

IEO RESEARCH NEWSLETTER

n. 10 – March 2026



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WHAT'S NEW IN SCIENCE?

| | |
|--|--------------------------|
| Idrossiclorochina per ridurre la recidiva inibendo l'autofagia delle cellule tumorali. <i>Hydroxichloroquine to reduce recurrence by inhibiting cancer cell autophagy.</i> | pag 3 page 49 |
| Le cellule CART per il trattamento del neuroblastoma pediatrico – risultati incoraggianti da uno studio clinico di fase 1/2. <i>CART cells for the treatment of pediatric neuroblastoma – encouraging results from a phase1/2 clinical trial.</i> | pag 6 page 51 |
| Anticorpi bi-specifici per il trattamento del linfoma follicolare: risultati dello studio clinico di fase III EPCORE FL-1. <i>Bispecific antibodies for the treatment of follicular lymphoma: Results of the EPCORE FL-1 phase III clinical trial.</i> | pag 8 page 53 |
| La modulazione della risposta immunitaria antitumorale da parte del microbiota intestinale – uno sguardo al meccanismo. <i>Gut microbiota modulation of anti-tumor immune response - mechanistic insights.</i> | pag 10 page 55 |
| L'aneuploidia nell'evoluzione del tumore – il cancro del colon-retto. <i>Aneuploidy in tumor evolution – colorectal cancer.</i> | pag 13 page 57 |
| Condivisione di dati e campioni – un bene o un male? L'importanza del contesto. <i>Data and specimen sharing – good or bad? The importance of the context.</i> | pag 16 page 59 |

WHAT'S NEW IN SCIENCE?

| | |
|--|--------------------------|
| I segnali di Wnt nel microambiente che regolano la divisione cellulare. <i>The Wnt signal from the microenvironment regulating cell division.</i> | pag 18 page 61 |
| Definire il microbioma intestinale sano attraverso informazioni nutrizionali e marcatori dello stato di salute. <i>Defining a healthy gut microbiome through the evaluation of nutrition and common health-related markers.</i> | pag 21 page 64 |
| Il trapianto di microbiota fecale in clinical trial: tumore renale, polmonare e melanoma. <i>Fecal microbiota transplantation in clinical trial: renal cancer, lung cancer and melanoma.</i> | pag 24 page 66 |
| Una nuova combinazione di farmaci contro i linfomi aggressivi? Risultati di studi preclinici. <i>A new drug combination against aggressive lymphoma? Results of preclinical studies.</i> | pag 29 page 71 |
| ChatGPT in ambito sanitario – il punto di vista della gente. <i>Employing ChatGPT in the medical field – the users' perspective.</i> | pag 31 page 73 |
| Le informazioni in codice nelle modificazioni post-traduzionali degli istoni – Un nuovo strumento computazionale per decifrarle. <i>The secret code of the histone post-translational modifications – A new computational tool for the decryption.</i> | pag 35 page 76 |
| Tumore al seno nelle giovani: più cura ormonale dimezza metastasi e recidive. | pag 37 |

| | |
|--|--|
| <i>Breast cancer in young women: Longer hormone-based therapy halves the risk of metastases and recurrence.</i> | <i>page 78</i> |
| La metformina per contrastare la progressione del glioblastoma – risultati di studi preclinici. <i>Metformin to counter glioblastoma progression – results of preclinical studies.</i> | <i>pag 39</i> <i>page 80</i> |
| Studio Clinico NO-CUT. <i>NO-CUT clinical trial.</i> | <i>pag 42</i> <i>page 83</i> |

NEWS, INITIATIVES AND EVENTS FROM THE IEO WORLD

| | |
|--|--|
| Heine H. Hansen Award 2026 al Prof. Filippo de Marinis. <i>Heine H. Hansen Award 2026 to Prof. Filippo de Marinis.</i> | <i>pag 44</i> <i>page 85</i> |
| Una nuova cura per le aritmie più gravi. <i>A new treatment approach for the most severe arrhythmias.</i> | <i>pag 45</i> <i>page 86</i> |
| Il progetto NovaRNA selezionato per il programma Accelerator di PerfeTTO. <i>The NovaRNA project selected for the PerfeTTO Accelerator Program.</i> | <i>pag 45</i> <i>page 86</i> |
| Partecipa al workshop SEMM "The Proteomics Revolution: Advancing Science and Society"! <i>Join the SEMM Workshop "The Proteomics Revolution: Advancing Science and Society"!</i> | <i>pag 47</i> <i>page 88</i> |
| Al via l'attività del nuovo blocco operatorio di IEO 3! <i>Surgeries rooms of IEO 3 are now up and running!</i> | <i>pag 48</i> <i>page 89</i> |

THE BRIEFING

| | |
|---|-----------------|
| What else is new from IEO researchers? | <i>page 91</i> |
| What else is new in science? | <i>page 108</i> |

notes...

page 120

THIS MONTH WE WELCOME

page 121

What if...

page 122

Leggi qui gli altri numeri della IEO Research Newsletter!
Read here the other volumes of the IEO Research Newsletter!



What's new in science?

Idrossiclorochina per ridurre la recidiva inibendo l'autofagia delle cellule tumorali.

Nonostante i progressi notevoli degli ultimi decenni nel trattamento del tumore al seno, la malattia metastatica rimane ancora una sfida importante per molte pazienti. Infatti, sebbene la diagnosi precoce e il trattamento tempestivo aumentino notevolmente le probabilità di cura, molte pazienti, pur rispondendo inizialmente alla terapia, e nonostante i benefici derivanti dalla terapia adiuvante (ovvero somministrata dopo la chirurgia), manifestano recidiva con malattia metastatica incurabile. La recidiva è dovuta alla cosiddetta malattia minima residua (MRD), ovvero la presenza di cellule tumorali che sono riuscite a sopravvivere al trattamento e, rimanendo in uno stato dormiente a volte anche per mesi o anni dopo la rimozione del tumore primario, alimentano infine la ricrescita del tumore.

Precedenti studi preclinici *in vivo* hanno mostrato che in modelli murini di tumore al seno, che ricapitolano i tratti salienti delle cellule tumorali umane, le cellule tumorali residue dormienti hanno una signaling di mTOR alterata; inoltre, queste cellule sfruttano meccanismi di autofagia per sopravvivere allo stress terapeutico ed alimentare la recidiva.

Per valutare se agendo in maniera specifica sui meccanismi biologici alla base della sopravvivenza delle cellule dormienti sia possibile eradicare la MRD e di conseguenza ridurre l'incidenza di recidiva, i ricercatori hanno valutato gli effetti degli inibitori della signaling di mTOR e dell'autofagia sia in modelli preclinici *in vivo* che nel contesto di uno studio clinico prospettico.

Eliminazione delle cellule tumorali dormienti in modelli preclinici *in vivo*. Innanzi tutto, i ricercatori hanno valutato, in modelli preclinici *in vivo* di tumore al seno con MRD (ovvero che presentavano cellule tumorali disseminate), gli effetti sulla recidiva dell'inibizione contemporanea della signaling di mTOR e dell'autofagia, attraverso la somministrazione combinata di everolimus (EvE) e idrossiclorochina (HCQ), rispettivamente. EvE è un trattamento approvato contro il tumore al seno, comunemente somministrato negli stadi avanzati della malattia; HCQ è un farmaco approvato per il trattamento delle malattie autoimmuni (con un profilo di tossicità più favorevole rispetto alla cloroquina, CQ).

Confermando studi precedenti che utilizzavano Rapamicina, l'inibizione del pathway di mTOR da parte di EvE riduceva la recidiva nei modelli di malattia, sia quando somministrato in maniera cronica che quando somministrato in maniera transiente (una modalità di somministrazione più facilmente applicabile in un contesto clinico); l'entità della riduzione della recidiva correlava con la durata del trattamento. Inoltre, l'inibizione dell'autofagia attraverso CQ o HCQ riduceva la recidiva, sebbene lievemente, sia se i due farmaci venivano somministrati da soli, sia quando erano somministrati insieme agli inibitori di mTOR.

L'ulteriore debole riduzione della recidiva ottenuta attraverso la doppia inibizione del pathway di mTOR e dell'autofagia indicava che i due farmaci agivano probabilmente su meccanismi diversi: da un lato, gli inibitori di mTOR riducevano la proliferazione delle cellule tumorali residue, limitando la crescita delle metastasi;

Alex, puoi scrivere qualcosa sull'autofagia?

L'autofagia è un processo di "riciclo" della cellula, che degrada organelli e proteine danneggiate per mantenere l'equilibrio energetico e la sopravvivenza in condizioni di stress. Nel cancro svolge un doppio ruolo. Nelle fasi iniziali può sopprimere la tumorigenesi limitando danni al DNA e infiammazione. Una volta formato il tumore, però, le cellule cancerose sfruttano l'autofagia per resistere a carenza di nutrienti, ipossia e stress terapeutico. Per questo l'autofagia è sia un meccanismo protettivo sia un bersaglio terapeutico.

dall'altro, gli inibitori dell'autofagia riducevano la sopravvivenza delle cellule tumorali dormienti, agendo così in sinergia nel limitare la recidiva.

La quantificazione del numero di cellule tumorali residue dopo EvE e HCQ ha infatti rivelato che, nonostante l'effetto più evidente degli inibitori di mTOR, sia EvE che HCQ riducevano il numero di cellule tumorali residue, in maniera proporzionale alla durata del trattamento. Durante il trattamento con gli inibitori dell'autofagia, alcune cellule tumorali ricominciavano a proliferare, sostenendo la recidiva; ciò non accadeva quando veniva contemporaneamente bloccata anche la signaling di mTOR, sostenendo ulteriormente il concetto che i due meccanismi contribuivano in maniera diversa alla malattia metastatica.

I loro dati hanno anche evidenziato una correlazione tra il numero di cellule tumorali residue alla fine del trattamento e la sopravvivenza in assenza di recidiva: un numero minore di cellule tumorali residue correlava con una maggiore sopravvivenza in assenza di recidiva, indicando che la recidiva era di fatto dovuta alla MRD.

Inibizione di autofagia e mTOR in un contesto clinico – lo studio CLEVER. Sulla base dei risultati raccolti con gli studi preclinici, gli autori hanno valutato l'efficacia dell'inibizione combinata di mTOR e autofagia sulla recidiva in pazienti guarite dal tumore al seno. Nell'ambito dello studio, le pazienti (che erano state trattate chirurgicamente per il tumore primario, del sottotipo TNBC o ER+/HER2-, e che entro 5 anni dalla diagnosi di tumore avevano cellule tumorali disseminate) sono state casualmente assegnate a ricevere *i.* HCQ (15 pazienti), *ii.* EvE (15 pazienti), *iii.* HCQ+EvE (8 pazienti), *iv.* tre mesi di sorveglianza seguiti dal trattamento con HCQ e EvE (15 pazienti).

Tossicità. Sebbene in alcune pazienti, sia nel gruppo trattato in monoterapia sia nel gruppo trattato con terapia di combinazione, il dosaggio del farmaco sia stato modificato nel corso dello studio, non sono stati osservati eventi avversi di grado 4. Alcune pazienti hanno però manifestato eventi avversi di grado 1, 2, 3. Nel complesso, i due farmaci apparivano entrambi sicuri, sia somministrati da soli che in combinazione.

Quantificazione delle cellule tumorali disseminate. Il numero delle cellule tumorali disseminate diminuiva in tutti i gruppi di trattamento. La riduzione era però maggiore con la terapia di combinazione HCQ e EvE rispetto al trattamento con HCQ o EvE somministrati singolarmente. In alcune pazienti che, alla fine del ciclo di trattamento, avevano ancora cellule tumorali disseminate, cicli di terapia aggiuntivi riducevano ulteriormente il numero di cellule disseminate.

Efficacia. La sopravvivenza in assenza di recidiva era maggiore in quelle pazienti in cui, alla fine del trattamento, non venivano rilevate cellule tumorali residue.

Sebbene lo studio mostri solo un effetto aggiuntivo lieve dell'inibizione dell'autofagia tramite HCQ sul numero di cellule tumorali residue, rispetto all'inibitore del pathway di mTOR EvE, i risultati puntano fortemente all'esistenza di due diversi meccanismi di recidiva: da un lato, gli inibitori di mTOR, che agiscono sulla *proliferazione* delle cellule tumorali (ad esempio rallentando la proliferazione delle cellule che escono dalla dormienza e ricominciano a proliferare, pronte ad alimentare la colonizzazione delle metastasi), riducendo così in maniera significativa la recidiva. Dall'altro, gli inibitori dell'autofagia agiscono sul *mantenimento della dormienza*, interferendo con il meccanismo che le cellule tumorali sfruttano per sopravvivere allo stress associato alla terapia, inducendo appunto l'autofagia e rimanendo dormienti. Questo studio dimostra quindi che è di fatto possibile *intercettare* la recidiva agendo sul meccanismo biologico alla base della dormienza delle cellule tumorali per prevenire –

Alex, puoi scrivere qualcosa riguardo alla signaling di mTOR nel cancro?

mTOR è un regolatore centrale della crescita cellulare, del metabolismo e della sopravvivenza, e integra segnali da nutrienti, fattori di crescita e stress. Nel cancro, la signaling di mTOR è spesso iperattivata, favorendo proliferazione incontrollata, aumento della sintesi proteica e riprogrammazione metabolica. I tumori si affidano a mTOR per sostenere il loro elevato fabbisogno energetico e biosintetico. Per questo mTOR è un importante bersaglio terapeutico, sebbene feedback e ridondanze possano limitarne l'efficacia.

“questo studio dimostra quindi che è di fatto possibile intercettare la recidiva agendo sul meccanismo biologico alla base della dormienza delle cellule tumorali per prevenire –piuttosto che curare– il ri-manifestarsi della malattia”

piuttosto che curare– il ri-manifestarsi della malattia.

Sebbene la somministrazione combinata di entrambi gli inibitori riduca in maniera significativa la recidiva, eliminando la MRD, sono necessari studi ulteriori per poter definire l'effettivo contributo dei differenti meccanismi cellulari alla recidiva tumorale. In ogni caso, se confermati, gli effetti terapeutici di questo trattamento di combinazione appaiono promettenti. Attualmente sono in corso studi ulteriori volti a confermare questi risultati e valutare la durabilità degli effetti osservati sulla recidiva tumorale.

