versus 6 months) and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer.	Zampino	6	89
Intensification Radiotherapy with accelerated fractionation or chemotherapy and local excision after 3D external radiotherapy.	Leonardi	11	25
Chromoscopy-guided endomicroscopy with the PENTAX EC 3870CIFK/EC 3870-CILK confocal colonoscopes for the detection of intraepithelial neoplasias in subjects with long standing ulcerative colitis.	Crosta	0	22
Preservation of genito-urinary function in colorectal cancer patients undergoing surgery through robotic technique.	Valvo	0	74
Phosphoproteomic analysis for the targeted therapy of the liver metastasis of colorectal carcinoma (TASK 2).	Chiappa	0	2
Randomized multicenter open label phase II study of RO5083945 in combination with FOLFIRI vs FOLFIRI plus cetuximab or FOLFIRI alone as second line treatment in patients with KRAS wild-type or mutant metastatic colorectal cancer. BP25438	Zampino	0	3
ITACA-S 2 (Intergroup Trial in Ajuvant Chemotherapy for Adenocarcinoma of the Stomach).	Fazio	1	4
An open label multi center randomized phase III study of S-1 and cisplatin compared with 5-FU and cisplatin in patients with metastatic diffuse gastric cancer previously untreated with chemotherapy. TPU S1303	Fazio	2	3
ROLARR: RObotic versus LAparoscopic Resection for Rectal cancer. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer.	Luca	13	15
ROLARR: RObotic versus LAparoscopic Resection for Rectal cancer. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer.	Bianchi	17	20
A multi-center, open-label clinical trial to evaluate the objective response rate of bevacizumab in combination with modified FOLFOX-6 followed by one year of maintenance with bevacizumab alone in patients with initially not or borderline resectable colorectal liver metastases. ABOVE Study (ML25625)	Zampino	8	10
A non-interventional follow-up to the MOSAIC study (multicenter international study of oxaliplatin/5 Fluorouracil/ leucovorin in the adjuvant treatment of colon cancer) up to 10 years, and translational research.	Zampino	0	7
Clinical outcomes after radical surgical treatment and biological characteristics of colorectal cancers screen detected vs. non-screen detected vs intervallic. AMICOR Study	Andreoni	21	37
Colonic J-Pouch reconstruction vs colorectal anastomosis after low anterior resection for direct rectal cancer. Impact on deisenza anastomotic intestinal function and quality of life.	Chiappa	4	4
A randomized phase III study of low-docetaxel oxaliplatin, capecitabine (low-TOX) vs epirubicin, oxaliplatin and capecitabine (EOX) in patients with locally advanced unresectable or metastatic gastric cancer.	Fazio	3	3
A Non-Interventional Follow-Up to the VELOUR study (multicentre international study of aflibercept versus placebo in combination with FOLFIRI for metastatic colorectal cancer) – Translational Research.	Zampino	7	7
Microparticle Enhanced Cytotoxic Transarterial Embolization Therapy A Pilot Study of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma (mCRC) by Embozene TANDEM™ Drug-Eluting Microspheres Embolization (MIRACLE III-Study).	Orsi	2	2
Prostate			
A randomized double blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration resistant prostate cancer. CA180-227	Nolè	0	13
Circulating tumor cells and acetylation status as predictors of prognosis in localized prostate cancer.	Nolè	0	18
Short-term high precision radiotherapy for early prostate cancer with concomitant boost on the dominant lesion.	Orecchia	0	0
Lymphomas			
Multicenter randomized trial of chlorambucil versus chlorambucil plus Rituximab versus Rituximab alone in extranodal marginal-zone B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma).	Martinelli	0	38

Multicentric pilot phase II study for use of 90 Y ibritumomab tiuxetan (Zevalin) in refractory or relapsed gastric non hodgkin's lymphoma previously treated by chemotherapy, adjuvant radiotherapy or immunotherapy with rituximab.	Martinelli	0	13
A prospective open randomized trial on the efficacy of gonadotropin-releasing hormone agonist depot-triptorelin to prevent chemotherapy-induced premature ovarian failure for lymphoma.	Martinelli	0	26
Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial. SAKK 35/03	Martinelli	0	77
Pegfilgrastim in the treatment of recurrent or refractory malignant lymphomas.	Martinelli	0	112
A phase II study about the use of intensified hybrid chemotherapy regimen ChLVVP/ABVVP in advanced Hodgkin lymphoma patients.	Martinelli	13	102
Prospective evaluation of the predictive value of PET in patients with diffuse large B-cell-lymphoma under R-CHOP-14. A multicentre study.	Martinelli	0	37
Prospective collection of data in patients with peripheral T-cell lymphoma.	Laszlo	2	11
A phase II multicenter randomized open-label study to determine the efficacy of Lenalidomide (Revlimid) versus investigator's choice in patients with relapsed or refractory mantle cell lymphoma. CC-5013-MCL-002	Martinelli	0	2
A prospective study on the stem cell mobilization in malignant lymphomas.	Laszlo	0	5
An observational study of Cyclophosfamide, Non Peghylated Liposomal Doxorubicine (Myocet), Vincristine e Prednisone in "fragile" diffuse lymphoma patients.	Martinelli	11	24
A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase(ALK). CLDK378X2101	De Pas	3	10
A multicenter, randomized, double blind, placebo controlled, phase III study of adjuvant RAD001 treatment in patients with diffuse large B cell lymphoma (DLBCL) vs placebo after a colplete response to first line treatment with rituximab. CRAD001N2301	Martinelli	5	13
A Multicenter Phase II study to evaluate the clinical activity and the safety profile of everolimus (RAD001) in marginal zone B-cell lymphomas (MZL).	Martinelli	0	1
A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma.	Martinelli	0	1
A phase III international multicentre randomised controlled open label study to investigate the pharmacokinetics efficacy and safety of rituximab SC in combination with CHOP or CVP vs rituximab IV in combination with CHOP or CVP in patients with previously untreated follicular lymphoma followed by maintenance treatment with either rituximab SC or rituximab IV. BO22334	Martinelli	3	7
A phase III multicenter open label randomized trial comparing the efficacy of GA101 (RO5072759) in combination with CHOP (G-CHOP), vs RITUXIMAB and CHOP, (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL). BO21005	Martinelli	0	6
A Phase 2/3 Multicenter, Randomized Open-Label Study to Compare the Efficacy and Safety of Lenalidomide (Revlimid®) Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma. CC-5013-DLC001	Martinelli	0	1
Randomized open label, multicenter, phase II trial with rituximab plus lenalidomide or rituximab monotherapy for untreated patients with follicular lymphoma in need of therapy.	Martinelli	4	18
A multicenter pilot phase II study for the preliminary evaluation of feasibility, activity and safety of the administration of Bendamustine and Ofatumumab in combination in marginal zone B-cell lymphomas MZL.	Martinelli	3	6
A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL).	Martinelli	3	3
A Phase 3, Open-label, Multicenter, Randomized Study of Sequential Zevalin (ibritumomab tiuxetan) versus Observation in Patient at Least 60 Years of Age with Newly Diagnosed Diffuse Large B-cell Lymphoma in PET-negative Complete Remission After R-CHOP or R-CHOP-like Teraphy.	Martinelli	1	1
A phase II study of BKM120 in patients with relapsed and refractory mantle cell lymphoma, follicular lymphoma and diffuse large B cell lymphoma.	Martinelli	1	1
A Randomized, Controlled, Double-Blind Phase III Trial to Compare the Efficacy, Safety and Pharmacokinetics of GP2013 plus Cyclophosphamide, Vincristine, Prednisone vs. MabThera® plus Cyclophosphamide, Vincristine, Prednisone, Followed by GP2013 or MabThera® Maintenance Therapy in Patients with Previously Untreated, Advanced Stage Follicular Lymphoma.	Martinelli	0	0