Referenze: **1)** Targeting dormant tumor cells to prevent recurrent breast cancer: a randomized phase 2 trial. *Angela DeMichele, Amy S. Clark, Emily Shea et al.*, Nature Medicine 2025. doi: 10.1038/s41591-025-03877-3. **2)** Intervening on dormancy to prevent breast cancer recurrence. *Tanja Fehm & Hans Neubauer*. Nature reviews clinical oncology 2025. doi: 10.1038/s41571-025-01087-x.

What's new in science?

Le cellule CART per il trattamento del neuroblastoma pediatrico – risultati incoraggianti da uno studio clinico di fase 1/2.

Il neuroblastoma è il tumore solido più comune nell'infanzia. Sebbene una comprensione più approfondita della biologia di questo tumore abbia permesso dei notevoli passi avanti nella gestione della malattia, soprattutto grazie ad una più accurata stima del rischio, la sua elevata eterogeneità limita l'efficacia delle attuali terapie. Precedenti studi clinici hanno mostrato dei risultati positivi in pazienti con neuroblastoma trattati con anticorpi monoclonali contro la proteina GD2 (in combinazione con chemioterapia). La malattia, però, spesso si rimanifestava alla fine del trattamento. In questo scenario, le cellule CART offrono il vantaggio di una risposta più duratura. Un lavoro precedente ha riportato i promettenti risultati preliminari di uno studio clinico di fase 1/2; i dati hanno mostrato una buona efficacia del trattamento con cellule CART-GD2 (ovvero l'infusione di cellule CART ingegnerizzate per colpire in maniera specifica le cellule tumorali che esprimevano la proteina GD2) in cinque pazienti pediatrici affetti da neuroblastoma resistente a terapie precedenti. Più recentemente, gli autori hanno riportato i risultati finali di questo studio clinico, in una coorte più ampia di 35 pazienti, valutando sicurezza del trattamento, dose tollerata, ed efficacia.

I risultati finali hanno confermato quelli dell'analisi intermedia: nei pazienti che ricevono la dose ottimale di cellule CART, e in cui l'impatto della patologia è minore, si osserva una risposta del 80% circa, il 50% mostra una risposta completa al trattamento e la sopravvivenza a lungo termine (a 5 anni) è quasi del 70%.

Gli autori hanno anche identificato degli aspetti chiave da considerare per massimizzare la risposta alla terapia, come l'isolamento dai pazienti delle cellule T da ingegnerizzare prima dell'inizio di qualsiasi trattamento, così da ottenere cellule CART vitali e attive. La persistenza a lungo termine (per oltre un anno) delle cellule CART nei pazienti trattati suggerisce che questo approccio possa consentire un controllo migliore della malattia, possibilmente prevenendo la recidiva. I loro risultati

suggeriscono inoltre fortemente che l'infusione delle CART nelle fasi iniziali della malattia (ovvero non oltre due precedenti cicli di terapia) sia un fattore critico per un'efficacia ottimale del trattamento.

Sebbene la tossicità associata al trattamento non fosse trascurabile, i sintomi erano quelli comunemente associati alle terapie cellulari –sebbene più forti, probabilmente per via della maggiore attività delle cellule CART– e nel complesso gestibili. Infine, non sono state osservate neoplasie secondarie delle cellule T in seguito all'infusione.

Incoraggiati dai risultati positivi di questo studio, in cui il trattamento ha permesso di indurre una remissione duratura in alcuni pazienti con neuroblastoma resistente alla terapia o ad alto rischio di recidiva, è attualmente in fase di pianificazione uno studio clinico internazionale di fase II, per corroborare i risultati raccolti nel contesto di coorti di pazienti più ampie e in fasi precedenti della malattia (dopo il primo ciclo di terapia), così da massimizzare le possibilità di cura.

“I risultati finali hanno confermato quelli dell'analisi intermedia: nei pazienti che ricevono la dose ottimale di cellule CART, e in cui l'impatto della patologia è minore, si osserva una risposta del 80% circa, il 50% mostra una risposta completa al trattamento e la sopravvivenza a lungo termine (a 5 anni) è quasi del 70%. Incoraggiati dai risultati positivi di questo studio, è attualmente in fase di pianificazione uno studio clinico internazionale di fase II, per corroborare i risultati raccolti nel contesto di coorti di pazienti più ampie e in fasi precedenti della malattia, così da massimizzare le possibilità di cura”

----- TELL ME MORE! -----

I 35 pazienti inclusi nello studio erano bambini con malattia metastatica che si erano già

precedentemente sottoposti ad altre terapie. I linfociti T sono stati isolati dai pazienti ed ingegnerizzati per poter essere successivamente re-infusi. Le cellule ingegnerizzate erano vitali e dotate di una forte attività antitumorale (come mostrato dalla citotossicità osservata in saggi *in vitro*).

Tossicità. La tossicità associata al trattamento non era trascurabile, ma gestibile. Alcuni pazienti hanno manifestato eventi avversi di grado 2, 3 e anche 4. La tossicità si manifestava soprattutto a livello ematologico e sottoforma di una reazione infiammatoria eccessiva (sindrome da rilascio di citochine, CRS. La gravità di quest'ultima non era associata allo stato della malattia). Pur non avendo osservato alcuna associazione tra l'abbondanza di molecole infiammatorie nel sangue e la risposta al trattamento, gli autori hanno evidenziato una correlazione con la gravità della CRS. Queste CART sono ingegnerizzate per esprimere oltre alla proteina in grado di riconoscere e legare la proteina GD2 sulle cellule tumorali, il cosiddetto "gene del suicidio", ovvero il gene che, quando indotto dal trattamento con uno specifico farmaco (rimiducid), uccide la cellula CART che lo esprime, permettendo così di controllare la vitalità/morte della cellula in caso di eventi avversi gravi associati al trattamento che possono mettere a rischio la vita del paziente. In caso di grave tossicità, i pazienti sono stati trattati con farmaci anti-infiammatori e con la molecola per attivare il "gene del suicidio", ottenendo una rapida riduzione del numero di cellule CART e un miglioramento della sintomatologia. Le cellule CART che sopravvivevano all'attivazione del gene del suicidio non venivano eliminate neanche in seguito a somministrazioni successive del farmaco, ma la loro persistenza non si accompagnava a tossicità.

Efficacia. I ricercatori hanno osservato nel complesso il 31% dei pazienti trattati andare incontro a risposta completa, il 26% ad una risposta

parziale, mentre il 6% ha mostrato solo una risposta minima. Nel 15% dei pazienti, la malattia è progredita nonostante l'infusione delle cellule CART, nel 19% dei pazienti la malattia è rimasta stabile. Alcuni pazienti (23% a 1 anno, 38% a 5 anni), pur rispondendo inizialmente alla terapia, andavano incontro a recidiva. Le cellule CART persistevano nel sangue per oltre 12 mesi nel 60% circa dei pazienti. La sopravvivenza a un anno era intorno al 50%, a 5 anni intorno al 30%.

Quando i ricercatori hanno analizzato in maggiore dettaglio la sottopopolazione di pazienti in cui l'impatto della patologia era minore (minore "disease burden") che avevano ricevuto la dose ottimale di CART, hanno osservato una risposta migliore alla terapia: il 50% dei pazienti mostrava una risposta completa e la sopravvivenza a 5 anni era del 70%. Anche in questa popolazione, non c'era una forte correlazione tra la durata della risposta e la persistenza delle CART, indicando l'esistenza di altri fattori per poter spiegare appieno gli effetti osservati.

La sopravvivenza a lungo termine (a 5 anni) era associata con il numero di cicli di terapia precedenti all'infusione di CART, in particolare, nei pazienti che avevano ricevuto 1-2 cicli precedenti di terapia la sopravvivenza a lungo termine dei pazienti era migliore rispetto a quella dei pazienti che avevano già ricevuto 3 o più cicli precedenti di trattamento. In questi pazienti, la sopravvivenza a 5 anni era quasi del 90% (rispetto al 40% in quelli trattati dopo il fallimento del terzo ciclo di terapia). Inoltre, quando le cellule da ingegnerizzare erano isolate al momento della diagnosi piuttosto che dopo trattamenti precedenti, la sopravvivenza a 5 anni era significativamente migliore (100% rispetto al 33%).

Dopo l'infusione, le cellule CART si espandevano in tutti i pazienti per circa due settimane e persistevano mesi dopo l'infusione.

Referenza: GD2-targeting CAR T cells in high-risk neuroblastoma: a phase 1/2 trial. Franco Locatelli, Daria Pagliara, Maria A. De Ioris et al., Nature Medicine 2025. doi: 10.1038/s41591-025-03874-6.

What's new in science?

Anticorpi bi-specifici per il trattamento del linfoma follicolare: risultati dello studio clinico di fase III EPCORE FL-1.

Il linfoma follicolare (FL) è un linfoma non-Hodgkin. I pazienti sono solitamente trattati con chemio-immunoterapia e, in caso di recidiva, viene loro somministrata una combinazione di lenalidomide + rituximab (R2). Solo nel 50% circa dei pazienti si osserva però una risposta completa, sottolineando la necessità di definire degli approcci terapeutici nuovi e più efficaci.

Studi precedenti hanno quindi valutato, nel contesto di uno studio clinico (di fase 1b/2), l'efficacia della tripla combinazione con Rituximab, Lenalidomide ed Epcoritamab (R3), in pazienti con FL resistenti alla terapia convenzionale. Epcoritamab è un anticorpo bi-specifico che lega sia la proteina CD20 (sui linfociti B) che la proteina CD3 (sui linfociti T) inducendo la morte, mediata dai linfociti T, delle cellule B neoplastiche. La combinazione di Epcoritamab con Rituximab e lenalidomide ha mostrato una risposta forte e durevole.

Più recentemente, sono state valutate efficacia e sicurezza di questa nuova tripla combinazione per la prima volta nel contesto di uno studio clinico di fase 3 (EPCORE FL-1), rispetto al trattamento R2, mostrando 83% di risposta completa e duratura e una riduzione del 79% del rischio di progressione della malattia. Sebbene l'analisi intermedia non abbia potuto valutare a fondo gli effetti a lungo termine del trattamento, soprattutto in termini di sopravvivenza (data la durata del followup, relativamente breve; aspetto importante per questa malattia), i risultati hanno mostrato dei tempi più lunghi prima del successivo trattamento antitumorale ed un minore numero di decessi per malattia, sia nella popolazione a basso rischio che in quella ad alto rischio. La maggiore incidenza di eventi avversi nel gruppo R3 rispetto al gruppo R2 richiede tuttavia un'attenta analisi dei rischi/benefici e una gestione ottimizzata degli eventi avversi. In ogni caso, i risultati di questo studio clinico mostrano una maggiore efficacia di questa tripla combinazione (priva di chemioterapia), rispetto alla terapia R2, in pazienti con FL resistente, con una maggiore risposta completa, minore rischio di progressione della malattia, ed un profilo di sicurezza nel complesso gestibile, proponendo quindi Rituximab-Lenalidomide-Epcoritamab come la nuova terapia standard per il trattamento di questi pazienti, offrendo loro un'opzione terapeutica nuova, più efficace e priva degli effetti collaterali gravosi associati al trattamento chemioterapico. Infine, dal punto di vista della ricerca, studi traslazionali futuri –focalizzati sull'identificazione di biomarcatori di risposta, dei meccanismi di resistenza, del ruolo della malattia minima residua– e clinici –volti a definire il razionale e valutare l'efficacia di nuove combinazioni terapeutiche, con immunoterapia o altre terapie emergenti– potrebbe consentire la selezione dei pazienti e di conseguenza ottimizzarne l'efficacia clinica.

“i risultati di questo studio clinico mostrano una maggiore efficacia della tripla combinazione Rituximab-Lenalidomide-Epcoritamab, priva di chemioterapia. Dal punto di vista della ricerca, studi traslazionali futuri –focalizzati sull'identificazione di biomarcatori di risposta, dei meccanismi di resistenza, del ruolo della malattia minima residua– e clinici –volti a definire il razionale e valutare l'efficacia di nuove combinazioni terapeutiche, con immunoterapia o altre terapie emergenti– potrebbe consentire la selezione dei pazienti e di conseguenza ottimizzarne l'efficacia clinica”

TELL ME MORE!

EPCORE FL-1 è stato uno studio clinico randomizzato, di fase III, che ha coinvolto 189 centri di ricerca in 30 diversi paesi, in Africa, Asia, Australia, Europa, Nord e Sud America. Lo studio ha

reclutato pazienti in stadio II, III, IV. Epcoritamab è stato somministrato per via sottocutanea; Rituximab (che induce una citotossicità dipendente dal complemento e una citotossicità cellulare

mediata dalle cellule NK e anticorpo-dipendente, così come fagocitosi da parte dei macrofagi) e Lenalidomide (che aumenta l'attivazione delle cellule T e NK) sono stati somministrati per via sistemica. Questo articolo raccoglie i risultati della seconda analisi *ad interim*, programmata (a maggio 2025), in 488 pazienti. Lo studio continuerà ad analizzare i dati di followup a lungo termine.

I pazienti reclutati sono stati assegnati casualmente a ricevere la combinazione R2 (245 pazienti) o R3 (243 pazienti). Quasi tutti i pazienti avevano ricevuto precedentemente una terapia con anticorpi anti-CD20 più chemioterapia e il 37% di loro era resistente agli anticorpi anti-CD20.

Efficacia. La risposta generale (*objective response rate* –ORR– 95% vs 79%), la sopravvivenza in assenza di progressione della malattia (*progression-free survival* –PFS–, con una riduzione del rischio di progressione della malattia o di morte del 79%), la risposta completa (83% vs 50%) erano

tutti significativamente più elevati nel gruppo R3 rispetto al gruppo R2, sia nella popolazione a basso rischio che in quella ad alto rischio.

Sicurezza. Eventi avversi gravi (di grado 3 o più) erano osservati più spesso nel gruppo R3 rispetto al gruppo R2. In ogni caso, non sono stati osservati effetti collaterali nuovi (erano tutti noti per essere associati alla somministrazione dei tre farmaci in monoterapia). Eventi avversi fatali sono stati osservati nel 2% dei pazienti del gruppo R3 rispetto al 4% nel gruppo R2. 19% dei pazienti nel gruppo R3 hanno interrotto il trattamento per via di eventi avversi associati alla terapia, rispetto al 12% nel gruppo R2. Uno specifico dosaggio (ovvero dosi crescenti di R2 su tre cicli di terapia, ognuno seguito dalla somministrazione di Epcoritamab al dosaggio pieno) hanno permesso di ridurre l'incidenza e la gravità della sindrome da rilascio di citochine, che è quindi risultata essere lieve e reversibile. La qualità di vita era preservata.

Referenze: 1) Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial. *Lorenzo Falchi, Marcel Nijland, Huiqiang Huang et al.*, Lancet 2025. doi: 10.1016/S0140-6736(25)02360-8. **2)** A step forward in the treatment of relapsed or refractory follicular lymphoma. *Laura Magnano, Andrea Rivero.* Lancet 2025. doi: 10.1016/S0140-6736(25)02436-5.

What's new in science?

La modulazione della risposta immunitaria antitumorale da parte del microbiota intestinale – uno sguardo al meccanismo.

Diversi studi hanno mostrato la capacità del microbioma intestinale di regolare l'efficacia dell'immunoterapia con inibitori dei checkpoint immunitari (ICI). Ad oggi, i meccanismi coinvolti non sono ancora completamente chiari, ma evidenze sperimentali suggeriscono, da un lato, che ciò avvenga attraverso il rilascio nel sangue di alcuni metaboliti da parte del microbiota che a loro volta influenzano la risposta immunitaria antitumorale; dall'altro è stato proposto che potrebbe essere in parte dovuto alla cosiddetta "tumor mimicry" (letteralmente "imitazione del tumore"), in cui alcune molecole espresse sulla superficie dei microorganismi intestinali, simili a specifiche proteine tumorali, potrebbero modulare direttamente il sistema immunitario, istruendolo ed inducendolo ad attaccare le cellule tumorali che esprimono tali proteine. I ricercatori IEO hanno precedentemente mostrato che alcuni peptidi batterici, come la flagellina della specie *Lachnospiraceae* (Flach), sono molto simili ad alcune proteine del melanoma e preferenzialmente espresse sui tumori dei pazienti che rispondono ad immunoterapia. Inoltre, hanno mostrato che i linfociti T sono più reattivi contro i peptidi di FLach isolati dal sangue dei pazienti che rispondono alla terapia e, *in vitro*, inducono una maggiore espansione dei linfociti intratumorali (TIL) isolati dal melanoma e possiedono una maggiore capacità di uccidere le cellule tumorali, dimostrando la loro abilità nel potenziare la risposta immunitaria antitumorale, antigene-specifica, contro il melanoma, che potrebbe essere sfruttata a fini terapeutici.

“uno specifico microrganismo intestinale –SFB– modula il sistema immunitario, aumentando l'efficacia degli inibitori dei checkpoint immunitari nel contrastare la crescita dei tumori che esprimono le proteine antigeniche in comune con SFB”

Scoperta principale.

In un articolo recente, i ricercatori hanno mostrato che uno specifico microrganismo intestinale –SFB– modula il sistema immunitario, aumentando l'efficacia degli ICI nel contrastare la crescita dei tumori che esprimono le proteine antigeniche in comune con SFB; le cellule immunitarie "attivate" dal batterio intestinale si infiltrano nel tumore dove, in seguito al trattamento con ICI, diventano pro-infiammatorie. Il rimodellamento del microambiente tumorale immunitario indotto dal batterio intestinale e da ICI promuove il reclutamento e l'attivazione/proliferazione di linfociti T citotossici, che contrasta la crescita del tumore, dimostrando così che le specie del microbiota intestinale possono essere sfruttate per modulare l'attività dei linfociti T e aumentare l'efficacia antitumorale del sistema immunitario.

Dettagli.

Gli autori hanno ingegnerizzato una linea cellulare di melanoma, perché esprimesse una proteina di un batterio intestinale –SFB– (i lisati di queste cellule ingegnerizzate attivavano in maniera efficace le cellule T, *ex vivo*, dimostrando la validità di questo modello).

Efficacia di ICI in topi colonizzati da SFB. Le cellule di melanoma ingegnerizzate sono state trapiantate in animali riceventi, il cui intestino era colonizzato dal microrganismo intestinale SFB, e trattati con ICI (anti-PD1). Mentre il trattamento con ICI contrastava la crescita delle cellule di melanoma ingegnerizzate e trapiantate in animali colonizzati da SFB, aumentando la sopravvivenza degli animali, non si osservava alcun effetto di ICI né negli animali trapiantati con cellule di melanoma non ingegnerizzate, né negli animali privi di SFB nell'intestino. Inoltre, gli animali sopravvissuti rigettavano, nel caso di un secondo trapianto, le cellule tumorali di melanoma

ingegnerizzate anche in assenza di trattamento con ICI, dimostrando che il sistema immunitario aveva acquisito una certa memoria contro la specifica proteina di SFB espressa dalle cellule tumorali ingegnerizzate. La crescita del tumore era notevolmente ridotta negli animali trattati con ICI soprattutto se SFB era somministrato nelle fasi iniziali del processo di tumorigenesi (ovvero poco dopo il trapianto delle cellule tumorali). Lo stesso aumento dell'efficacia di ICI indotto da SFB si osservava in altri due modelli di tumore (colon e polmone).

Cellule T CD8 intratumorali in animali colonizzati da SFB e trattati con ICI. Dato che la terapia con ICI funziona potenziando l'attività antitumorale del sistema immunitario, mediata dai linfociti T (attraverso la rimozione di un "freno" all'attività dei linfociti T), hanno caratterizzato i linfociti T intratumorali isolati dai tumori ingegnerizzati (e non) cresciuti in animali trattati con ICI, colonizzati (o no) dai batteri SFB. Innanzitutto, negli animali colonizzati da SFB, le cellule T CD8 intratumorali erano più numerose delle T regolatorie (Treg) quando confrontate con tumori non ingegnerizzati e tumori ingegnerizzati isolati da topi privi di SFB (non si osservava alcun effetto sul rapporto CD8/Treg nell'intestino sano dei topi trattati con ICI). Inoltre, le cellule T CD8 isolate dai tumori ingegnerizzati cresciuti in topi trattati con ICI e colonizzati da SFB esibivano una maggiore funzione effettrice (ovvero c'era una maggiore frequenza di cellule T CD8 che producevano citochine infiammatorie come IFNgamma e TNFalfa).

Cellule T CD4 intratumorali in animali colonizzati da SFB e trattati con ICI. Nei tumori isolati da animali colonizzati con SFB c'era una maggiore abbondanza di cellule T CD4 specifiche per i tumori ingegnerizzati trapiantati, caratterizzati da un fenotipo maggiormente pro-infiammatorio, che producevano livelli elevati di IFNgamma e TNF, rispetto ai tumori isolati da topi privi di SFB, contribuendo al rimodellamento del microambiente immunitario tumorale e alla maggiore risposta

“la modulazione della risposta alla terapia con ICI da parte del microbiota intestinale è stata dimostrata sia a livello clinico che a livello preclinico. Questo lavoro propone una spiegazione meccanicistica alla base degli effetti clinici osservati, mostrando che, ‘imitando’ proteine antigeniche tumore-specifiche, alcuni microorganismi intestinali sono in grado di istruire il sistema immunitario, inducendo un rimodellamento del microambiente tumorale immunitario che sostiene l'efficacia di ICI”

alla terapia con ICI. In altri tipi di tumore, la composizione di cellule T era paragonabile, con SFB che promuoveva l'accumulo nel tumore delle cellule T CD4 con un particolare fenotipo pro-infiammatorio che produceva IFNgamma.

Le cellule T CD4 e CD8 lavorano insieme per aumentare la risposta a ICI. I loro dati indicavano che la colonizzazione dell'intestino da parte di SFB induceva un aumento, all'interno del tumore, sia delle cellule T CD8 che delle cellule T CD4 pro-infiammatorie, che insieme aumentavano la risposta a ICI. Infatti, l'eliminazione, *in vivo*, delle cellule T CD4 o CD8 comprometteva la risposta a ICI. Mentre l'eliminazione delle cellule T CD8 aveva un effetto modesto sulla proporzione di cellule T CD4 nel tumore, negli animali in cui venivano eliminate le cellule T CD4, le cellule T CD8 erano meno attive, mostrando che le cellule T CD8 necessitano delle cellule T CD4 tumore-specifiche per la loro piena attività antitumorale. Analisi trascrittomiche su singola cellula hanno rivelato che le cellule infiltranti il tumore da animali colonizzati con SFB e privi di SFB erano trascrizionalmente differenti.

Migrazione delle cellule T CD4 dall'intestino al tumore. La colonizzazione di SFB induceva la migrazione delle cellule T CD4 specifiche per SFB dall'intestino (dalla lamina propria intestinale) al tumore; una volta nel tumore, acquisivano un fenotipo diverso, pro-infiammatorio, che sosteneva la risposta a ICI.

La “tumor mimicry” funziona solo per alcuni microorganismi intestinali. Infine, i ricercatori hanno osservato che l'effetto sulla crescita del tumore era specifico per i batteri SFB, perché quando i topi con il tumore erano

“il microbiota intestinale e ICI agiscono in sinergia in una finestra temporale limitata, suggerendo l'importanza del giusto tempismo nell'esposizione degli antigeni microbici per una buona efficacia antitumorale”

invece colonizzati con un altro batterio (*Helicobacter hepaticus*, Hh), l'efficacia di ICI sulla crescita del tumore (ingegnerizzato con una proteina specifica di Hh) non era influenzata, nonostante l'espansione delle cellule T CD4 Hh/tumore-specifiche e la migrazione all'interno del tumore. Tuttavia, le cellule T CD4 Hh-specifiche esibivano un fenotipo pro-infiammatorio meno pronunciato (producendo minori concentrazioni di IFNgamma e TNF) e le cellule T CD8 non erano influenzate.

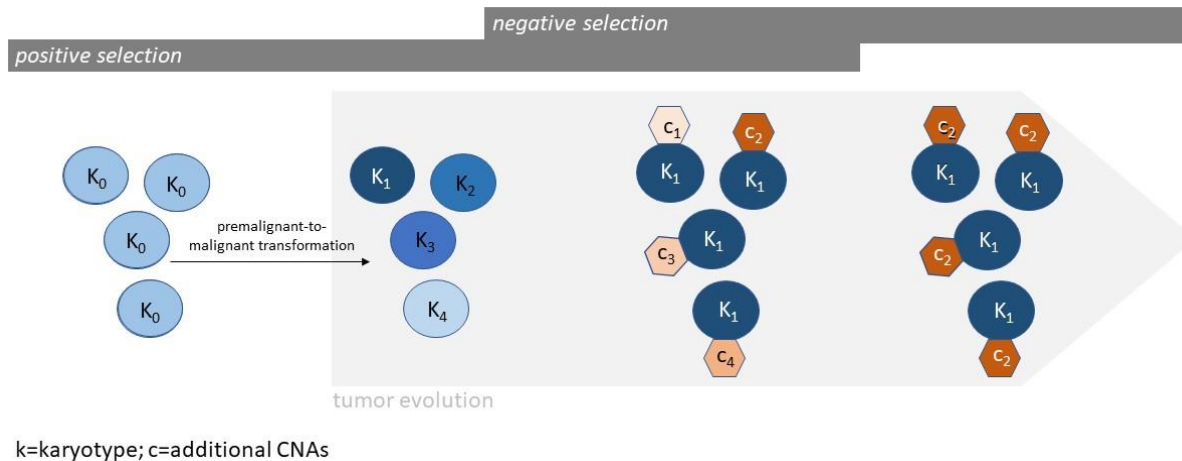
Conclusioni.

La modulazione della risposta alla terapia con ICI da parte del microbiota intestinale è stata dimostrata sia a livello clinico che a livello preclinico. Questo lavoro propone una spiegazione meccanicistica alla base degli effetti clinici osservati, mostrando che, “imitando” proteine antigeniche tumore-specifiche, alcuni microorganismi intestinali sono in grado di istruire il sistema immunitario, inducendo un rimodellamento del microambiente tumorale immunitario verso un'immunità più pro-infiammatoria e antitumorale, che sostiene l'efficacia di ICI. Questi risultati sono in linea con le osservazioni cliniche che mostrano una correlazione tra l'efficacia di ICI e la presenza di alcune specie del microbioma intestinale. E' interessante sottolineare anche che, dimostrando che il microbiota intestinale e ICI agiscono in sinergia in una finestra temporale limitata, gli autori suggeriscono l'importanza del giusto tempismo nell'esposizione degli antigeni microbici per una buona efficacia antitumorale.

Referenza: Microbiota-induced T cell plasticity enables immune-mediated tumour control. *Tariq A Najar, Yuan Hao, Yuhan Hao, Gabriela Romero-Meza, Alexandra Dolynuk, Emma Almo, Dan R Littman*. Nature 2026. doi: 10.1038/s41586-025-09913-z.

What's new in science?

L'aneuploidia nell'evoluzione del tumore – il cancro del colon-retto.



L'alterato numero di cromosomi (aneuploidia) è una caratteristica diffusa di molti tumori. Le cellule riescono a gestire un certo grado di aneuploidia, grazie a specifici meccanismi di compensazione; in questi casi, l'aneuploidia può offrire un vantaggio proliferativo alle cellule tumorali, con l'acquisizione di nuove caratteristiche che sostengono la sopravvivenza e la proliferazione. Se però i meccanismi di compensazione non sono sufficienti, la conseguente eccessiva alterazione genomica può rappresentare una minaccia alla sopravvivenza della cellula. Lo stato aneuploide delle cellule tumorali è infatti dinamico ed evolve durante la progressione tumorale, come risultato dell'azione di forze di selezione positive e negative: durante l'evoluzione del tumore, alcune alterazioni genomiche vengono positivamente selezionate – e mantenute –, altre vengono negativamente selezionate – e perse.

Scoperta principale.

I ricercatori hanno utilizzato il tumore del colon-retto –spesso aneuploide– come modello di malattia per tracciare l'evoluzione del genoma alterato delle cellule durante la progressione tumorale, dalle lesioni pretumorali (adenomi), alla trasformazione maligna, alla metastasi. I loro risultati mostrano che dopo un'iniziale notevole modificazione genomica, durante la trasformazione da lesione pre-maligna a maligna, il cariotipo delle cellule tumorali del colon-retto rimane nel complesso stabile durante la successiva progressione del tumore – fino alla metastasi. Alterazioni genomiche aggiuntive acquisite dalle cellule tumorali vengono però progressivamente selezionate (tramite un processo di selezione negativa), riducendo l'eterogeneità genetica intratumorale, perché con la progressione del tumore le cellule con il corredo di alterazioni più vantaggioso (cioè con le alterazioni genomiche che conferiscono un vantaggio nei confronti delle altre cellule) vengono selezionate, sopravvivono, proliferano e sostengono la crescita del tumore.