Leukemia			
Nonmyeloablative PBSC allografting from HLA matched related donors using fludarabine and/or low dose TBI with disease-risk based immunosuppression, for patients with acute and chronic myeloproliferative and lymphoprolipherative disorders.	Martinelli	0	29
Five versus seven days subcutaneous administration of cladribine in Hair cell leukemia.	Martinelli	0	6
A phase III multicenter randomized open label parallel group study of the efficacy and safety of LENALIDOMIDE (REVLIMID) vs CLORAMBUCIL as first line therapy for previously untreated elderly patients with b-cell chronic lymphocytic leukemia. ORIGIN CC-5013-CLL-008	Martinelli	0	2
Rituximab-2cda + Rituximab maintenance in Chronic Lymphocytic Leukaemia and Small Lymphocytic Lymphoma.	Martinelli	11	29
A phase II multicentre randomized double blind parallel group study of the safety and efficacy of different Lenalidomide (Revlimid) dose regimens in subjects with relapsed or refractory B-cell chronic lymphocytic leukemia.	Martinelli	0	2
REL registry of chronic myeloid leukemia.	Martinelli	3	3
REL registry of chronic lymphocytic leukemia.	Martinelli	6	6
Gynaecological			
Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO Ib2, IIa>4cm or IIb cervical cancer.	Landoni	0	32
A randomised, multicentre, phase III study of Erlotinib (TARCEVA) versus observation in patients with no evidence of disease progression after first line, platinum based chemotherapy for high risk stage I and stage II -IV ovarian epithelial, primary peritoneal, or fallopian tube cancer.	Colombo	0	7
Stealth liposomal doxorubicin versus carboplatin / paclitaxel in patients with advanced ovarian cancer between six and twelve months of previous treatment with platinum: multicentre randomized study. MITO-8	Colombo	0	1
A phase III study to evaluate the efficacy and safety of Pazopanib monotherapy versus placebo in woman who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube or primary peritoneal cancer (AGO-OVAR16/VEG110655).	Colombo	0	20
A randomized controlled multicenter clinical trial to evaluate two regimens of different intensity to the follow-up examinations in patients treated for endometrial carcinoma. TOTEM study	Landoni	0	4
International Ovarian Tumor Analysis (IOTA) Phase III. A multicentre study on the preoperative characterisation of ovarian tumours based on artificial intelligence models.	Franchi	0	239
Multicenter randomised double blind phase III trial to investigate the efficacy and safety of BIBF 1120 in combination with standard treatment of carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer. BI 1195.15 (LUME-OVAR1)/AGO OVAR 12	Colombo	0	16
A Phase II, Open-Label, Randomised, Comparative, Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients with Platinum Sensitive Advanced Serous Ovarian Cancer. D0810C00041	Colombo	0	7
Phase III randomized clinical trial of laparoscopic or robotic radical hysterectomy vs abdominal radical hysterectomy in patients with early stage cervical cancer.	Landoni	0	6
Randomized, non comparative, phase II study to evaluate trabectedine or gemcitabine + taxotere in patients with local or distant recurrent leiomiosarcoma of the uterus already treated with conventional chemotherapy.	Colombo	1	4
Lymphadenectomy in ovarian neoplasm. LION. An open randomized prospective multi center trial.	Aletti	0	47
INOVATYON: Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum.	Colombo	0	2
Global study to assess the addition of bevacizumab to carboplatin and paclitaxel as front-line treatment of epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma.	Colombo	0	35
A phase II single arm study of orally administered BKM120 as second line therapy in patients with advanced endometrial carcinoma. CBKM120C2201	Colombo	0	1
Phase I study of oral administration of S 78454 given with a fixed dose infusion of pegylated liposomal doxorubicin in the treatment of primary platinum-resistant and partially platinum sensitive, epithelial ovarian, fallopian tube or primary peritoneal carcinoma. C11-78454-003	Colombo	0	2

A phase III randomized double blind trial of pegjlated liposomal Doxorubicin plus AMG 386 or placebo in women with recurrent partially platinum sensitive or resistant epithelial ovarian primary peritoneal or fallopian tube. TRINOVA 2. 20060517/ENGOT-ov-6	Colombo	9	11
A phase II multicentre double blind placebo controlled randomized study of Ombrabulin in patients with platinum sensitive recurrent ovarian cancer treated with Carboplatin/Paclitaxel. ECF10260	Colombo	0	10
A phase I/II study evluating intermittent and continuous OSI-906 and weekly paclitaxel in patients with recurrent ephitelial ovarian cancer. OSI-906-202	Colombo	9	25
NGR018: randomized phase II study of NGR-hTNF plus pegylated liposomal doxorubicin (PLD) vs PLD in platinum resistant ovarian cancer. IPR/24	Colombo	0	19
Network for Observation of Women already submitted or to be submitted to Conservative therapy for CIN or condyloma and the evaluation of the possible response to a proposed vaccine. (IEO-NEOTEC)	Sideri	2	12
International Endometrial Tumor Analysis (IETA). An observational non-interventional academic multicentre study on the ultrasound features of the endometrium.	Franchi	52	87
A phase III randomized double blind trial of weekly paclitaxel plus AMG 386 or placebo in women with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers. 20090508	Colombo	0	7
A phase III randomized double blind placebo controlled multicenter study of AMG 386 with paclitaxel and carboplatin as first line treatment of subjects with FIGO stage III-IV ethelial ovarian, primary peritoneal or fallopian tube cancer. PROT 20101129	Colombo	7	8
European clinical evaluation of the BD HPV assay in the BD ViperTM LT system.	Sideri	459	683
A Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced (stage III-IV) or recurrent endometrial cancer.	Colombo	10	10
A two-part, randomized phase II, double-blind, multicenter trial assessing the efficacy and safety of pertuzumab in combination with standard chemotherapy vs placebo plus standard chemotherapy in women with recurrent platinum resistant epithelial ovarian cancer and low her3 mRNA expression.	Colombo	12	12
Ovarian Tumour Analysis (IOTA) Phase V.	Franchi	226	230
A phase II, open label, single arm, non-randomized, multi-center, study to evaluate the efficacy of oral TKI258 as second- line therapy in patients with either FGFR2 mutated or wild-type advanced and/or metastatic endometrial cancer.	Colombo	3	3
Multicenter, randomized, non comparative, open label phase II trials on the efficacy and safety of the combination of bevacizumab and trabectedin with or without carboplatin in adult women with platinum partially sensitive recurring ovarian cancer.	Colombo	8	8
A multicenter study in patients with stage III-IV epithelial ovarian cancer treated with carboplatin/paclitaxel with bevacizumab: clinical and biological prognostic factors.	Colombo	20	20
Randomized phase II study of NGR-hTNF plus an anthracycline vs an anthracycline alone in platinum resistant ovarian cancer.	Colombo	1	1
A Double-blind, Placebo-controlled, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of Maintenance Therapy With PankoMab-GEX™ After Chemotherapy in Patients With Recurrent Epithelial Ovarian Carcinoma.	Colombo	2	2
A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer following First Line Platinum Based Chemotherapy.	Colombo	1	1
A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy.	Colombo	0	0
Urological			
Sunitinib either before or after cytoreductive nephrectomy. A phase II trial in patients with metastatic renal cell carcinoma. GIR 1	Nolè	0	6
Study VEG108844, a Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma.	Nolè	0	1
Medical optimization of TORisel (MoTOR): multicenter phase II evaluation of Torisel as II-line treatment for metastatic RCC patients progressing after cytokine therapy, tyrosine kinase or angiogenesis inhibitors.	Nolè	0	1
Randomized phase II study assessing the combination of Vinflunine with Gemcitabine and Vinflunine with Carboplatin in patients ineligible to cisplatin with advanced or metastatic transitional cell carcinoma of the urothelium. Lo0070 IN 213 P1.	Nolè	0	1
Melanoma & Sarcomas			
PEG-Intron versus observation after regional lymph node dissection in AJCC stage III (TxN1-2Mo) melanoma patients: a randomized phase III trial. EORTC 18991	Testori	0	57
Multicenter Selective Lymphadenectomy Trial II (MSLT II): A Phase III Multicenter Randomized Trial of Sentinel Lymphadenectomy and Complete Lymph Node Dissection versus Sentinel Lymphadenectomy Alone in Cutaneous Melanoma Patients with Molecular or Histopathological Evidence of Metastases in the Sentinel Node.	Testori	5	93
Phase II study of dacarbazine with anti-vascular endothelial growth factor antibody (bevacizumab) in patients with unresectable/metastatic melanoma. Prot. ML18727	Munzone	0	36
A multicenter, randomized, double-blind, two-arm, phase III study in patients with untreated stage III (unresectable) or IV melanoma receiving Dacarbazine plus 10 mg/kg of Ipilimumab (MDX-010) vs Dacarbazine with placebo.	Testori	0	11
Prospective multicentre study of elettrochemotherapy, for patients with cutaneous and subcutaneous metastases unresponsive to, or ineligible for standard treatments.	Testori	0	40
A phase III clinical trial to evaluate the safety and efficacy of treatment with 2 mg intralesional Allovectina-7 compared to Dacarbazine (DTIC) or Temozolamide (TMZ) subjects with recurrent metastatic melanoma.	Testori	0	11
A multinational, randomized, double-blind placebo controlled study of AVE8062 (25 mg/m^2) administered every 3 weeks, in patients with advanced-stage soft tissue sarcoma treated with cisplatin (75 mg/m^2) after failure of anthracycline and ifosfamide chemotherapies.	De Pas	0	1
A double blind randomized placebo controlled phase III study to assess the efficacy of recMAGE-A3 + AS15 ASCI as adjuvant therapy in patients with MAGE-A3 positive resected stage III melanoma. GSK 2132231A DERMA	Testori	0	29
Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (Ipilimumab) versus placebo after complete resection of high-risk stage III melanoma: A randomized double-blind phase 3 trial of the EORTC melanoma group.	Testori	0	32
Phase III, randomized, double blind trial on Vitamin D supplementation for resected stage II melanoma patients. MelaVid.	Testori	19	37
An open, single-arm trial to assess the clinical activity of recMAGE-A3 + AS15 in patients with unresectable MAGE-A3-positive metastatic cutaneous melanoma. 111476 MAGE3-AS15-MEL-001	Testori	0	5
An open label multicentre phase III trial of ABI-007 vs Dacarbazine in previously untreated patients with metastatic malignant melanoma. CA033	Testori	0	17
BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients with Unresectable Stage IIIC or Stage IV Melanoma.	Testori	0	14
An open, dose escalation phase I/II study to assess the safety, immunogenicity and clinical activity of recPRAME+AS15 antigen specific cancer immunotherapeutic as first line treatment of patients with PRAME-positive metastatic melanoma. 113173	Testori	0	10
An Open-Label, Multicenter, Randomized, Phase Ib/II Study of E7080 in Combination with Dacarbazine versus Dacarbazine Alone as First Line Therapy in Patients with Stage IV Melanoma.	Testori	0	13
NIBIT-M1: A phase II study of the combination of Ipilimumab and fotemustine in patients with unresectable locally advanced or metastatic malignant melanoma.	Testori	0	9
The TEAM trial (Tasigna efficacy in advanced melanoma): A randomized, phase III, open label, multi-center, two-arm study to compare the efficacy of Tasigna versus dacarbazine (DTIC) in the treatment of patients with metastatic and/or inoperable melanoma harboring a c-Kit mutation. CAMN107B2301	Testori	0	2
MEK114267 A Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma.	Testori	0	1
A prospective, multicenter, randomized, open-label, activecontrolled, two-parallel groups, phase 3 study to compare the efficacy and safety of masitinib at 7.5 mg/kg/day to dacarbazine in the treatment of patients with non-resectable or metastatic stage 3 or stage 4 melanoma carrying a mutation in the juxta membrane domain of c-kit.	Testori	6	6
Constitution of a clinical national melanoma registry.	Testori	29	63
Localized high risk soft tissue sarcomas of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadjuvant chemotherapy. ISG-STS 10-01	De Pas	1	2
An open label multicentre expanded access study of RO5185426 in patients with metastatic melanoma. MO25515	Testori	0	45