Dettagli.

Gli autori hanno analizzato (tramite sequenziamento del genoma, *whole genome sequencing*, WGS) le alterazioni genomiche in regioni differenti delle lesioni pre-tumorali, delle lesioni tumorali iniziali e avanzate (stadio II/III) in campioni isolati dai pazienti.

Quantificazione del grado di aneuploidia. Le alterazioni genomiche (nello specifico, le alterazioni del numero di copie, CNA) erano meno numerose (8.5%) nelle lesioni pre-tumorali che nelle lesioni tumorali (27%). Le acquisizioni di porzioni del genoma erano prevalenti rispetto alle perdite. Le popolazioni cellulari (subcloni)

caratterizzate da una specifica CNA erano più grandi negli adenomi che nelle lesioni tumorali, suggerendo che le cellule aneuploidi, una volta acquisita una CNA vantaggiosa che le distingue dalle altre cellule, si espandono (come clone cellulare), sostenendo la progressione del tumore, acquisendo infine alterazioni aggiuntive, che producono popolazioni cellulari più piccole (subcloni). Con la progressione del tumore, queste sottopopolazioni/subcloni sono meno numerosi che nelle fasi iniziali e l'eterogeneità intratumorale (genetica) si riduce.

Comparsa delle CNA. Nelle fasi iniziali dello sviluppo del tumore, emergevano delle CNA che sostenevano la trasformazione da lesione premaligna a maligna e che, in presenza di forze di selezione, generavano cellule tumorali aneuploidi con un vantaggio proliferativo.

Un cariotipo "core". Dopo la trasformazione maligna, tutte le sottopopolazioni cellulari all'interno della massa tumorale (cloni cellulari) avevano un cariotipo "core", che rimaneva pressoché stabile durante la successiva progressione del tumore; alcune di queste sottopopolazioni avevano però anche delle CNA aggiuntive (subclonali) che contribuivano all'eterogeneità intratumorale.

Un tumore che progredisce è una popolazione di cellule ad elevata fitness definita da una selezione positiva e negativa. In presenza di forze di selezione positiva, le CNA si accumulavano continuamente (l'accumulo di CNA infatti non procedeva attraverso "burst" di CNA –come è stato invece descritto nel tumore al seno– che si accumulavano durante l'evoluzione del tumore fino a definire il cariotipo maligno "più adatto", o "vincente"), ma, durante l'evoluzione del tumore, le CNA acquisite venivano selezionate negativamente, fino alla definizione di un cariotipo con la fitness più alta.

Studi precedenti hanno suggerito l'azione della selezione positiva sull'acquisizione delle CNA e, in questo studio (attraverso l'analisi scDNAseq in linee cellulari e organoidi di pazienti), gli autori l'hanno dimostrata fornendo prove ulteriori.

Per dimostrare l'azione della selezione *negativa* sulla definizione del cariotipo "finale", gli autori hanno ipotizzato che ogni tumore in evoluzione rappresenti la condizione ottimale in termini di fitness, ovvero dotato di tutte le caratteristiche che, sotto la specifica pressione selettiva di un particolare microambiente tumorale, determinano la sopravvivenza e la proliferazione della cellula tumorale. Per verificare questa ipotesi, hanno sviluppato un modello matematico, che ha difatti confermato la loro ipotesi: la selezione negativa dà forma al cariotipo "vincente" (con la fitness più elevata, a livello di popolazione), con il numero e il tipo giusto di CNA. Infatti, utilizzando questo modello, hanno osservato che *i.* se le mutazioni avvenivano in un tumore senza selezione negativa, l'eterogeneità intratumorale aumentava; *ii.* in presenza di selezione negativa, invece, il numero di CNA differenti diminuiva e l'eterogeneità intratumorale si riduceva. Questi risultati sono stati validati tramite *single cell sequencing*.

L'evoluzione del tumore durante la disseminazione metastatica e il trattamento. Durante la disseminazione metastatica, le cellule tumorali, con il loro corredo unico di CNA che ne ha permesso la sopravvivenza e la crescita nel tumore primario, affrontano nuove e forti pressioni selettive (nel flusso sanguigno e nel nuovo organo da colonizzare), che potrebbero selezionare il pattern di CNA (cariotipo) per la colonizzazione del nuovo organo. I ricercatori hanno quindi confrontato i campioni metastatici e di tumore primario e hanno osservato che, anche dopo la metastatizzazione, le cellule tumorali conservavano il loro cariotipo "core", ma all'interno delle metastasi erano presenti anche delle piccole sottopopolazioni cellulari (subcloni cellulari) caratterizzate da specifici pattern di CNA. Analisi spaziali e temporali hanno rivelato che, pur mantenendo il cariotipo "core" stabile, l'acquisizione di un set di CNA aggiuntive variava ampiamente tra i diversi campioni analizzati e i diversi pazienti, ma, nel complesso, le differenze erano più evidenti tra campioni primari e metastatici (probabilmente per sopravvivere nel nuovo organo) che tra metastasi e metastasi, e tra campioni isolati in momenti diversi rispetto a campioni isolati nello stesso momento (cioè allo stesso time point). È interessante sottolineare che il trattamento non aveva un effetto significativo sul pattern di CNA, suggerendo che la sopravvivenza al trattamento potrebbe essere più probabilmente legata ad altri meccanismi, come la plasticità cellulare legata all'espressione genica.

----- Conclusioni.-----

Il tumore è una popolazione di cellule (ad elevata fitness) definita da una selezione positiva e negativa esercitata dal microambiente tumorale durante la progressione, che determina la sopravvivenza o la morte della cellula tumorale/sottopopolazione cellulare con un determinato set di alterazioni genomiche. Il

trattamento non ha invece un effetto significativo sulla selezione della sottopopolazione (clone) cellulare tumorale con determinate caratteristiche genomiche, indicando che la sopravvivenza delle cellule tumorali al trattamento potrebbe essere più probabilmente legata ad altri meccanismi, come la plasticità cellulare legata all'espressione genica.

Referenza: Negative Selection Maintains Grossly Altered but Broadly Stable Karyotypes in Metastatic Colorectal Cancer. William C H Cross #, Salpie Nowinski #, George D Cresswell #, Maximilian Mossner #, Abhirup Banerjee #, Bingxin Lu #, Marc J Williams, Georgios Vlachogiannis, Laura J Gay, Ann-Marie Baker, Christopher Kimberley, Frederick J H Whiting, Hayley L Belnoue-Davis, Pierre Martinez, Maria Traki, Viola Walther, Kane Smith, Javier Fernandez-Mateos, Erika Yara-Romero, Erica A Oliveira, Salvatore Milite, Giulio Caravagna, Chela T James, George Elia, Alison Berner, Chang-Ho Ryan Choi, Pradeep Ramagiri, Ritika Chauhan, Nik Matthews, Jamie Murphy, Anthony Antoniou, Susan K Clark, Miriam Mitchison, Jo-Anne Chin Aleong, Enric Domingo, Inmaculada Spiteri, Stuart A C McDonald, Darryl Shibata, Miangela M Laclé, Lai Mun Wang, Morgan Moorghen, Ian P M Tomlinson, Marco Novelli, Marnix Jansen, Alan Watson, Nicola Valeri, Nicholas A Wright, John A Bridgewater, Manuel Rodriguez-Justo, Chris P Barnes, Hemant M Kocher, Simon J Leedham, Andrea Sottoriva, Trevor A Graham. Cancer Discov 2026. doi: 10.1158/2159-8290.CD-24-0813.

What's new in science?

Condivisione di dati e campioni – un bene o un male?

L'importanza del contesto.

La prognosi dei pazienti oncologici è migliorata in maniera significativa negli ultimi decenni, aumentando in maniera notevole la sopravvivenza e consentendo la guarigione di molti di loro. Ciò è stato possibile grazie alla ricerca. Il lavoro dei ricercatori, nel settore pubblico e privato, in istituti profit e non-profit, condividendo l'obiettivo comune di migliorare la salute dei pazienti attraverso la comprensione approfondita della biologia del tumore e dei meccanismi alla base dell'efficacia di un farmaco, insieme alla condivisione reciproca, strutturata e regolata di dati e campioni clinici, ha portato ai progressi notevoli della ricerca in ambito oncologico.

Negli Stati Uniti, la condivisione regolamentata dei dati è cominciata all'inizio degli anni 2000, quando ai ricercatori è stato richiesto di condividere i dati raccolti nel contesto di progetti di ricerca che prevedevano finanziamenti pubblici. Successivamente, altri enti finanziatori hanno richiesto ai candidati di includere una sezione sulla condivisione dei dati al momento dell'invio di una richiesta di finanziamento. Enti europei come EMA hanno iniziato a pubblicare i dati clinici inviati dalle aziende farmaceutiche come parte della documentazione a supporto delle loro domande di approvazione, al fine di evitare la duplicazione degli studi clinici, promuovere l'innovazione, permettere la rivalutazione dei dati clinici da parte di accademici e ricercatori e per costruire la fiducia del pubblico nei processi scientifici e decisionali di EMA¹.

Analogamente, per quanto riguarda i campioni clinici dei pazienti spesso raccolti a scopo diagnostico nell'ambito dei clinical trial, istituti di ricerca –accademici e non– sono incoraggiati a garantire una custodia responsabile dei campioni (e dei dati associati) a nome dei partecipanti allo studio clinico, assicurando allo stesso tempo accesso alle procedure e ai campioni secondo la volontà dei partecipanti.

Nonostante le difficoltà nell'effettiva implementazione delle linee guida sulla condivisione dei dati e dei campioni, riguardanti principalmente la proprietà –di dati e campioni– da parte dello sponsor degli studi clinici, esistono diverse storie di successo, collaborazioni fruttuose –nel e tra il settore privato e accademico– nella ricerca clinica, dove un'appropriata condivisione dei dati e dei campioni nel contesto di grandi gruppi di collaborazione ha permesso di raccogliere informazioni scientifiche/cliniche critiche, per portare avanti la ricerca traslazionale e clinica, per la definizione di nuovi approcci terapeutici e nuovi dispositivi medici, per l'identificazione di biomarcatori che potessero informare le scelte terapeutiche e rifinire il design degli studi clinici.

Nel mondo della ricerca preclinica, la condivisione dei dati è diventata ormai pratica comune, attraverso lo sviluppo di database pubblici di dati omici armonizzati e informazioni sugli studi clinici. In ambito clinico, è possibile superare gli ostacoli esistenti e massimizzare i risultati del lavoro di ricercatori traslazionali e clinici, attribuendo il giusto valore al contributo dei pazienti (in termini di dati e campioni) ed accelerare il progresso scientifico? In altre parole, in che modo tutte le parti coinvolte possono lavorare insieme per la ricerca clinica? Recentemente, sono state proposte delle linee guida pratiche, che includono diversi aspetti, come assicurarsi che aziende farmaceutiche, enti accademici, pazienti ed esperti in ambito normativo condividano la leadership degli studi clinici (anche quando sponsorizzati dalle aziende farmaceutiche) e il potere di modificare il design dello studio clinico, al fine di garantire gli interessi dei partecipanti allo studio e dei futuri pazienti, e massimizzare l'utilizzo di dati e campioni. In questo frangente, sarebbe importante redarre, in collaborazione, un piano per la condivisione di dati (e campioni) al momento del design dello studio. Aumentare la condivisione dei dati potrebbe consentire di raggiungere la significatività statistica che potrebbe andare persa negli studi individuali (*i.*). Il maggiore coinvolgimento dei pazienti nel design degli studi clinici potrebbe contribuire a massimizzare la condivisione dei dati; i pazienti potrebbero infatti richiedere attivamente la condivisione dei

propri dati per studi successivi, pur assicurando la privacy e in ottemperanza con le leggi vigenti (ii.). La condivisione (post-approvazione) di dati armonizzati come requisito per l'approvazione di un nuovo farmaco/dispositivo medico potrebbe permettere analisi successive, ad esempio in sottogruppi di pazienti definiti sulla base di specifici biomarcatori in cui uno determinato trattamento potrebbe risultare maggiormente efficace, accelerandone così l'approvazione e il rimborso (iii.). Anche la standardizzazione nella raccolta dei campioni e delle procedure impiegate (enunciata in maniera prospettica al momento del design dello studio clinico), così come l'armonizzazione dei dati, sono condizioni necessarie per una condivisione efficace (iv.). La condivisione/pubblicazione dei risultati (sia positivi che negativi) degli studi clinici, come accade normalmente per i dati grezzi della ricerca preclinica, permetterebbe anche di massimizzare i benefici derivanti dalla ricerca clinica (v.). Infine, nell'era dell'Intelligenza Artificiale (AI), la condivisione dei dati per l'addestramento degli algoritmi di AI diventa estremamente importante per permettere lo sviluppo di strumenti solidi, a beneficio dei pazienti, del sistema sanitario e della società in generale (vi.).

Allineare gli interessi di tutte le parti coinvolte per una effettiva condivisione di dati e campioni non è un compito facile. Eppure, i benefici che ne possono derivare, per le persone che in primo luogo hanno fornito le loro informazioni e i loro campioni, rende questo compito un obbligo etico. Una collaborazione e una comunicazione efficace, guidate dall'obiettivo comune di migliorare la salute dei pazienti, può certamente contribuire a definire lo scenario necessario perché ciò diventi possibile.

Referenza: Enhancing Clinical Cancer Research Through Sharing of Data and Biospecimens. Hans Wildiers, Virginie Adam, Seamus O'Reilly, Josephine Van Cauwenberge, Amal Arahmani, Carlos L Arteaga, Philippe L Bedard, Judith Bliss, Panayota Boussis, Etienne Brain, Marc Buyse, Carmela Caballero, David Cameron, Fatima Cardoso, Eva Carrasco, Ana Casas, Boon Chua, Giuseppe Curigliano, Angela DeMichele, Laura Esserman, Giuseppe Floris, Matthew P Goetz, Theodora Goulioti, Benjamin Haibe-Kains, Christine Hodgdon, Michail Ignatiadis, Marleen Kok, Denis Lacombe, Barbro Linderholm, Sherene Loi, Christopher J Lord, Mairead MacKenzie, Julia Maues, Lydie Meheus, Judy Needham, Patrick Neven, Heather Parsons, Martine Piccart, Lajos Pusztai, Evangelia Razis, Shigehira Saji, Eva Schumacher-Wulf, Gabe S Sonke, Tania Spanic, Ian F Tannock, Andrew Tutt, Ander Urruticoechea, Laura van 't Veer, Ines Vaz-Luis, Gustavo Werutsky, Douglas Yee, Khalil Zaman, Christine Desmedt. JAMA Oncol 2025. doi: 10.1001/jamaoncol.2025.5376.

What's new from IEO researchers?

I segnali di Wnt nel microambiente che regolano la divisione cellulare.

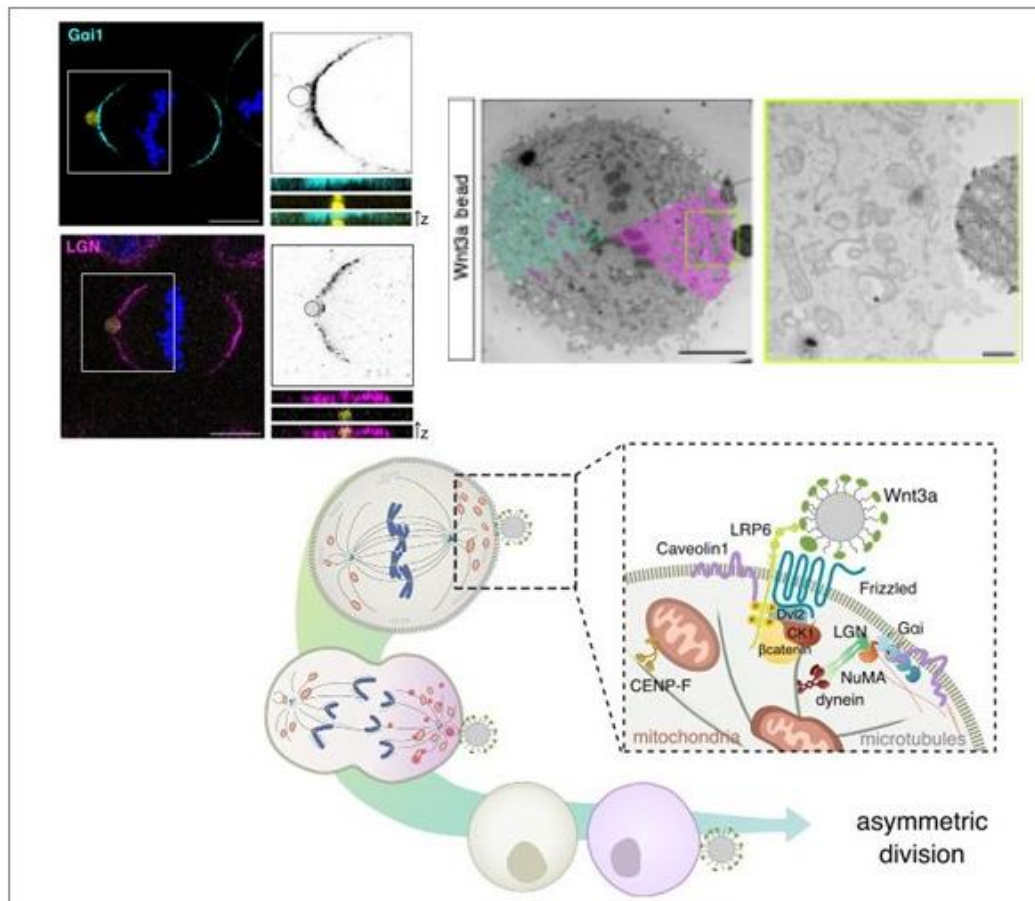


Figure adapted from Eli, Rauso et al., 2025 (an open access [article](#) under the [CC BY](#) license)

Fisiologicamente, la self-renewal delle cellule staminali avviene tramite divisione asimmetrica delle cellule, che porta alla generazione di due cellule con due destini differenti: una che manterrà i tratti staminali e una che andrà incontro a differenziamento. La divisione cellulare asimmetrica richiede la separazione asimmetrica delle componenti intracellulari all'interno della cellula, lo specifico posizionamento della cellula che si divide rispetto al microambiente, il corretto orientamento del fuso mitotico (la struttura cellulare critica il cui assemblaggio e allineamento rispetto al substrato è necessario per la corretta divisione cellulare). Fattori extracellulari chiave in questo processo sono le proteine Wnt. Wnt è secreto nel microambiente, lega il suo recettore sulla membrana delle cellule staminali ed attiva la signaling che determina la polarità/asimmetria cellulare. La signaling di Wnt coinvolge l'attivazione del recettore Frizzled, i corecettori LRP5/LRP6, la stabilizzazione della β -catenina (attraverso l'inibizione della degradazione della β -catenina indotta da Wnt e dipendente da GSK β) e l'espressione dei geni target di Wnt, contemporaneamente alla modulazione della polarità cellulare, dell'adesione cellulare e della riorganizzazione del citoscheletro. La signaling di Wnt (nello specifico, di Wnt3a) è anche collegata all'orientamento della divisione cellulare.

In un articolo recente di Eli, Rauso et al., gli autori, guidati da Marina Mapelli –Group leader del dipartimento di oncologia sperimentale di IEO– hanno delineato i meccanismi molecolari alla base della divisione cellulare regolata da Wnt: i loro risultati hanno rivelato che Wnt3a induce l'orientamento del fuso mitotico

promuovendo l'assemblaggio del complesso proteico costituito da NuMA/ β -Catenina/corecettore LRP6. Questo processo, indotto da Wnt, coinvolge la proteina caveolina e la proteina MACF1 associata all'actina, ed induce una locale riorganizzazione dell'actina che sostiene la divisione cellulare orientata. Inoltre, hanno mostrato che i segnali localizzati di Wnt inducono anche una distribuzione asimmetrica dei mitocondri all'interno della cellula in divisione, con il successivo aumento, al momento della divisione, del numero di mitocondri –così come della β -catenina– in una delle cellule figlie. Rivelando i fattori molecolari implicati nella divisione cellulare orientata, gli autori hanno dimostrato come questa sia il risultato dell'integrazione di due diversi segnali: quello che media l'adesione cellulare e quello che media l'orientamento del fuso. Ciò coinvolge proteine di membrana e componenti del citoscheletro, traducendo segnali chimici localizzati in forze diverse, il cui equilibrio assicura la divisione cellulare correttamente orientata.

La definizione di questo meccanismo sia nelle cellule staminali che in una linea cellulare tumorale indica che lo stesso processo potrebbe essere rilevante sia nello sviluppo che in un contesto patologico.

“Nel complesso –spiega Marina Mapelli, ultimo autore del lavoro– le nostre scoperte supportano un cambio di paradigma per quello che riguarda i principi che governano la self-renewal mediata da Wnt nei vertebrati, in cui i segnali localizzati a livello della *niche* regolano la distribuzione asimmetrica delle componenti cellulari, inclusi i mitocondri, per promuovere l'asimmetria nel destino delle cellule figlie e il potenziale metabolico. Dato che la signaling di Wnt è fortemente alterata in molti tumori intestinali, l'associazione tra attivazione di Wnt, metabolismo e identità cellulare potrebbe aprire la strada allo sviluppo di nuove strategie terapeutiche.

----- TELL ME MORE! -----

Segnali localizzati di Wnt e fattori molecolari per l'orientamento del fuso.

Utilizzando cellule HeLa (una linea cellulare di origine umana di tumore cervicale) e delle microbiglie coniugate alla proteina Wnt (Wnt-microbiglie), gli autori hanno scoperto che i segnali localizzati di Wnt3a (ovvero, le *niche* di Wnt3a generate artificialmente immobilizzando Wnt3a sulle microbiglie) erano sufficienti per la divisione cellulare asimmetrica. Nello specifico, ciò avveniva attraverso una locale riorganizzazione del citoscheletro di actina e il successivo assemblaggio del fuso. Le forze che modulavano l'orientamento del fuso agivano insieme alle forze di adesione, determinando l'orientamento finale del fuso. Dal punto di vista molecolare,

l'orientamento del fuso in risposta ai segnali localizzati di Wnt3a e l'allineamento al substrato richiedevano fattori come LRP6, β -catenina, Dvl1 e Dvl2. L'espressione genica regolata da Wnt, invece, non influenzava la

divisione orientata. L'orientamento del fuso indotto da Wnt era regolato anche dal complesso proteico NuMA/LGN/G α i. Queste proteine erano infatti abbondanti e localizzate a livello del sito di contatto tra le Wnt-microbiglie e la membrana cellulare e, quando queste proteine erano assenti,

“rivelando i fattori molecolari implicati nella divisione cellulare orientata, gli autori hanno dimostrato come questa sia il risultato dell'integrazione di due diversi segnali: quello che media l'adesione cellulare e quello che media l'orientamento del fuso. Ciò coinvolge proteine di membrana e componenti del citoscheletro, traducendo segnali chimici localizzati in forze diverse, il cui equilibrio assicura la divisione cellulare correttamente orientata”

l'orientamento del fuso era alterato. La modulazione dell'orientamento del fuso da parte del complesso NuMA avveniva attraverso il reclutamento dei motori microtubulari dineina/dinactina a livello di aree circoscritte (ovvero, a livello dei contatti tra cellula e Wnt-microbiglie); ciò era cruciale nel generare le forze che –tirando– posizionavano/orientavano correttamente il fuso.

Analisi proteomiche identificano altri fattori nell'orientamento del fuso.

Dopo aver messo a punto un nuovo protocollo per l'analisi proteomica delle aree della cellula vicini a Wnt (per identificare le componenti del proteoma citoplasmatico e di membrana reclutate localmente a livello del sito di

attivazione di Wnt3a), gli autori hanno trovato che altre proteine erano reclutate a livello della membrana cellulare dai segnali localizzati di Wnt, insieme al complesso NuMA/LGN/G α i.

Infatti, numerose proteine erano abbondanti a livello del sito di contatto Wnt-microbiglia/cellula, come le chinasi CK1 α e CK2 α , β -catenina, caveoline, R-spondina3, il regolatore della fosfatasi PP2A (PPP2R1A), il proteoglicano transmembrana sindecana1, G α 1 e G α 3, la depolimerasi dei microtubuli Kif2A, i

membri della famiglia miosina-1 (miosina1B e miosina1C) e MACF1. Le proteine identificate erano implicate in processi cellulari come la progressione della mitosi, l'organizzazione dell'actina, la dinamica della membrana. Inoltre, queste analisi hanno mostrato che anche le proteine che legano l'RNA e le componenti mitocondriali erano reclutate a livello dei siti di contatto con Wnt3a. Sebbene queste proteine non contribuissero all'orientamento della divisione cellulare, la loro abbondanza suggerisce che potrebbero essere segregate in maniera asimmetrica e contribuire al destino della cellula figlia.

La trasduzione del segnale di Wnt a livello della membrana cellulare. Studi ulteriori degli altri fattori coinvolti nel tradurre il segnale iniziato da Wnt a livello della membrana fino al posizionamento del fuso hanno rivelato il reclutamento, indotto da Wnt, della caveolina, che a sua volta assicurava l'orientamento del fuso Wnt-dipendente – attraverso NuMA/LGN/Gai/dineina/dinactina–, la regolazione del citoscheletro actinico e microtubulare –rafforzando l'adesione cellulare–, il coinvolgimento della proteina MACF1 (abbondante a livello dei siti di contatto Wnt-cellula) e la chinasi CK1 α attivata da Wnt.

Separazione asimmetrica dei mitocondri. I segnali

localizzati di Wnt3a polarizzavano anche la distribuzione dei mitocondri, determinando un aumento del numero di mitocondri a livello dei siti di contatto Wnt-microbiglia/cellula e, in seguito alla divisione cellulare, nella cellula figlia, attraverso il trasporto dei mitocondri sui microtubuli, promosso dalla proteina CENP-F. La polarizzazione dei mitocondri indotta da Wnt3a nelle cellule epiteliali rappresenta una delle scoperte principali di questo studio.

I meccanismi molecolari indotti da Wnt nella divisione asimmetrica delle cellule staminali embrionali murine. Gli autori hanno mostrato che, in maniera analoga a ciò che accadeva nelle cellule HeLa, la polarizzazione cellulare indotta da Wnt e la divisione asimmetrica –con una cellula vicina a Wnt (ricca di β -catenina) pluripotente e una cellula distante da Wnt che invece differenziava– avveniva anche nelle cellule staminali embrionali murine (mESCs). Analogamente, la densità mitocondriale era modulata dai segnali di Wnt; i mitocondri diventavano infatti molto numerosi a livello dei siti di contatto Wnt/cellula. Anche LRP6 appariva coinvolta in maniera critica nella distribuzione asimmetrica dei mitocondri, dato che la deplezione di LRP6 interferiva con la distribuzione asimmetrica dei mitocondri.

Referenza: Localized Wnt-signaling promotes asymmetric NuMA-dependent oriented divisions and unequal apportioning of mitochondria. Susanna Eli, Greta Rauso, Paola Ghezzi, James L. A. Szczerkowski, Michela Bruzzi, Francesca Rizzelli, Fabiola Iommazzo, Alessia Loffreda, Francesco Castagna, Federico Donà, Chiara Gaddoni, Ambra Dondi, Mattia Marenda, Simona Rodighiero, Pierre Tournier, Zeno Lavagnino, Dario Parazzoli, Nils C. Gauthier, Simone Tamburri, Diego Pasini, Shukry James Habib & Marina Mapelli. Nature communications 2025. doi: 10.1038/s41467-025-65775-z.

What's new from IEO researchers?

Definire il microbioma intestinale sano attraverso informazioni nutrizionali e marcatori dello stato di salute.