A randomized open label multi center phase III study to compare the efficacy and safety of Eribulin with Dacarbazine in subjects with soft tissue sarcoma. E7389-G000-309	De Pas	1	3
Research Project MultiMEL Role of genes in high-and low-incidence susceptibility to multiple melanoma.	Testori	13	72
A phase III, randomized double-blind study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first line therapy in subjects with unresectable (stage IIIC) or metastatic (stage IV), BRAF V600E/K mutation-positive cutaneous melanoma. MEK115306	Testori	0	5
A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma.	Testori	2	2
Prognostic role of melanoma follow up. A prospective randomised study.	Testori	2	2
Phase III, randomized, double-blind, placebo-controlled study of Vemurafenib (RO5185426) adjuvant therapy in patients with surgically-resected cutaneous BRAF mutant melanoma at high risk for recurrence (BRIM8).	Testori	1	1
Adjuvant Pegylated-Interferon-alpha2b (SylatronTM) for 2 years vs Observation in patients with an ulcerated primary cutaneous melanoma with T(2-4)bN0M0: a randomized phase III trial of the EORTC Melanoma Group.	Testori	0	0
A multicentre, open label, randomized Phase II trial of the MEK inhibitor pimasertib or dacarbazine in previously untreated subjects with N-Ras mutated locally advanced or metastatic malignant cutaneous melanoma.	Testori	3	3
A phase III, double-blind, placebo-controlled study of vemurafenib + placebo versus vemurafenib in combination with GDC-0973 in previously untreated BRAF V600 -mutation positive patients with unresectable locally advanced or metastatic melanoma.	Testori	0	0
A phase III, randomized, double-blind study of Dabrafenib (GSK2118436) in combination with trametinib GSK1120212) versus placebo in the adjuvant treatment of high-risk BRAF V600E/K mutation-positive melanoma after surgical resection.	Testori	0	0
A Randomized, Open-Label Phase 3 Trial of BMS-936558 versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy.	Testori	5	5
A phase III, randomized, double-blind study of BMS-936558 vs dacarbazine in subjects with previously untreated unresectable or metastatic melanoma.	Testori	1	1
An open Phase I study of immunization with the recNY-ESO-1 + AS15 Antigen-Specific Cancer Immunotherapeutic in patients with NY-ESO-1 positive unresectable and progressive metastatic cutaneous melanoma.	Testori	0	0
A randomized open label multicenter phase II study of Ipilimumab retreatment vs chemotherapy for subject of advanced melanoma who progressed after initially achieving disease control with ipilumumab therapy.	Testori	1	1
A Phase III, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma.	Testori	11	11
Miscellanea			
Thalidomide in the treatment of patients with primitive cancer of the liver. A clinical/biological study.	Fazio	0	24
Application of confocal endomicroscopy in the staging of pre malignant and neoplastic lesions of the gastrointestinal tract.	Crosta	0	365
Fears, prejudices, expectations and perceptions of cancer patients deriving from the proposal to participate in a clinical trial.	Catania	0	208
Clinical phase II trial to evaluate the safety and efficacy of treosulfan based conditioning prior to allogeneic haematopoietic stem cell transplantation in patients with haematological malignancies.	Martinelli	0	15
A new induction therapy (ThalDoDex) for multiple myeloma. A phase II study.	Martinelli	0	38
Early feeding after gynecologic laparotomy: a randomized controlled trial.	Maggioni	0	193
A randomized double-blind placebo-controlled multicenter phase III in patients with advanced carcinoid tumor receiving Sandostatin LAR® e RAD001 10 mg/d or Sandostatin LAR® and placebo (CRAD001C2325).	Fazio	0	11
Phase I/II study of the tumor-targeting human L19IL2 monoclonal antibody-cytokine fusion protein in combination with gemcitabine in patients with advanced pancreatic cancer.	Catania	1	5

Piperacillin/Tazobactam plus Tigecycline as empirical therapy for febrile neutropenic cancer patients: a prospective, randomised, multicentre, study.	Martinelli	0	10
Effect of mechanical bowel preparation with polyethylene glicol plus bowel enema (glycerin 5%) vs bowel enema alone in patients candidates to colorectal resection for malignancy. Prospective randomized trial.	Biffi	23	308
A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET). CRAD001C2324	Fazio	0	6
Study on the impact of GARDASIL vaccination program within a population of 18th years old girls.	Sideri	0	753
Prevention of atrial fibrillation in patients undergoing thoracic surgery for lung cancer (PRESAGE study).	Cardinale	35	320
A randomised, double blind, placebo controlled, multicentre, phase III study of post-operative adjuvant Lapatinib or placebo and concurrent chemoradiotherapy followed by maintenance Lapatinib or placebo monotherapy in high risk subjects with resected squamous cell carcinoma of the Head and Neck (SCCHN).	Nolè	0	4
A phase I pharmacokinetic and pharmacodynamic study of PF-03446962 in patients with advanced solid tumors. A8471001	Noberasco	0	18
Imatinib mesylate in advanced low grade solid tumors expressing imatinib mesylate targets.	De Pas	0	15
Neoadjuvant Docetaxel plus Cisplatin and 5-Fluorouracil (TPF) followed by radiotherapy plus concomitant chemo or Cetuximab versus radiotherapy plus concomitant chemo or Cetuximab in patients with locally advanced squamous cell carcinoma of the head & neck. A randomized phase III factorial study.	Nolè	0	29
A dose-finding, pharmacokinetic, Phase Ib/II study of the tumour-targeting human F16IL2 monoclonal antibody-cytokine fusion protein in combination with doxorubicin in patients with advanced solid tumours.	Catania	0	10
A dose-finding pharmacokinetic phase Ib/II study of the tumor-targeting human F16IL2 monoclonal antibody-cytokine fusion protein in combination with Paclitaxel in patients with advanced solid tumours. PH-F16IL2TAXO-05/07	Catania	2	20
A Phase III, Randomized, Open-Label, 3-Arm Study To Determine the Efficacy and Safety of Lenalidomide (RevlimidÒ) Plus Low-Dose Dexamethasone When Given Until Progressive Disease or for 18 Four-Week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Patients with Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation (IFM 07-01).	Martinelli	0	3
A multi center randomized blinded efficacy and safety study of pasireotide LAR versus ocreotide LAR in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by somatostatin analogues. CSOM230C2303	Fazio	0	1
Eps8 gene and deafness: from mouse to man through genomic and proteomic study.	Goldhirsch	0	44
Phase I/II trial with sorafenib in combination with RAD001 administered orally in patients with advanced solid tumors, selected on the base of molecular targets.	De Pas	0	17
Allogenic hematopoietic cell transplantation using a non myeloablative preparative regimen of total lymphoid irradiation and anti-thymocyte globulin for patients with hematologic malignancies. TLI-001-2007	Martinelli	2	6
Pharmacoepidemiological cohort study, prospective, non-randomized, open-label, multicenter study to evaluate, on the basis of clinical and histopathological data specific for diagnostic purposes, the magnitude of the potential risk of developing a systemic fibrosis. PERI study 13701	Bellomi	0	12
A non interventional observational post authorisation safety study of subjects treated with lenalidomide.	Martinelli	4	21
Expectations and fears of women before and after the diagnosis of breast cancer: analysis according to family history and stage of disease.	Catania	0	250
An open-label, multi-centre, dose escalating, phase I/ randomized phase II study to investigate the safety and tolerability of RO5072759 given as monotherapy in patients with CD20+ malignant disease.	Martinelli	0	8
A randomized double blind multicentre phase III study of Brivanib versus Sorafenib as first line treatment in patients with advanced hepatocellular carcinoma.	Noberasco	0	5
RAMSETE: A single arm multicenter single-stage phase II trial of RAD001 in advanced and metastatic silent neuro endocrine tumours in europe.	Fazio	0	3
Phase IIB Randomized, Placebo Controlled Trial of Pioglitazone for Oral Premalignant Lesions. An Inter-Consortium Collaborative Study.	Chiesa	1	9
An open label phase I dose escalation trial of intravenous BI 6727 in combination with oral BIBF 1120 in patients with advanced solid tumours with repeated administration in patients with clinical benefit.	De Pas	0	18

Nonmyeloablative Hematopoietic Stem Cell Transplantation for Patients with High-Risk Hematologic Malignancies using Related, HLA-Haploidentical Donors: A Phase II Trial of Combined Immunosuppression Before and After Transplantation.	Pastano	3	19
An open label dose escalation phase I study to determine the maximum tolerated dose recommended dose pharmacokinetics and pharmacodynamics of the dual VEGFR-FGFR tyrosine kinase inhibitor E-3810,given orally as single agent to patients with advanced solid tumours.	Noberasco	0	12
Isotonic contrast (iodixanol) administration vs low osmolar contrast (iopromide) use: evaluating risk of contrast induced nephropathy in cancer patients at very low risk.	Bellomi	8	56
A clinical biological study in patients with non poorly differentiated enteropancreatic new neuroendocrine carcinoma with liver metastasis treated with RAD001 (EVEROLIMUS).	Fazio	5	12
New molecular tests in the diagnosis and the follow up after treatment of pre-malignant lesions.	Sandri	15	188
Phase I dose escalation study of oral administration of the Pan-Histone Deacetylase (HDAC) Inhibitor S 78454 in combination with standard hypofractionated radiotherapy in patients with advanced solid tumour. CI1-78454-004	Noberasco	0	6
PR.O.C.I. (PReoperative Oral Carbohydrate Ingestion) - Effects on glucose metabolism and post-operative infectious complications' rate.	Biffi	13	67
Perspective evaluation ofQTC-interval in an unselected population with malignant tumor who received chemotherapy treatments (associated or not with other anticancer drugs).	Cardinale	0	0
Dose escalation safety pharmacokinetic and pharmacodynamic "first in men" study of SAR 125844 single agent administered as slow intravenous infusion in adult patients with advanced malignant solid tumors. TED 11449.	Spitaleri	7	18
Survey on the incidence of abnormalities and irritant contact dermatitis (ICD) in patients colo-ileo-urostomies using a shapeable barrier (RADIC Study).	Tarantino	0	23
Identification of the mitochondrial mechanisms and markers of cardiotoxicity to improve antineoplastic drugs tolerance.	Cipolla	30	41
A randomized, open-label phase II multicenter study evaluating the efficacy of oral Everolimus alone or in combination with Pasireotide LAR i.m. in advanced progressive pancreatic neuroendocrine tumors (PNET) – The COOPERATE-2 study CSOM2301 2201.	Fazio	0	8
Evaluation of early smoking reduction or cessation by means of electronic cigarette added to standard counseling.	Cipolla	19	72
Phase II study of everolimus in patients with thimoma and thimic carcinoma previously treated with chemotherapy.	De Pas	6	11
A phase III trial comparing bortezomib, cyclophosphamide and dexamethasone versus lenalinomide cyclophosphamide and dexamethasone in patients with multiple myeloma at first relapse.	Martinelli	1	1
Lymphatic mapping in oropharyngeal neoplasms: comparison between Dynamic Lymphoscintigrafy and Fluorescence Lymphografy using indocyanine green dye (ICG). Validation study.	Calabrese	4	6
A single arm open label phase II multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma. MO25616	Testori	1	9
An open label multi center extension study of Trastuzumab-MMCC-DM1 (T-DM1) administered as a single agent or in combination with other anti-cancer therapies in patients previously treated with the equivalent T-DMM1 regimen in Genentech and/or F.Hoffman la Roche ltd sponsored T-DM1 study. TDM4529 97BO25430	Goldhirsch	0	1
Patient Empowerment.	Munzone	59	93
A prospective observational study of related donors of hematopoietic stem cells.	Laszlo	11	27
A multicenter randomized double blind placebo controlled phase III trial of E7080 In 131 I refractory differentiated thyroid cancer.	Nolè	0	1
A randomized phase III study of weekly ABI-007 plus Gemcitabine vs Gemcitabine alone in patients with methastatic adenocarcinoma of the pancreas.	Fazio	0	1
A multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTAo-Tyr3-Octretate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors.	Paganelli	3	3
A randomized double blind multicenter phase III study of everolimus (RAD001) plus best supportive care vs placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin. CRAD001T2302 - RADIANT4	Fazio	4	10
A single arm open label international multicenter study of the efficacy of sunitinib malate (SU011248, Sutent) in patients with progressive advanced metastatic well differentiated unresectable pancreatic neuroendocrine tumors. A61181202	Fazio	6	9
Prevention of anthracycline-induced cardiotoxicity: a multicentre randomized trial comparing two therapeutic strategies.	Cipolla	10	10
Nonmyeloablative Hematopoitic Stem Cell Transplantation for patients with high risk solid tumors using Related HLA-identical donors or irrelate HL- Haploidentical Donors: a monocentric phase II trial.	Pastano	0	0
A randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of afatinib (BIBW 2992) as adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced head and neck squamous cell carcinoma.	Cossu Rocca	0	0
Pilot study of counselling in oncology.	Bonanni	38	38
Axillary Web Syndrome auto-diagnosis questionnaire validation.	Simoncini	0	88
A multicenter, two stage, phase II study, evaluating the efficacy of oral BEZ235 plus best supportive care (BSC) versus placebo plus BSC in the treatment of patients with advanced pancreatic neuroendocrine tumors (pNET) after failure of mTOR inhibitor therapy. CBEZ235F2201	Fazio	3	3
Feasibility study to assess safety of high dose of Lanreotide in patients with NET poorly controlled by standard doses of SSA.	Fazio	6	6
Evaluation of the use of dermocosmetic products in the prevention of skin side effects expected during anti-cancer therapies.	Orecchia	6	6
TOTAL 2013		**3602**	**23922**

Ongoing Grants, Research Agreements and Fellowships - 2013 & 2014

Agenzia Italiana del Farmaco

- Valutazione del rischio di nefropatia da mezzi di contrasto isotonici (iodixanolo) vs. mezzi di contrasto a bassa osmolarità (Iopromide) nei pazienti oncologici a rischio molto basso. (M. Bellomi)

Association for International Cancer Research

- Functional contribution of L1 to tumor/microenvironment interactions in pancreatic carcinoma. (U. Cavallaro)
- Functional dissection of the epigenetic basis of glioma recurrence. (G. Testa)
- Myc-induced senescence: biological and therapeuthic implications. (B. Amati)
- Characterization of the genomic regulatory landscape of tumor-associated macrophages. (G. Natoli)
- DNA damage- and oncogene- induced checkpoints in adult stem cells. (P.G. Pelicci)
- Study of the role of endogenous and exogenous TLR4 ligands in skin carcinogenesis. (M. Rescigno)