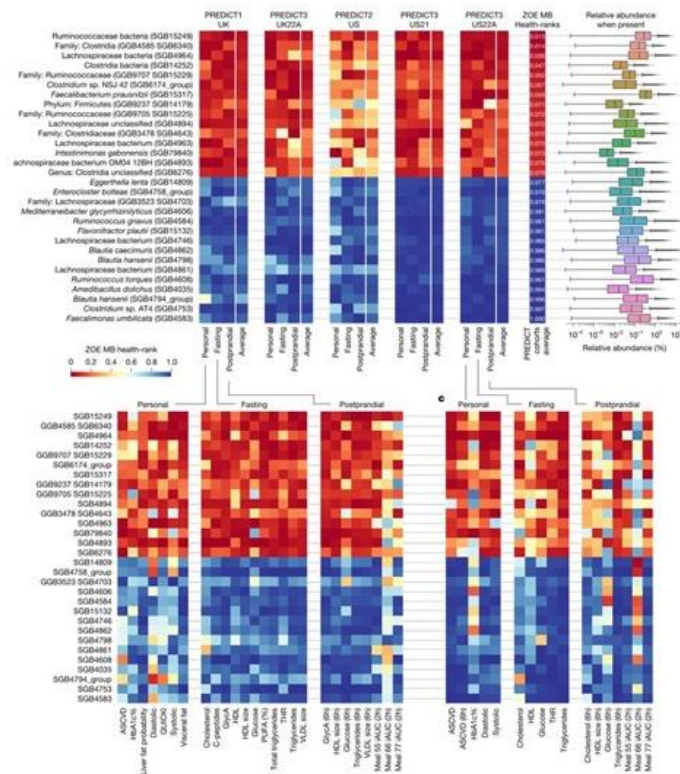


Image from Asnicar et al., 2025 (an open access [article](#) under the CC BY license)

Numerosi studi hanno dimostrato l'associazione tra la composizione del microbioma intestinale e la salute umana. Una dieta sana, con un consumo elevato di alimenti di origine vegetale e un consumo limitato di cibi processati, è generalmente consigliata per ridurre il rischio di malattie croniche e il microbiota intestinale rappresenta l'anello di congiunzione e la ragione meccanicistica per queste raccomandazioni. Studi precedenti hanno mostrato che attraverso il profilo del microbioma intestinale è possibile distinguere le persone che si nutrono con una dieta onnivora, vegetariana e vegana, e hanno evidenziato che mentre il microbioma degli individui che si nutrono con una dieta onnivora (ricca di carne rossa) correla negativamente con la salute umana –in particolare la salute cardiometabolica–, il microbioma associato ad una dieta vegana correla positivamente con la salute cardiometabolica. Dato che la dieta è un fattore facilmente modificabile, sia in termini di prevenzione che a scopo terapeutico, i ricercatori hanno approfondito la comprensione dell'associazione tra

microbioma intestinale, nutrizione e salute, mostrando che un cambiamento nelle abitudini alimentari può di fatto modificare la composizione del microbioma intestinale, influenzando di conseguenza la salute umana. In questo scenario, la “nutrizione di precisione” si pone l'obiettivo di identificare gli specifici fattori che modulano l'interazione tra la dieta e la salute in ogni essere umano. Tuttavia, questo è complicato dall'elevata variabilità inter-individuale del microbioma intestinale, che è il risultato dell'interazione tra numerosi fattori. I ricercatori IEO hanno precedentemente investigato l'associazione tra microbioma intestinale e consumo di caffè, scoprendo come questo fosse caratterizzato dalla presenza di una specifica specie batterica intestinale – *Lawsonibacter asaccharolyticus* –, dimostrando il link causale tra il caffè e questo microrganismo intestinale (dato che il caffè stimolava la crescita *in vitro* dei batteri), identificando i metaboliti più abbondanti nei consumatori di caffè e rivelando il legame tra uno specifico microrganismo intestinale e uno specifico alimento. In un articolo recentemente pubblicato su *Nature*, i ricercatori coordinati da Nicola Segata –Group leader al dipartimento di oncologia sperimentale di IEO e professore all'Università di Trento– hanno sfruttato le conoscenze sull'associazione tra una dieta sana e la salute umana da un lato (ovvero, una dieta sana correla con la salute umana) e il l'associazione tra dieta e microbioma intestinale, rivelando l'esistenza di un asse diretto, modificabile, nutrizione-microbioma-salute umana, e le specie microbiche intestinali correlate con una

dieta sana e con la salute umana. Nella difficoltà di definire la composizione del microbioma sano, approcciando la questione da un diverso punto di vista, gli autori si sono chiesti “quali sono le specie del microbioma intestinale che correlano con la salute umana, come una dieta sana o marcatori dello stato di salute?”. In questo modo, analizzando i dati metagenomici di circa 34.000 persone –superando così i problemi associati con l’elevata variabilità del microbioma intestinale– e i corrispondenti dati nutrizionali e sui marcatori di salute (come dati biochimici e antropometrici), sono riusciti a stilare una lista delle (50) specie più strettamente associate con la salute umana, in un dataset che, per via della sua eterogeneità, può essere facilmente generalizzabile, non solo in termini geografici (sebbene si tratti comunque di condizioni associate con uno stile di vita occidentale), ma anche in diverse condizioni patologiche. Inoltre, l’abbondanza di queste specie si è rivelata modificabile attraverso un cambio di dieta, rendendolo un target interessante di interventi a scopo terapeutico, con risultati che possono essere stimati a priori.

I ricercatori IEO hanno precedentemente utilizzato approcci di metagenomica per analizzare, ad elevata risoluzione, le specie del microbioma coinvolte nel processo di trasformazione maligna, dimostrando che la presenza nell’intestino di specie tipicamente presenti nella cavità orale sono associate a tumore del colon-retto e che le analisi a livello della specie del microbioma intestinale possono distinguere in maniera abbastanza accurata i pazienti oncologici dai soggetti sani, così come distinguere i diversi stadi del tumore. Inoltre, i loro studi hanno precedentemente dimostrato che l’abbondanza di uno specifico microrganismo eucariotico intestinale –*Blastocystis*– è associato alla dieta, inversamente correlato con la salute cardiometabolica, suggerendo fortemente un suo potenziale ruolo attivo sulla salute umana. Hanno mostrato il ruolo chiave di *Blastocystis*, specialmente nel contesto della salute cardiometabolica, e i dati suggeriscono una maggiore abbondanza negli individui sani rispetto agli individui malati in diverse condizioni patologiche, tra cui il tumore del colon-retto, suggerendo un ruolo favorevole di specifici microrganismi intestinali, come *Blastocystis*, nella salute umana.

----- TELL ME MORE! -----

Gli autori hanno assemblato il più grande dataset contenente i dati metagenomici sul microbioma intestinale, informazioni nutrizionali e misure antropometriche, di oltre 34.000 individui in US e UK. Le loro analisi hanno rivelato una forte associazione tra composizione del microbioma, marcatori biochimici di salute (e.g. livelli di glucosio nel sangue, trigliceridi,...), fattori antropometrici (e.g. l’indice di massa corporea, BMI) e nutrizione (e.g. abitudini nutrizionali salutari come ad esempio quelli misurati sulla base della diversità di una dieta a base di alimenti di origine vegetale). Hanno quindi analizzato in maggiore dettaglio le specifiche specie del microbioma intestinale associate con i **marcatori di salute** o con una **dieta sana** e hanno stilato una lista (ranking) delle specie del microbioma più strettamente correlate (o inversamente correlate) con i marcatori di salute o i marcatori di una dieta sana. Le specie associate (ovvero più in alto nel ranking) con i marcatori di salute erano anche associate con marcatori di una dieta sana. Dato che

“nella difficoltà di definire la composizione del microbioma sano, approcciando la questione da un diverso punto di vista, gli autori si sono chiesti ‘quali sono le specie del microbioma intestinale che correlano con la salute umana, come una dieta sana o marcatori di uno stato di salute umana?’ ”

il BMI è un fattore antropometrico spesso utilizzato per identificare pazienti a maggior rischio di incidenza di alcune malattie, i ricercatori hanno anche analizzato la correlazione tra specie del microbioma e **BMI**, mostrando che le specie del microbioma che correlavano con lo stato di salute erano inversamente correlate con il BMI e viceversa.

Le specie identificate, associate con *i.* marcatori di salute; *ii.* BMI sano, *iii.* dieta salutare, erano diversamente abbondanti nei controlli sani rispetto agli individui malati; ovvero le specie più fortemente correlate con lo stato di

salute erano più abbondanti nei controlli che nelle persone malate, e viceversa.

Le specie del microbioma più in alto nel ranking potevano essere usate anche per distinguere i singoli individui di controllo dagli individui sani.

Infine, sfruttando i dati di studi clinici, gli autori hanno analizzato il modo in cui i cambiamenti della dieta influenzavano l’abbondanza delle specie del microbioma del ranking, dimostrando che alcune

specie erano significativamente influenzate dagli interventi dietetici volti a migliorare la dieta tramite somministrazione di prebiotici o regimi dietetici personalizzati: in seguito allo stesso tipo di

intervento, alcune specie associate con una buona salute aumentavano, mentre alcune correlate con un peggiore stato di salute diminuivano.

Referenza: Gut micro-organisms associated with health, nutrition and dietary interventions. *Francesco Asnicar, Paolo Manghi, Gloria Fackelmann, Gabriel Baldanzi, Elco Bakker, Liviana Ricci, Gianmarco Piccinno, Elisa Piperni, Katarina Mladenovic, Federica Amati, Alberto Arrè, Sajaysurya Ganesh, Francesca Giordano, Richard Davies, Jonathan Wolf, Kate M Bermingham, Sarah E Berry #, Tim D Spector #, Nicola Segata #*. Nature 2025. doi: 10.1038/s41586-025-09854-7.

What's new from IEO researchers?

Il trapianto di microbiota fecale in clinical trial: tumore renale, polmonare e melanoma.

Nonostante il successo dell'immunoterapia con inibitori dei checkpoint immunitari (ICI), in alcuni pazienti la malattia progredisce; in quel caso, le opzioni terapeutiche sono limitate. Evidenze scientifiche sempre più numerose indicano che il microbioma intestinale potrebbe influenzare l'efficacia degli ICI. Ad esempio, è stato osservato che l'utilizzo degli antibiotici, distruggendo il microbioma intestinale, riduce l'efficacia degli ICI; determinate specie del microbioma sono state associate con la risposta alla terapia, con studi preclinici che mostrano gli effetti del trapianto di microbiota fecale (FMT) sulla risposta ad ICI e studi clinici che mostrano i benefici clinici di FMT nei pazienti resistenti a ICI (soprattutto nel melanoma), senza eventi avversi gravi.

Nel contesto dello studio clinico di fase II (randomizzato, placebo-controllato) **TACITO**, i cui risultati sono stati recentemente pubblicati sulla rivista *Nature Medicine*, i ricercatori tra cui Nicola Segata –Group leader del dipartimento di oncologia sperimentale di IEO e professore ordinario dell'Università di Trento–, che ha coordinato l'analisi del microbioma, hanno valutato l'efficacia di FMT (da pazienti che avevano avuto una risposta completa a ICI, *complete responder*) nel migliorare la risposta al trattamento combinato con anti-PD1 pembrolizumab e inibitore di VEGF axitinib in pazienti con carcinoma renale metastatico (mRCC).

Dal punto di vista clinico, lo studio ha mostrato che FMT (da responder) era sicuro –in linea con le scoperte di studi precedenti– ed aumentava l'efficacia della terapia, aumentando il tasso di risposta (*objective response rate*, ORR), che era 52% nel gruppo FMT e 32% nel gruppo placebo, e la sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS) pari a 24 mesi nei pazienti che avevano ricevuto FMT rispetto ai 9 mesi di coloro che erano nel gruppo placebo. L'efficacia del trattamento era ancor più evidente soprattutto nel gruppo di pazienti con prognosi scarsa/intermedia, in cui le terapie che modulano l'attività del sistema immunitario hanno di solito un maggior effetto.

Dal punto di vista microbiologico, lo studio ha evidenziato che l'acquisizione, in seguito a FMT, di alcune specie microbiche “benefiche”, come *Blautia wexlerae* (un batterio che produce acidi grassi a catena corta –SCFA– già

associato con la risposta a chemioterapia neoadiuvante in pazienti con tumore rettale, ed effetti anti-infiammatori), era associata con un migliore esito clinico. Non solo, anche la perdita di specie “nocive”, come *Akkermansia massiliensis* (una specie diversa da *Akkermansia muciniphila* che è stata precedentemente associata con risposta a ICI), correlava con un migliore esito clinico. Inoltre, dato che solitamente le specie di *Akkermansia* non vengono facilmente sostituite da altre specie, i loro dati suggeriscono che i pazienti con un'abbondanza adeguata di *A. muciniphila* prima del FMT potrebbero non venire colonizzati da una specie nociva come *A. massilinesis*, e la combinazione di specie benefiche (*A. muciniphila* e *B. wexlerae*) insieme alla perdita di una specie nociva (*A. massilinesis*) potrebbe contribuire al successo clinico del FMT.



Nicola Segata

Nel contesto di un diverso studio clinico, multicentrico, di fase II –FMT-LUMINate–, i cui risultati sono stati pubblicati nello stesso numero di *Nature Medicine*, i ricercatori (tra cui Nicola Segata) hanno valutato

sicurezza ed efficacia del FMT (da donatori sani) nell'aumentare l'efficacia dell'immunoterapia con ICI nel trattamento del tumore al polmone (con anti-PD1) e del melanoma (con anti-PD1 e anti-CTLA4).

Dal punto di vista clinico, i risultati dello studio FMT-LUMINate hanno dimostrato l'efficacia di FMT nel migliorare la risposta a due diversi ICI, in due diversi tipi di tumore, riportando una ORR del 80% nel tumore polmonare –la più alta mai osservata (di solito tra il 39% e il 46%)– e una ORR del 75% nel melanoma (di solito tra il 50% e il 58% con ipilimumab e nivolumab).

Dal punto di vista del meccanismo, i loro risultati suggeriscono che l'efficacia clinica sia legata all'eliminazione di alcune specie deleterie piuttosto che dalla colonizzazione da parte di determinate specie del donatore, che si accompagna a cambiamenti a livello sistemico come la riduzione dei livelli di alcuni metaboliti del pathway del triptofano (come acido quinolinico e kinerunina) nel sangue, e cambiamenti a livello del sistema immunitario, con un aumento del numero di cellule T CD8 citotossiche e un ridotto numero di cellule T regolatorie, così come un aumento dei livelli di molecole pro-infiammatorie, evidenziando una risposta immunitaria più forte nei pazienti trattati con ICI e FMT che rispondevano al trattamento. E' interessante aggiungere che gli effetti sulle molecole circolanti erano il risultato dell'eliminazione di specie microbiche differenti nei pazienti con tumore al polmone e nei pazienti con melanoma, che convergevano sugli stessi processi biochimici. Anche nel trial TACITO l'eliminazione di alcune delle specie microbiche intestinali nocive in seguito a FMT (solo nel gruppo che riceveva FMT e non nel gruppo placebo) correlava con l'esito clinico. Lo stesso fenomeno si osservava rianalizzando i dati di altri trial pubblicati precedentemente, sottolineando la validità di questa osservazione in diversi tipi di tumore (e regioni geografiche – Asia, Europa, Nord America). Inoltre, tramite esperimenti preclinici *in vivo*, i ricercatori hanno mostrato l'insorgenza di resistenza a ICI in seguito all'introduzione negli animali riceventi di quelle specie nocive non più presenti nei responder in seguito a FMT, fornendo ulteriori evidenze meccanicistiche degli effetti negativi di queste specie batteriche sull'efficacia clinica di ICI e FMT.