Associazione Italiana per la Ricerca sul Cancro

- New and innovative technologies in the integrated surgical treatment of breast carcinoma. (A. Luini)
- The spindle assembly checkpoint as a target in anti-tumor therapy. (A. Musacchio)
- Phase III study of low dose tamoxifen in women with breast intraepithelial neoplasia. (B. Bonanni)
- Metformin: genetic profiling and treatment of women with early breast cancer. (B. Bonanni)
- Short-term high precision radiotherapy for early prostate cancer with concomitant boost on the dominant lesion.(B. Jereczek)
- Characterization of epigenetic mechanisms of transcriptional regulation in differentiation and cancer. (D. Pasini)
- New therapeutic targets for the treatment of NPMc+ Acute myeloid leukaemia. (E. Colombo)
- Molecular crosstalk between cancer and aging: the p53-p66Shc signalling pathway. (E. Migliaccio)
- Targeting adipose cell contribution to breast cancer angiogenesis, local and metastatic growth. (F. Bertolini)
- From resistance to anti-VEGF drugs to “next generation” anti-angiogenic therapies of cancer. (F. Bertolini)
- Dissecting the influences of genotype and environment on the proliferation dynamics of colorectal cancer. (F. Ciccarelli)
- Study of the cross-talk between neutrophils and invariant Natural Killer T (iNKT) cells in IBD-associated colorectal cancer. (F. Facciotti)
- Dissecting transcriptional control of cytologic grading in pancreatic cancer: a reverse epigenomic approach. (G. Natoli)
- 177Lu-DOTATATE+metronomic capecitabine in pts with aggressive gastro-entero-pancreatic neuroendocrine tumors. (G. Paganelli)
- Study of the molecular mechanisms mediating the development of brain metastasis in breast cancer. (G. Pelicci)
- Silencing chromatin in the pathogenesis of brain cancer. (G. Testa)
- Lung cancer early detection with low dose CT scan and molecular markers. (G. Veronesi)
- Breath test in lung cancer patients. (L. Spaggiari)
- Comparative analysis of genomic and epigenomic alterations induced by leukemogenic AML1/RUNX1 fusion proteins. (M. Alcalay)
- Bridging mmWeave biophysics, safety and imaging. (M. Bellomi)
- Mechanisms of mitotic spindle coupling to cellular polarity in normal and cancer stem cells. (M. Mapelli)
- Evaluation of gap junction-dependent antigen cross presentation in human DCs and of combinatorial therapies. (M. Rescigno)
- Regulation of kinetochore activity and chromosome segregation by the novel, conserved kinetochore kinase Rio1. (P. De Wulf)
- Mechanisms of de-regulation of self-renewal and differentiation in cancer stem cells. (P.G. Pelicci)
- Replication, plasticity and survival of cancer stem cells: intrinsic and extrinsic mechanisms regulated by p53 and p21. (P.G. Pelicci)
- Understanding how cancer stem cells drive breast cancer growth and how to exploit them as its Achilles’ heel. (P.P. Di Fiore)
- Analysis of characteristics of Plasma Focus beams: its future oncological applications. (R. Orecchia)
- Carbon ions boost followed by pelvic photon radiotherapy for high risk prostate cancer. (R. Orecchia)
- Role of p53 in mediating the tumour suppressor activity of caloric restriction. (R. Pallavi)

- Regulation of chromosome segregation by the conserved Cdc14 phosphatase and Cdc5 kinase. (R. Visintin)
- Post-translational modification of proteins. (S. Chiocca)
- Functional epigenomics of cancer. (S. Minucci)
- Functional epigenomics of acute myeloid leukemia initiation and maintenance. (S. Minucci)
- Melanocortin 1 receptor variants in skin carcinogenesis: a pooled analysis. (S. Raimondi)
- A multi-tiered approach to target Numb dysfunction in human cancer. (S.Pece)
- The code of methylation for epigenetic therapy: proteomics deciphers the methylome and its regulatory enzymes. (T. Bonaldi)
- The functional role and clinical implications of cancer stem cells in ovarian carcinoma. (U. Cavallaro)

Consiglio Nazionale delle Ricerche

- Le cellule staminali tumorali come bersaglio di nuovi farmaci epigenetici. (S. Minucci)
- Ruolo epigenetico della metilazione dell’istone H3 sulla lisina 27 e sulla lisina 4 nella riprogrammazione neuronale diretta e nella riacquisizione della pluripotenza. (G. Testa)
- ChroP come approccio per lo studio del proteoma delle regioni regolatorie dei geni coinvolti nell’infiammazione. (T. Bonaldi)

European Commission

- Developing a global understanding of the PRC and NuRD complexes in stem cell From data sharing and integration via VPH models to personalised medicine (p-Medicine). (A. Goldhirsch)
- Connecting the activities of c-Myc in genome regulation, cellular growth control and oncogenesis (MYCNEXT). (B. Amati)
- Role of human papillomavirus infection and other co-factors in the aetiology of head and neck cancer in India and Europe. (HPV AHEAD). (F. Chiesa)
- A European platform for translational cancer research (EUROCANPLATFORM). (G. McVie)
- The genomic blueprint of macrophages: dissecting players and mechanisms through an integrative approach (NORM). (G. Natoli)
- Systems biology of liver cancer: an integrative genomic-epigenomic approach (MODHEP). (G. Natoli)
- Modeling disease through cell reprogramming: a translational approach to the pathogenesis of syndromes caused by symmetrical gene dosage imbalances (DISEASEAVATARS). (G. Testa)
- AnThocyanin and polyphenol bioactives for Health Enhancement through Nutritional Advancement (ATHENA). (M. Giorgio)
- Mucosal dendritic cells in intestinal homeostasis and bacteria-related diseases (DENDROworld). (M. Rescigno)
- 7kDa TSLP as a novel type of anti-inflammatory agent to re-establish immune homeostasis (7TRelmHo). (M. Rescigno)
- Universal Flu Vaccine (UniVacFlu). (M. Rescigno)
- Health-promoting cross-talk between intestinal microbiota and Humans (CROSSTALK). (M. Rescigno)
- Immune mechanisms that control the homeostasis of the gut and that are deregulated in intestinal pathologies cancer (HomeoGUT). (M. Rescigno)
- A BLUEPRINT of haematopoietic epigenomes (BLUEPRINT). (P.G. Pelicci)
- Inside mechanisms sustaining cancer stem cells (InMec). (P.G. Pelicci)
- Developing a global understanding of the PRC and NuRD complexes in stem cell differentiation, in health and disease (4D-CellFate). (S. Minucci)
- Supporting innovative learning approaches through Mobile Integration in the workpLacE - Oncology Nursing (SMILEON) (A. Milani)

European Organisation for Research and Treatment of Cancer

- Evaluation of Maspin as a new prognostic and predictive marker for melanoma patients. (C. Martinoli)

European Hematology Association

- Obesity-associated FLT3 mutations in Acute Promyelocytic Leukemia: investigating novel paradigm for the cancer-promoting effect of obesity. (L. Mazzarella)

Fondation Jerome Lejeune

- A cell reprogramming-based approach to understand neuronal disfunction in Williams Beuren Syndrome. (G. Testa)

Fondazione Giancarla Vollaro

- Cellule staminali neoplastiche e terapie innovative (P.G. Pelicci)

Fondazione Italiana per la Ricerca sul Cancro

- Clonal tracking and high throughput shRNA screening in murine AMLs. (A. Cammarata)
- Defining the interplay between EGFR endocytosis,signaling and cancer through predictive modeling and wet-lab experiments. (A. Conte)
- Role of polycomb group proteins in cancer development. (A. Piunti)
- Role of Polycomb proteins in intestinal development and in colorectal cancer formation. (A. Rossi)
- Investigating epigenetic patterns induced by diet for cancer prevention. (A. Russo)
- Electrochemical Imaging of Single Cell Warburg Effect. (A. Soldà)
- Monoclonal antibodies from phage libraries: new tools for the study of breast cancer stem cells. (A. Villa)
- HPVs manipulations of the SUMO pathway: implications for the host immune system elusion. (D. Mattoscio)
- Hemichannels of gap junctions in the release of tumor peptides. (E. Mazzini)

- A novel network regulating chromosome segregation: functional characterization of the Cdc14 dependent pathway. (F. Tili)
- Role of different isoforms of TSLP in colorectal cancer. (G. Fornasa)
- Correlation between NK cell functionality and response to trastuzumab treatment in HER2+ breast cancer patients. (I. Spadoni)
- Immunogenic cell death as possible predictive marker of response to EGFR-targeted therapy in CRC patient. (K. Tsilingiri)
- A bioinformatic approach to identify repressive chromatin networks in gliomagenesis. (P. Laise)
- Role of H3K27 methylation in gliomagenesis. (P. Tripathi)
- Dissecting the role of LSD1 in Acute Promyelocytic Leukemia. (P.L. Rossi)
- Function of complement and neutrophils in tumor-immunosurveillance. (S. Guglietta)
- The epigenome of tumor-associated macrophages and its functional implications. (S. Polletti)
- The role of Myc in the normal and malignant mammary gland. (T. Vlachou)
- MS-based proteomics to study the impact of protein methylation on structure and stability of the Microprocessor complex. (V. Spadotto)

Fondazione Telethon

- Animal models of neuroferretinopathies for the study of the role of iron in neurodegeneration. (M. Giorgio)
- An integrated strategy to functionally dissect the genetic and epigenetic mechanisms underlying Kabuki Syndrome. (G. Testa)
- Neurodevelopmental alterations in Weaver syndrome: a cell reprogramming-based approach to the elucidation of epigenetic disease mechanisms. (G. Testa)

Fondazione Umberto Veronesi

- Identificazione di biomarcatori in donne ad aumentato rischio familiare/genetico di tumore al seno con l'impiego del sistema HALO breast test.(B. Bonanni)
- Epigenetics of inflammation-driven intestinal tumorigenesis (D. Pasini)
- Genomics of treatment relapse in acute myeloid leukaemia in the over 60s.(F. Bertolini)
- Identificazione di non-coding RNAs serici come marcatori molecolari per la diagnosi dei tumori mediante "next-generation sequencing".(F. Nicassio)
- Genome Remodeling in Luminal B and Ductal Triple Negative Breast Cancer Metastasis and Xenograft: Targeting driver pathways to overcome resistance. (G. Curigliano)
- Peptide Receptor Radionuclide Therapy with 90Y-DOTATOC in resistant/refractory diffuse large B-cell NHL patients. (G. Paganelli)
- CLIC1 (Chloride intracellular channel 1) as a possible prognostic indicator and therapeutic target in glioblastoma. (G. Pelicci)
- Endoscopic treatment of broncho-pleural fistula by autologous stem cells transplantation. (L. Spaggiari)
- Targeting mitochondrial p53 impacts on tumorigenesis. (M. Giorgio)
- A phase II study of low-dose vaginal estrogens in pre- and postmenopausal breast cancer patients with urogenital atrophy. (M. Mazza)
- A randomized trial comparing sentinel lymph node biopsy vs. no axillary surgical staging in patients with small breast cancer and a negative preoperative axillary assessment. (O. Gentilini)
- Radioguided minimally invasive resection of early colon cancer and detection of sentinel lymphatic area. (P. Bianchi)
- Biomarkers studies on stage II melanoma patients treated with Vitamin D. (S. Gandini)
- Relationship between microbiota, Vitamin D and colorectal cancer: towards new possible cancer prevention strategies. (S. Gandini)
- New tools for diagnosis and therapy in lung carcinoids. (T. De Pas)

In addition, Fondazione Umberto Veronesi funded 28 fellowships in 2013 and 38 fellowships in 2014 through its *Young Investigator Program*.

Fondazione Centro Europeo di Nanomedicina

- Development of antibody functionalized PEG-PLGA nanoparticles for the specific delivery of chemotherapeutic drugs to human acute myeloid and T-lymphoblastic leukemia. (P.G. Pelicci)

Heinz Italia S.p.A.

- Studio delle proprietà funzionali di matrici fermentate su campioni di biopsie di intestino, cellule immunitarie derivate da sangue o modelli animali. (M. Rescigno)

Istituto Nazionale Assicurazione contro Infortuni sul Lavoro

- Sviluppo di un sistema integrato per la sorveglianza di esposti ed ex esposti amianto. (G. Veronesi)

Ministero della Salute

- The role of leukaemia-specific mutant of NPM1 in activation of Wnt signalling, retinoic acid sensitivity in NPMc+AML. (A. Gruszka)
- Identification of critical p53 co-regulators and effectors during tumor suppression. (B. Amati)
- Prevenzione del tumore mammario con fenretinide in donne giovani ad aumentato rischio familiare-genetico (TEVERE). (B. Bonanni)
- Activity of metformin on cell proliferation in patients with early breast cancer. (B. Bonanni)
- Unraveling the molecular mechanisms of RAI pro-invasive function in glioblastoma derived cancer stem cells. (B. Ortensi)
- Prevention of anthracycline-induced cardiotoxicity: a multicentre randomized trial. (C. Cipolla)

- The kinetochore NDC80 complex as a novel anticancer drug target. (C. Pagliuca)
- Epigenetic regulation of transcription in cellular differentiation and cancer formation. (D. Pasini)
- Role of Polycomb Repressive Complexes in Intestine Development and Colorectal Cancer Formation. (D. Pasini)
- Self-Extinction of Stem Cells and the Spontaneous Regression/ Dormancy of Breast Cancer. (D. Tosoni)
- Identification and validation of new therapeutic targets in Acute Myeloid Leukaemia. (E. Colombo)
- Biomarker-driven development of 3rd generation anti-angiogenic cancer therapies. (F. Bertolini)
- Set up of high sensitivity mutational assay to detect cancer-associated genomic instability using next-generation sequencing technology. (F. Ciccarelli)
- Genotype and environment influences on the tumor proliferation dynamics inferred with next generation sequencing. (F. Ciccarelli)
- Il paziente oncologico lungo sopravvivente. Ridurre il rischio di complicanze riproduttive: un modello per le pratiche assistenziali di preservazione della fertilità. (F. Peccatori)
- CD3 and CD20 lymphocytes infiltration predict chemosensitivity in patients with triple negative breast cancer (UGI1). (G. Curigliano)
- Defining the cis-regulatory bases for variability in inflammatory gene expression in humans: a 3-D analysis in the nuclear space. (G. Natoli)
- Peptide receptor radionuclide therapy with 177Lu-DOTATATE associated with metronomic capecitabine in patients affected by aggressive gastro-entero-pancreatic neuroendocrine tumors. (G. Paganelli)
- The role of Polycomb group proteins in oncogenesys and cell reprogramming. Applications in cancer therapy and regenerative medicine. (G. Testa)
- The Epigenomics of Eating Disorders - "FOOD For THOUGHT (F4T)". (G. Testa)
- Epigenetics of glioblastoma multiforme: pathogenetic role of the genes controlling H3K27 methylation. (G. Testa)
- Targeting strategies in Numb-defective cancers. (I. Colaluca)
- Obesity-associated Flt3 mutations in Acute Promyelocytic Leukemia: investigating a novel paradigm for the cancer-promoting effect of obesity. (L. Mazzarella)
- Predective factors in endocrine unresponsive breast cancer patients. (M. Colleoni)
- Targeting late recurrence after adjuvant treatment for early breast cancer. (M. Colleoni)
- An image-analysis platform for automated in-situ high-content and resolution analysis of tumor heterogeneity: targeting genomic, epigenetic, and functional diversity in tissues by fluorescence microscopy. (M. Faretta)
- Epigenetic control of breast cancer progression: animal and clinic studies. (M. Giorgio)
- Designing strategies to target cancer stem cells: a study on the molecular bases of mitotic spindle coupling to polarity cues in mammalian asymmetric divisions. (M. Mapelli)
- The role of the lymphatic system in inflammatory bowel disease pathogenesis: a novel therapeutic target (M. Rescigno)
- Study of coagulation and tumor-associated neutrophils in intestinal cancer development. (M. Rescigno)
- Analysis of the role of different isoforms of thymic stromal lymphopoietin and the microbiota in T cell activation in inflammatory conditions of the gut. (M. Rescigno)
- Prospective Characterization of Circulating Tumor Cells in Patients with Hormone Receptor Positive Metastatic Breast Cancer. (M.T. Sandri)
- La gestione del rischio clinico attraverso un approccio integrato: definizione di standard minimi per le organizzazioni sanitarie italiane. (O. Rinaldi)
- Tailored accreditation model of comprehensive cancer centers: validation through the applicability of the experimental OECI-based model to the netwok of cancer IRCCS of Alleanza Contro il Cancro. (P. Deriu)
- Identification of molecular targets of anti-tumor effect of caloric restriction. (R. Pallavi)
- Regulation of mitotic transitions. (R. Visintin)
- Reorganization of the macrophage epigenome during sustained inflammation and its functional implications. (S. Ghisletti)
- Development of cytochrome c assay marker of ischemia/ reperfusion damage to the heart. (S. Rapino)
- Quantitative proteomics to decipher the molecular code of protein methylation: the dynamic methylome dissected by MS and its role in cancer. (T. Bonaldi)
- ChroP, a combined ChIP-Mass Spectrometry proteomics approach, to dissect composition and plasticity of the modificome and intractome of cis-regulatory regions of inflammatory genes. (T. Bonaldi)
- Immune Cells as Predictors for Early Diagnosis and Chemotherapy Toxicity in Ovarian Cancer (ImPECT). (M. Sideri)

Ministero dell'Istruzione, dell'Università e della Ricerca

- Epigenetica e alterazioni metaboliche nella patogenesi molecolare delle neoplasie: impatto della restrizione calorica nella prevenzione e terapia dei tumori (P.G. Pelicci)
- Infiammazione e cancro: approcci innovativi basati su nanotecnologie. (G. Natoli)
- Nanosistemi avanzati per una nuova oncologia molecolare (P.P. Di Fiore)

National Institutes of Health

- A mitochondrial longevity pathway: p66shc. (P.G. Pelicci)

National Institute on Aging

- Shcs, mitochondria, healthy aging and longevity. (P.G. Pelicci)

Intercept Pharmaceuticals, Inc.