Sebbene la tossicità (osservata nel trial FMT-LUMINate) associata con la presenza di *Prevotella* in seguito alla somministrazione sia di anti-PD1 che di anti-CTLA4 nel melanoma necessiti di particolare attenzione, entrambi questi studi supportano l'efficacia di FMT nel contesto dell'immunoterapia con ICI, in diversi tipi di tumore e forniscono informazioni importanti di tipo meccanicistico per spiegare i processi alla base dei risultati clinici osservati.

----- TELL ME MORE! -----

Lo studio clinico TACITO.

Lo studio ha arruolato 50 pazienti con RCC metastatico. Tutti i pazienti hanno ricevuto pembrolizumab e axitinib (P+A) e sono stati casualmente assegnati a ricevere FMT da pazienti con tumore renale che avevano avuto una risposta completa alla terapia con ICI (responder completi). L'efficacia è stata valutata in termini di numero di pazienti privi di segni di malattia per 12 mesi, sopravvivenza mediana in assenza di malattia (PFS), sopravvivenza generale (OS). Sono stati valutati anche i cambiamenti del microbioma indotti da FMT e la tossicità.

Efficacia. Sebbene lo studio suggerisca che gli effetti potrebbero essere maggiormente evidenti se valutati sul lungo termine (ovvero dopo i 12 mesi), i risultati mostrano una migliore risposta a ICI nei pazienti trattati con FMT (gruppo FMT) rispetto al gruppo di controllo, a cui è stato somministrato P+A e un placebo al posto del FMT (gruppo placebo). La

PFS mediana era migliore nei pazienti che ricevevano FMT (24 mesi) rispetto ai pazienti nel gruppo placebo (9 mesi). I decessi dovuti al tumore erano più frequenti nel gruppo placebo (50%) che nel gruppo FMT (26%). La sopravvivenza generale appariva più lunga (sebbene non in maniera significativa) nel gruppo FMT (41 mesi) rispetto al gruppo placebo (28 mesi). Il numero di pazienti in cui la malattia non progrediva ed ancora vivi alla data cut-off erano più numerosi nel gruppo FMT che in quello placebo (71% vs 38%). La ORR era 52% nel gruppo FMT rispetto al 32% nel gruppo placebo. La risposta completa è stata osservata in due pazienti del gruppo FMT e in nessuno di quelli del gruppo placebo.

Analisi post-hoc. Un'analisi *post-hoc* (ovvero non originariamente inclusa nel design dello studio) ha valutato l'efficacia in quei sottogruppi di pazienti in cui il trattamento P+A era di solito più efficace (ovvero nei pazienti con prognosi scarsa o

intermedia) rispetto a quelli con una buona prognosi (in cui il trattamento P+A era solitamente meno efficace). Nel sottogruppo di pazienti con prognosi scarsa/intermedia, le differenze tra il gruppo FMT e il gruppo placebo erano più evidenti, con una PFS mediana di 18.8 mesi nel gruppo FMT vs 5.5 nel placebo; la PFS a 12 mesi era 63% nel FMT rispetto al 27% nel placebo, e la OS era 41 mesi nel FMT rispetto a 21.5 mesi nel placebo. La ORR era 50% nel FMT rispetto a 8% (1 paziente) nel gruppo placebo.

Sicurezza. Il trattamento era nel complesso ben tollerato, e gli eventi avversi erano rari. Non si sono osservati decessi associati al trattamento e nessuna infezione in seguito a FMT. Tuttavia, gli eventi avversi associati a P+A erano più frequenti (28%) nel gruppo FMT che nel gruppo placebo (16%).

Cambiamenti del microbioma. I campioni fecali sono stati raccolti e analizzati con approcci metagenomici, ad elevata risoluzione, in diversi momenti durante lo studio. Prima di FMT, il microbioma di donatori e riceventi era, in termini di numero di specie diverse, nel complesso molto simile, ma la specifica composizione del microbioma (ovvero i diversi tipi di microrganismi che lo componevano) dei donatori era differente e caratterizzato soprattutto dall'abbondanza di *Bifidobacterium adolescentis*, *Akkermansia massiliensis*, e dall'assenza di *Akkermansia muciniphila* (che era invece abbondante nei riceventi). Dopo 4 settimane di trattamento, però, la diversità (in termini di numero di specie microbiche differenti nell'intestino, "ricchezza") aumentava nel gruppo FMT (mentre non si osservava alcun aumento nel gruppo placebo, confermando che, dal punto di vista microbiologico, il FMT aveva avuto successo). Inoltre, molte specie che erano completamente assenti prima del FMT, venivano acquisite dopo FMT ed alcune specie dopo FMT scomparivano. In generale, dopo FMT c'era un rimodellamento del

La diversità di tipo **Alfa** misura il numero di specie (la "ricchezza") e la loro relativa abbondanza. La diversità di tipo **Beta** misura le differenze nella composizione microbica tra i campioni ("uniformità").

microbioma che favoriva la risposta clinica. Il numero di strain del donatore che colonizzavano l'intestino del ricevente non era associato

acquisite o perse dopo FMT ha rivelato una correlazione tra l'acquisizione di una particolare strain (*Blautia wexlerae*) e una maggiore PFS, e una correlazione inversa tra l'acquisizione di una specie ad oggi ancora non descritta (SGB14845) della famiglia delle *Oscillospiraceae* con PFS. Infine, mentre la perdita di *Rimunococcus bromii* era associata con una minore PFS, la perdita di *Escherichia coli*, o di una specie non caratterizzata di *Clostridium*, era associata con una PFS più lunga.

Lo studio clinico FMT-LUMINate.

Lo studio ha arruolato 20 pazienti con tumore al polmone (*non-small cell lung cancer*, NSCLC, che non avevano mutazioni actionable) e 20 pazienti con melanoma (indipendentemente dalla mutazione BRAF-V600). I pazienti con NSCLC sono stati trattati con FMT e ICI (anti-PD1); i pazienti con melanoma sono stati trattati con FMT e ICI (anti-PD1 e anti-CTLA4). La fonte di FMT erano (diversamente dallo studio TACITO in cui i donatori erano responder completi) donatori sani differenti (10 diversi donatori per il tumore al polmone, 6 per il melanoma). Quasi tutti i pazienti erano in stadio IV.

Efficacia. L'efficacia di FMT nell'aumentare la risposta a ICI è stata calcolata in termini di ORR, PFS a 1 anno, OS a 1 anno, controllo della malattia, e durata della risposta. Nel NSCLC, la ORR era dell'80% (rispetto al 39-46% solitamente osservato con ICI), il tasso di controllo della malattia era del 95%, PFS e OS a un anno erano del 65% e 100% rispettivamente. Nel melanoma, la ORR era del 75% (rispetto al 50-58% solitamente osservato con ipilimumab e nivolumab), il tasso di controllo della malattia era del 75%, PFS e OS a un anno erano del 58% e 79% rispettivamente. Nel complesso, la combinazione di FMT e ICI si mostrava quindi clinicamente efficace sia nel NSCLC che nel melanoma.

Sicurezza. Gli eventi avversi indotti dalla somministrazione di FMT (che avveniva prima della terapia con ICI) erano minimi (35% di pazienti mostravano eventi avversi di grado 1); tuttavia, eventi avversi (sebbene non di grado 3 o maggiore) erano osservati nell'85% dei pazienti NSCLC trattati con FMT e ICI. Nei pazienti con melanoma, FMT + ICI causava eventi avversi nel 95% dei pazienti; 60% di questi manifestavano eventi avversi di grado 3 e uno solo di grado 4. Il 70% dei pazienti con melanoma ha interrotto il trattamento per via della tossicità. In ogni caso, il trattamento combinato con

FMT e ICI è stato considerato sicuro da parte di una commissione esterna, con eventi avversi considerati in linea con il profilo di tossicità notoriamente associato con ICI (sebbene i pazienti del gruppo FMT potrebbero aver manifestato gli eventi avversi più precocemente rispetto a quanto normalmente osservato nei pazienti trattati solo con ICI).

Cambiamenti del microbioma. La maggioranza dei pazienti che mostravano eventi avversi più gravi avevano ricevuto il microbioma dallo stesso donatore; questo microbioma era ricco di *Prevotella*. Lo stesso microbioma non aveva però indotto particolari eventi avversi né in pazienti di studi precedenti trattati in monoterapia (solo anti-PD1, senza anti-CTLA4), né nei pazienti con tumore polmonare di questo studio. In ogni caso, i dati sottolineano l'importanza della selezione del donatore.

Analizzando i cambiamenti del microbioma in relazione all'esito clinico, i dati mostravano che mentre prima di FMT la diversità del microbioma – sia di tipo alfa che di tipo beta – era simile nei responder e nei non-responder, dopo FMT la diversità beta (ma non alfa) era diversamente associata con responder e non-responder, sia nel

melanoma che nei pazienti con NSCLC: le modificazioni nella composizione del microbiota correlavano con la risposta alla terapia. Nonostante l'effetto del donatore sulla tossicità, non si osservava alcun effetto del donatore in termini di efficacia clinica.

Nel complesso, in seguito a FMT il microbioma del ricevente diventava simile a quello del donatore, con un numero simile di specie che, dopo FMT, colonizzavano l'intestino dei responder e dei non-responder. A livello delle singole specie c'era però un arricchimento di specie batteriche benefiche nei responder (come *Faecalibacterium prausnitzii*, *Gemmiger formicilis*, *Akkermansia muciniphila*, nei pazienti con tumore al polmone, *Bacteroides eggerthii*, *Bacteroides faecis*, *Alistipes senegalensis* nei pazienti con melanoma, e specie precedentemente associate a risposta ad ICI) e arricchimento di specie batteriche deleterie nei non-responder (come *Streptococcus vestibularis* e *Fusobacterium nucleatum*).

E' importante sottolineare che, rispetto ai non-responder, i responder mostravano una perdita più evidente (dopo FMT vs prima di FMT) delle stesse specie sia nei pazienti con tumore al polmone che in quelli con melanoma. Le specie che si perdevano dopo FMT erano note essere nocive.

Le scoperte ottenute con le analisi metagenomiche sono state validate tramite altri approcci (qPCR). Inoltre, al fine di rafforzare ulteriormente la correlazione osservata tra la perdita di alcune specie batteriche e l'esito clinico, sono stati effettuati esperimenti di coltura: contando il numero di specie perse (cioè, impossibili da far crescere in coltura) nei campioni fecali dopo FMT (rispetto a prima di FMT), dai responder e dai non-responder, i ricercatori hanno confermato una più evidente perdita di specie nocive nei responder che nei non-responder. Inoltre, ri-analizzando i dati metagenomici pubblicati di precedenti esperimenti di FMT, i ricercatori hanno confermato ulteriormente queste scoperte, suggerendo che l'eliminazione di alcune specie preesistenti durante il rimodellamento del microbioma indotto da FMT potrebbe essere più critico per la risposta terapeutica

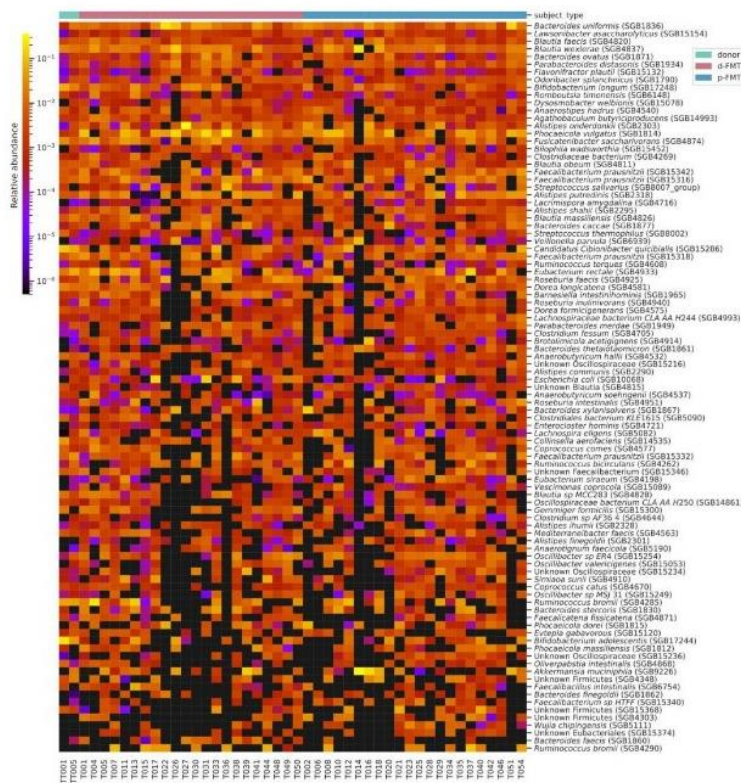


Image from Porcari, Ciccarese, Heidrich et al., Nature Medicine 2026
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rispetto alla colonizzazione di nuove specie derivanti dal donatore. Questi dati sono stati ulteriormente confermati utilizzando modelli preclinici *in vivo*: quando agli animali riceventi, che avevano già ricevuto le specie favorevoli, venivano somministrate le specie nocive isolate dai responder (che nei pazienti si perdevano dopo FMT, quindi quelle che, quando perse, conferivano risposta a ICI), la somministrazione delle specie nocive danneggiava la risposta a ICI, confermando che la perdita delle specie nocive era richiesta per la risposta alla terapia.