- Analysis of the activity of 6α-ethyl-3α,7α-dihydroxy-5β-cholan-24-oicacid (Obeticholic acid, OCA) and INT-767 on inflammation, intestinal tumorigenesis, blood endothelial barrier and mutual relationship with gut microbiota. (M. Rescigno)

OncoMed Pharmaceuticals, Inc.

- Pre-clinical assessment of the efficacy of anti-Notch receptor monoclonal antibodies using primary cells from breast and non-small cell cancers in ex-vivo cell-based assays. (P.P. Di Fiore)

Quanticel Phamaceuticals Inc.

- Post-translational modifications (PTMs) on Histone H3/H4 by high-resolution mass specrtometry analysis. (T. Bonaldi)

Regione Lombardia

- Discovery validation of anticancer drugs (DIVA). (M. Varasi)
- Progetto di farmacovigilanza FARMAMONITO (E. Omodeo Salé)
- Progetto ROL3: diffusione della Rete (O. Rinaldi)
- Riconoscimento precoce della cardiotossicità dei farmaci antitumorali ed effetti dell'intervento farmacologico con ACE-inibitore sulla sopravvivenza cellulare miocardica (Ricerca Indipendente). (C. Cipolla)
- Segnalazione di reazioni avverse precoci e tardive dovute all'uso di nuovi farmaci in ambito onco-ematologico. (FARMAREL). (G.Martinelli)
- Gruppo Collaborarivo Lombardo per i Tumori della Mammella - Progetto SOLE (Senologia Oncologica Lombarda di Eccellenza). (S. Zurrida)

STMicroelectronics

- Portable system for the measurement of microRNA pattern in blood content. (M. Giorgio)

The Giovanni Armenise Harvard Foundation

- Quantitative proteomics for the analysis of the epigenetic regulation of gene expression. (T. Bonaldi)

Seminars 2013
Basic science seminars (SEMM)

1 January 09 – Daniela Rotin (Toronto, Canada): "Regulation and Functions of the Ubiquitin Ligase Nedd4"

January 10 – Chiara Gorrini (Toronto, Canada): "Oxidative stress regulation in BRCA1-associated breast cancer"

January 18 – Luisa Iruela-Arispe (Los Angeles, USA): "Angiogenesis impairment in diabetes: Can we make molecular sense of it all?"

January 21 – Stephen Smale (Los Angeles, USA): "Selective regulation of transcription in macrophages"

January 22 – Pier Paolo Scaglioni (Dallas, USA): "Metabolic and signaling vulnerabilities of mutant KRAS lung adenocarcinoma"

2 February 04 – Göran Hermerén (Lund, Sweden): "Setting priorities in health care"

February 13 – Chiara Locarno, (Milan, Italy): "Biological effects of self-assembling peptides on neural stem cells proliferation and differentiation"

February 14 – Jirí Bártek (Copenhagen, Denmark): "DNA damage response: Mechanisms and relevance for cancer development and treatment"

February 18 – Leah Gheber (Negev, Israel): "S. cerevisiae Kinesin-5 motors in reverse gear"

February 22 – Rune Toftgård (Huddinge, Sweden): "Hedgehog Signalling and Skin Cancer Initiation"

3 March 01 – Silke Hauf (Tübingen, Germany): "Not all are equal: Drastic variation in spindle assembly checkpoint signaling capacity in a genetically homogenous population"

March 05 – Dan Littman (New York, USA): "Crosstalk of the microbiota and the immune system in health and inflammatory disease"

March 11 – Daniele Del Rio (Parma, Italy): "Dietary (poly) phenols in human health and disease prevention: new perspectives for an old paradigm"

March 15 – Brian Hendrich (Cambridge, UK): "Transcriptional control of stem cell fate"

March 22 – Matthias Peter (Zurich, Switzerland): "Regulation and function of Cullin-based E3 ubiquitin ligases"

March 25 – Giulia Guarguaglini (Rome, Italy): "The Aurora-A/TPX2 complex in mitosis and cancer"

4 April 05 – Danijela Vignjevic (Paris, France): "Actin cytoskeleton in cancer cell migration and invasion"

April 09 – Tim Hunt (London, UK): "Controlling mitosis: the importance of phosphatases"

April 15 – Andrea Ventura (New York, USA): "MicroRNAs in cancer and development: a tale of mice and men"

April 19 – Antonio Simeone (Naples, Italy): "The role of the transcription factor Otx2 in embryonic Pluripotent Stem Cells (ESCs and EpiSCs)"

April 22 – Rong Li (Kansas City, USA): "Mechanisms of actin-based force generation in cell motility and asymmetric cell division"

April 23 – Riccardo Dalla Favera (New York, USA): "The genomic landscape of diffuse large B cell lymphoma"

April 30 – Roberto Mosca (Barcelona, Spain): "Interactome3D: adding structural details to protein networks"

5 May 10 – Peter K. Rogan (Ontario, Canada): "Discovery and predicted consequences of non-coding sequence variants affecting gene expression on a genome-scale and in inherited breast cancer"

May 15 – Michele Caselle (Turin, Italy): "The role of transposable elements in shaping the combinatorial interaction of transcription factors"

May 17 – Nicoletta Bobola (Manchester, UK): "Shaping the vertebrate body plan: genome-wide maps of Hox and cofactors at work"

May 20 – Simone Cenci (Milan, Italy): "Autophagy in plasma cell ontogenesis and myeloma"

May 22 – Chris Ponting (Oxford, UK): "Shining a light on 'dark matter' genes: molecular mechanisms of lncRNAs"

May 23 – Weimiao YU (Singapore): "Computational Image Analysis: Quantitative Understanding of Migrating Cells"

May 24 – Nancy Kleckner (Cambridge, USA): "Four-dimensional imaging of E.coli chromosomes in living cells reveals a mechanical mechanism for sister segregation and a primordial cell cycle"

May 28 – Douglas Hanahan (Lausanne, Switzerland): "Genetic modifiers and micro-environmental control of tumor invasiveness"

May 31 – Luca Guidotti (Milan, Italy): "Advanced imaging to dissect the pathogenesis of HBV infection and HBV-associated liver cancer in animal models"

6 June 03 – Chrystelle Maric Antoinat (Paris, France): "DNA replication: from post-replicative joint DNA molecules to origin recognition complex dynamics"

June 07 – Gou Young Koh (Daejeon, Republic of Korea): "Organotypic Angiogenesis and Vascular Remodeling"

June 07 – Catherine Dargemont (Paris, France): "Ubiquitin conjugation: a timing mechanism for nuclear functions"

June 10 – Francesco Ferrari (Boston, USA): "Genome-wide chromatin interactions of the Nanog locus in pluripotency, differentiation and reprogramming"

June 10 – Nils G. Walter (Ann Arbor, USA): "Single molecule systems biology of microRNAs and DNA-damage response RNAs"

June 14 – Giampietro Schiavo (London, UK): "From the diary of a seasoned traveller: the axonal journey of a signalling endosome"

June 17 – Robert M. Brosh (Baltimore, USA): "Molecular Mechanisms and Pathways of DNA Helicases to Maintain Genomic Stability"

June 20 – Henri-Jacques Delecluse (Heidelberg, Germany): "microRNAs and Epstein-Barr Virus-mediated B cell transformation"

June 27 – Ina Poser (Dresden, Germany): "Mammalian BAC genetics"

June 28 – Francesca Cortini (Milan, Italy): "Genetic approach to the study of AD and FTLD pathogenesis"

7 July 05 – Frauke Melchior (Heidelberg, Germany): "Sumoylation in oxidative stress"

July 08 – Jean Christophe Andrau (Marseille, France): "From promoters and enhancers of transcription to transcription of enhancers and promoter, new insights to old dogmas"

July 12 – Johannes Zuber (Vienna, Austria): "Finding and probing cancer drug targets using advanced in-vivo RNAi"

July 16 – Katsuhiko Shirahige (Tokyo, Japan): "Regulation of Transcription by SMC Proteins"

July 17 – Mathias Francois (Brisbane, Australia): "SOX-F transcription factors from developmental biology to drug discovery"

July 18 – Jens Schwamborn (Esch-sur-Alzette, Luxembourg): "Fate specification in neural stem cells"

July 19 – Roberto Ferrari (Los Angeles, USA): "Epigenomics in cancer and Development"

July 19 – Elisa Guida (San Juan de Alicante, Spain): "Using Peptide Aptamers as new tools to manipulate proten-protein interaction networks"

9 September 16 – Matthieu Piel (Paris, France): "A few things we learned while torturing cells: how to produce moving saussages, and the the first universal law of cell migration"

September 20 – G.V. Shivashankar (Singapore): "Nuclear Mechanics and Genome Regulation"

September 23 – Pierre Leopold (Nice, France): "Coupling cell polarity with neoplastic growth in Drosophila"

September 27 – Peter Dröge (Singapore): "HMGA proteins: Oncofetal chromatin factors with chaperone function at stalled replication forks in stem and cancer cells"

10 October 01 – Zhao-Qi Wang (Jena, Germany): "Regulation of neuro-stem cell fate, brain size and neuro(de) generation"

October 04 – Robert J. Klose (Oxford, UK): "CpG islands, chromatin, and the Polycomb connection"

October 08 – Fabio Vandin (Providence, USA): "Computational methods to discover significantly mutated pathways in cancer"

October 10 – Stephen J. Klaine (Pendleton, USA): "Influence of antidepressants on fish brain chemistry and behavior"

October 14 – Michael Gimbrone (Boston, USA): "Vascular Endothelium: Nature's Container for Blood--New Insights into its Pathobiology"

October 28 – Anton Gartner (Dundee, UK): "C. elegans as a model for profiling mutational signatures of carcinogens and DNA repair"

October 31 – Aldo Ferrari (Zurich, Switzerland): "New and emerging engineering technologies for medical and biological applications"

11 November 04 – Ivan Dikic (Frankfurt, Germany): "Ubiquitin networks in regulation of autophagy and inflammation"

November 08 – Stephen Taylor (Manchester, UK): "Non-Genetic Heterogeneity In Response to Anti-Mitotic Chemotherapeutics"

November 12 – Andrés Aguilera (Seville, Spain): "Chromatin structure as a mediator of transcription and R-loop-associated recombination"

November 14 – Mark Winey (Boulder, USA): "Keeping Basal Bodies in Line: Centrins and SFR Proteins"

November 18 – Tomoyuki Tanaka (Dundee, UK): "Hidden functions of kinetochores: microtubule attachment and beyond"

November 19 – Oscar Fernandez-Capetillo (Madrid, Spain): "Deciphering the role of Mms21 and the SWMC5/6 complex with mouse genetics"

November 26 – Thomas Helleday (Stockholm, Sweden): "Replication stress, from basic science to novel anti-cancer treatments"

12 December 02 – Witold Filipowicz (Basel, Switzerland): "Mechanism and regulation of miRNA repression in mammalian cells including neurons"

December 05 – Jacob Hanna (Rehovot, Israel): "Molecular Mechanisms for Inducing and Maintaining Pluripotency"

December 09 – Susan Gasser (Basel, Switzerland): "TORC2 and actin dynamics impact the repair of oxidized bases: a chemicogenetic analysis of genome stability"

December 10 – Philip Avner (Rome, Italy): "X-chromosome Inactivation: An Epigenetic Paradigm Initiation and Plasticity"

December 13 – Salvador Aznar-Benitah (Barcelona, Spain): "Spatiotemporal regulation of epidermal stem cells in homeostasis, ageing, and cancer"

December 16 – Gerhard Christofori (Basel, Switzerland): "Transcriptional control of EMT and cancer metastasis"

December 17 – Eric So (London, UK): "Targeting epigenetic and self-renewal machineries in AML stem cells"

Seminars 2013
Clinical science seminars (IEO Education)

1 January 16 – Giuseppe Saglio (Turin, Italy): "Chronic Myelogenoius Leukemia: story of a success of molecular targeted therapy"

January 23 – Alberto Bardelli (Candiolo, Italy): "Targeted therapies for colorectal cancer"

2 February 13 – Fatima Cardoso (Lisbon, Portugal): "Update on ABC 1 Guidelines and perspectives for ABC 2"

February 20 – Romano Danesi (Pisa, Italy): "The role of enzymes of drug metabolism and transporters in cancer chemotherapy"

February 27 – Jonas Bergh (Stockholm, Sweden): "Some thoughts on breast cancer stem cells and the metastatic process"

3 March 13 – Garth Ballantyne (Augusta, USA): "Evolution of minimally-invasive general surgery from laparoscopy to robotic surgery"

March 20 – Dror Meirow (Tel-Aviv, Israel): "Mechanisms of ovarian toxicity and fertility preservation in breast cancer patients"

4 April 03 – Hani Gabra (London, UK): "The OPCML tumour suppressor: A regulator of Receptor Tyrosine Kinase networks in ovarian cancer?"

April 10 – Xavier Bosch (Barcelona, Spain): "Options for a rapid reduction of cervical cancer in Europe"

April 17 – Philippe Vielh (Villejuif, France): "Cytopathologist input in a one stop clinic for breast lesions"

April 24 – Bernard J. Park (Hackensack, USA): "Robotic surgery in thoracic oncology: state of the art and future perspectives"

5 May 8 – Emile Voest (Utrecht, The Netherlands): "Fatty acids mediate systemic resistance to chemotherapy"

May 22 – Fabrice Andrè (Villejuif, France): "Personalized medicine program at Institut Gustave Roussy"

May 29 – Douglas Hanahan (Lausanne, Switzerland): "Hallmarks of cancer: applications to cancer medicine?"

6 June 12 – Silvia Marsoni (Candiolo, Italy): "Markers, drug development & precision medicine"

June 20 – Clifford Hudis (New York, USA): "Obesity And Breast Cancer: An emerging challenge"

9 September 11 – Vittorio Rosti (Pavia, Italy): "Myelofibrosis, how to diagnose, how to treat, how to investigate"

10 October 30 – Peter Rogan (Ontario, Canada): "New genetic variants in inherited and somatic breast cancer: clinical implications"

11 November 27 – Elias Campo (Barcelona, Spain): "Clinical and pathogenetic impact of genomic analysis in chronic lymphocytic leukemia"

Acknowledgments

Sistema Sanitario Regione Lombardia

IEO has been registered as an accreditated organization by the Regional Health Care System since March 2000.

Joint Commission International for Hospitals

In December 2002 the European Institute of Oncology was the first Cancer Center to be accredited by Joint Commission International, confirming such result in January 2006, March 2009 and March 2012.

JACIE

In September 2009 the Haematopoietic Stem Cell Transplant program of theEuropean Institute of Oncology was accredited by Joint Accreditation Committee-ISCT (Europe) & EBMT; this result has been confirmed in Febrary 2014.

Certificazione ISO

The path that led to ISO 9001:2000 (and then 9001:2008) certification started in 2002, with the certification of Supply of Laboratory Medicine Services in Haematoncology and Supply of Laboratory Medicine services. In 2012 the processes certified are 10.

OECI

In December 2013 the European Institute of Oncology was the first Cancer Center in Italy to be accredited by OECI, Organisation of European Cancer Institutes.
IEO recived from OECI in March 2014 the designation as "Comprensive Cancer Center".

International Hospital Benchmarking Award Fondazione Bertelsmann

In 2007, the Institute was presented with the International Hospital Benchmarking Award as International "best practice" in the treatment of cancer patients.
It was the only European facility among the six awarded.

ONDa (National Observatory on Women's Health)

In 2007, 2010 and 2011, 2013 IEO obtained the "3 pink stamps" by ONDa for it's high and specific dedication to hospitalized women.

Best Work Place Italia

In 2003, IEO received the "Best Work Place Italia" award by Great Place to Work, as the only healthcare company (award also received in 2005, 2006 and last in 2009). This award is the result of the efforts aimed at creating an organisational climate and culture based on the respect of the individual, and on mutual development and trust.

Top Employers

In March 2011 the CRF Institute gave the European Institute of Oncology the "Top Employers 2011" award as one of the excellent Italian organizations in the management of human resources. In 2013 for the third year the European Institute of Oncology confirmed such result.

Cambiare Passo

On 7 April 2011 the European Institute of Oncology has received the award as the best company in the city of Milan to recruite people with disabilities.