Studi meccanicistici. Per determinare in che modo la perdita delle specie batteriche nocive osservata nei responder dopo FMT influenzasse la risposta alla terapia, gli autori hanno valutato i cambiamenti sistemici indotti, tramite analisi metabolomiche in campioni ematici. Hanno trovato, nei non-responder (che non mostravano la perdita di determinate specie batteriche intestinali), un maggiore aumento dei metaboliti del pathway del triptofano (cioè acido quinolinico e kinerunina),

che sono stati precedentemente associati con resistenza a ICI. Le analisi metabolomiche dei campioni fecali hanno mostrato invece una riduzione di questi metaboliti nei responder; queste riduzioni erano il risultato della perdita di specie distinte nei pazienti con tumore polmonare e nei pazienti con melanoma (a significare che la perdita di specie batteriche diverse, come evidenziato dalle analisi metagenomiche, convergeva sul pathway del triptofano). Inoltre, l'analisi proteomica ha rivelato una maggiore proporzione di marcatori infiammatori circolanti dopo FMT nei responder. Questi pazienti mostravano anche cambiamenti a livello del sistema immunitario, con un aumento di cellule T CD8 citotossiche e riduzione di cellule T regolatorie, suggerendo che la persistenza di specie nocive potrebbe sostenere, a livello sistemico, un ambiente metabolico e immunitario immunosoppressivo in grado di compromettere la risposta a ICI.

Referenze: 1) Fecal microbiota transplantation plus pembrolizumab and axitinib in metastatic renal cell carcinoma: the randomized phase 2 TACITO trial. Serena Porcari#, Chiara Ciccarese#, Vitor Heidrich#, Debora Rondinella, Gianluca Quaranta, Andrea Severino, Daniela Arduini, Sebastiano Buti, Giuseppe Fornarini, Francesca Primi, Luciano Stumbo, Diana Giannarelli, Giulia Claire Giudice, Alessandra Damassi, Julio Rodrigo Giron Berríos, Michal Punčochář, Thomas B Barbazuk, Gianmarco Piccinno, Federica Pinto, Federica Armanini, Francesco Asnicar, Giovanni Schinzari, Lisa Derosa, Guido Kroemer, Maurizio Sanguinetti, Luca Masucci, Antonio Gasbarrini, Giampaolo Tortora, Giovanni Cammarota, Laurence Zitvogel, Nicola Segata#, Roberto Iacovelli#, Gianluca Ianaro#. *Nat Med* 2026. doi: 10.1038/s41591-025-04189-2. **2)** Fecal microbiota transplantation plus immunotherapy in non-small cell lung cancer and melanoma: the phase 2 FMT-LUMINate trial. Sreya Duttgupta#, Meriem Messaoudene#, Sebastian Hunter, Antoine Desilets, Rahima Jamal, Catalin Mihalciou, Wiam Belkaid, Nicolas Marcoux, Marine Fidelle, Deborah Suissa, Mayra Ponce, Mallia Geiger, Julie Malo, Gianmarco Piccinno, Michal Punčochář, Alysé Filin, Vitor Heidrich, Diana Rusu, Babacar Mbaye, Sylvere Durand, Imen Ben Aissa, Vadim Puller, Raynald de Lahondès, Normand Blais, Mustapha Tehfe, Scott Owen, Karl Bélanger, Seema Nair Parvathy, Benjamin Shieh, Jacques Raphael, John Lenahan, Daniel Breadner, Jeffrey Rothenstein, Nicholas Rozza, Jade Maillou, Somayeh Nili, Diogjena Katerina Prifti, Federica Pinto, Federica Armanini, Seunghee Kim-Schulze, Thomas U Marron, Guido Kroemer, Lisa Derosa, Laurence Zitvogel, Michael Silverman, Nicola Segata, Saman Maleki Vareki, Bertrand Routy, Arielle Elkrief. *Nat Med* 2026. doi: 10.1038/s41591-025-04186-5.

What's new from IEO researchers?

Una nuova combinazione di farmaci contro i linfomi aggressivi? Risultati di studi preclinici.

Il linfoma diffuso a cellule B è un gruppo di neoplasie che include il linfoma *double-hit* (DHL, caratterizzato da alterazioni cromosomiche che comprendono i geni Myc e BCL2) e il linfoma *double-expressor* (DEL, caratterizzato da mutazioni nei geni Myc e BCL2, senza riarrangiamenti cromosomici). Entrambi i tumori sono molto aggressivi e le terapie ad oggi disponibili non sono molto efficaci.

La sovraespressione di Myc rende le cellule tumorali vulnerabili a farmaci che inibiscono alcuni processi mitocondriali: la tigeciclina (che inibisce i ribosomi mitocondriali) e IACS-010759 (IACS, che inibisce la catena di trasporto degli elettroni). Inoltre, la somministrazione di IACS o di tigeciclina con venetoclax (uno specifico inibitore di BCL2) ha mostrato effetti antitumorali in modelli preclinici *in vivo*.

Studi precedenti nel gruppo Amati hanno rivelato i meccanismi alla base degli effetti antitumorali di IACS nelle cellule che sovraesprimevano Myc, che includono l'ossidazione cellulare (la generazione di specie reattive dell'ossigeno, ROS), suggerendo che esacerbare lo stress ossidativo in queste cellule che, per via

della sovraespressione di Myc, hanno già un livello basale di ossidazione più elevato rispetto alle cellule sane, potrebbe contribuire alla morte di queste cellule, aumentando quindi gli effetti antitumorali di questi farmaci. I ricercatori IEO hanno infatti precedentemente mostrato che l'efficacia antitumorale di IACS può essere ulteriormente potenziata dalla combinazione con altri composti pro-ossidanti, come dosi elevate di vitamina C. Studi preclinici e clinici hanno però rivelato un livello di tossicità non trascurabile associato con la somministrazione di IACS.

Sfruttando la comprensione dei processi coinvolti, ottenuta attraverso gli studi meccanicistici, è possibile aumentare ulteriormente l'efficacia antitumorale di tigeciclina e IACS?

In uno studio recente, i ricercatori IEO coordinati da Bruno Amati –PI al dipartimento di oncologia sperimentale di IEO– e Giulio Donati –ricercatore nel gruppo Amati– hanno sfruttato la comprensione meccanicistica dell'efficacia antitumorale di questi farmaci e si sono focalizzati sulla combinazione di *tre* farmaci: la somministrazione di venetoclax-



Amati Lab

“sfruttando la comprensione dei processi coinvolti, ottenuta attraverso gli studi meccanicistici, è possibile aumentare ulteriormente l'efficacia antitumorale di tigeciclina e IACS?”

tigeciclina-vitamina C riduceva in maniera significativa la crescita del tumore (più che la somministrazione del farmaco da solo e di due farmaci insieme), aumentando la sopravvivenza, senza la tossicità osservata in seguito al trattamento con IACS. La maggiore efficacia della tripla combinazione suggerisce inoltre che la somministrazione di questi farmaci potrebbe permettere di ridurre il dosaggio, conservando la stessa efficacia, così da limitare eventuali effetti collaterali e aprendo la strada a nuove sperimentazioni cliniche.

----- **TELL ME MORE!** -----

Gli autori hanno mostrato, in modelli preclinici *in vitro*, che la combinazione di farmaci che inducono ossidazione cellulare, come IACS o tigeciclina, insieme a ventoclax e vitamina C ne aumenta gli effetti citotossici.

In vivo, la tripla combinazione rallentava in maniera significativa la crescita del tumore. Inoltre, è importante sottolineare che l'efficacia antitumorale era visibile anche quando i farmaci erano somministrati a dosaggi più bassi di quelli comunemente utilizzati nella doppia combinazione.

Data la nota neurotossicità associata con la somministrazione di IACS, i ricercatori si sono

focalizzati sulla tigeciclina e studi ulteriori, in modelli preclinici *in vivo*, hanno dimostrato gli effetti antitumorali della combinazione venetoclax-tigeciclina-vitamina C –così come la doppia combinazione tigeciclina-ventoclax–, che riducevano il tumore e aumentavano la sopravvivenza.

Infine, è interessante notare che mentre IACS da solo induceva neurotossicità, questo non accadeva se somministrato insieme a venetoclax o vitamina C, suggerendo un potenziale effetto protettivo fornito dagli altri due farmaci (che tuttavia richiede studi ulteriori).

Referenza: Combinatorial targeting of MYC/BCL2-associated vulnerabilities in high-grade B-cell lymphoma. *Giulio Donati, Paola Nicoli, Federica Miele, Paola Podini, Giorgia Dina, Angelo Quattrini, Bruno Amati*. Br J Haematol 2025. doi: 10.1111/bjh.70249.

What's new from IEO researchers?

ChatGPT in ambito sanitario – il punto di vista della gente.

Nell'ultimo decennio, l'intelligenza artificiale (AI) è entrata nella nostra vita quotidiana. Anche nel settore biomedico, gli strumenti basati su AI sono impiegati sempre più spesso, per diversi scopi. ChatGPT è un chatbot gratuito e dall'interfaccia semplice, sviluppato da openAI e ampiamente utilizzato dalla popolazione.

In uno studio recente di Durosini et al., i ricercatori IEO guidati da Gabriella Pravettoni –direttrice della Divisione di ricerca applicata per la scienze psicologiche e cognitive all'Istituto Europeo di Oncologia– hanno analizzato la percezione delle persone nei confronti dell'uso di questo strumento da parte di persone che, ricevuta una diagnosi di tumore, si sono rivolti a ChatGPT per avere chiarimenti e informazioni ulteriori. L'obiettivo dello studio era quello di identificare eventuali criticità, così da poterle correggere ed aprire la strada ad un utilizzo sempre più diffuso di questa tecnologia in ambito sanitario.

Pur enfatizzando la necessità del consulto medico, lo studio ha riconosciuto il valore aggiunto del chatbot nel fornire informazioni mediche ulteriori, contribuendo in questo modo a rassicurare le persone, sebbene restino da affrontare aspetti come la privacy e la sicurezza dei dati, l'ottemperanza alle leggi del GDPR, aspetti etici e legali (associati alla responsabilità in caso di errore o esito negativo) per poter aumentare la fiducia degli utilizzatori nei chatbot. Pur evidenziando i limiti dei chatbot e la necessità del consulto medico, lo studio ha sottolineato l'utile ruolo informativo di chatGPT nel processo di cura. Infine, dalle risposte dei partecipanti allo studio è emersa l'importanza dell'interazione umana tra i pazienti e i loro dottori nel complesso, emozionalmente gravoso, percorso dei pazienti oncologici, dalla diagnosi iniziale e per tutto il percorso di trattamento; in questo frangente, il ruolo del medico non può essere sostituito da un chatbot, per quanto rifinito e accurato possa essere.



Gabriella Pravettoni

----- TELL ME MORE! -----

Lo studio ha coinvolto 74 partecipanti sani; circa il 70% di essi avevano un livello di istruzione elevato. I partecipanti sono stati invitati a leggere uno scenario creato *ad hoc* in cui un utilizzatore ha usato ChatGPT per avere informazioni mediche dopo aver ricevuto una diagnosi di tumore. La conversazione con ChatGPT includeva spiegazioni dei termini medici presenti nel referto e le possibili fasi successive nel processo di cura. Dopo aver letto la conversazione con ChatGPT, ai partecipanti è stato chiesto di esprimere le loro sensazioni ed eventuali preoccupazioni collegate all'utilizzo di ChatGPT per scopi medici (nello specifico,

oncologici). Gli autori hanno quindi analizzato le risposte dei partecipanti: in breve, se un partecipante esprimeva preoccupazione sull'attendibilità delle informazioni fornite da ChatGPT, gli autori consideravano (e raggruppavano) le sue sensazioni come associate a "mancanza di fiducia"; se un partecipante esprimeva ansia al pensiero che le persone potessero utilizzare ChatGPT in maniera errata o eccessiva, consideravano le sue sensazioni come "paura"; se un partecipante esprimeva emozioni positive come una maggiore tranquillità derivante dal ricevere informazioni aggiuntive e chiarimenti,

consideravano le loro emozioni come “calma” e così via.

I partecipanti hanno riportato sia emozioni positive che negative: paura, mancanza di fiducia e incertezza, ma anche fiducia e soddisfazione associata all'utilità di questi strumenti.

I dubbi sull'utilizzo di chatGPT a questo scopo erano associati soprattutto all'impossibilità di comprendere i passaggi che portavano il chatbot a dare determinate risposte (ovvero il cosiddetto problema della “black box”, ancora non risolto e che contribuisce ad una mancanza di fiducia), così come le questioni riguardanti la privacy dei dati forniti al chatbot di AI. Inoltre, nonostante la preoccupazione riguardo all'affidabilità delle informazioni ottenute (evidenziando la necessità di una migliore trasparenza per quanto riguarda le fonti), la possibilità di accedere, attraverso il chatbot, ad un'enorme quantità di informazioni generava sensazioni positive. Alcuni partecipanti hanno anche proposto che l'utilizzo di questi strumenti potrebbe aiutare a diminuire il carico di lavoro dei professionisti in ambito sanitario, ad esempio riducendo il tempo necessario a fornire

informazioni accurate e comprensibili al paziente che, grazie al chatbot, potrebbe già avere una comprensione di base di alcuni concetti medici.

Sono stati espressi anche dei dubbi riguardo alla possibilità che le persone possano utilizzare ChatGPT nel modo sbagliato, come ad esempio per formulare della auto-diagnosi, senza il consulto medico (sebbene il chatbot incoraggi chiaramente l'utilizzatore nel richiedere il consulto medico) e la possibilità che queste conversazioni con il chatbot possano generare ansia (associata ad un uso eccessivo e a pensieri ipocondriaci). D'altro canto, altri partecipanti hanno espresso pensieri positivi riguardo all'utilità di integrare le informazioni fornite dai medici.

Infine, nonostante l'importanza di enfatizzare ulteriormente il fatto che il chatbot non può rimpiazzare l'expertise dei clinici e che il consulto medico rimane fondamentale, i partecipanti hanno sottolineato numerosi aspetti positivi, considerando i chatbot degli utili strumenti di supporto da integrare –piuttosto che sostituire– nel tradizionale consulto medico.

OpenAI sta introducendo ChatGPT salute, per rispondere al crescente utilizzo di ChatGPT da parte della popolazione sulle questioni relative alla salute e per affrontare problemi legati alla sicurezza e alla privacy dei dati, con uno strumento progettato *ad hoc*, sviluppato insieme ai medici ([ChatGPT salute](#)).

Alex, puoi spiegare brevemente 1) cos'è chatGPT salute/ChatGPT Health, 2) per chi è pensato (cioè quali sono gli utenti a cui è destinato), 3) quali sono le differenze/migliorie rispetto alla versione corrente di ChatGPT?

Certo — ecco una spiegazione sintetica e chiara di ChatGPT Salute /ChatGPT Health (la versione dedicata alla salute di ChatGPT):

1) ChatGPT Salute (o *ChatGPT Health*) è una esperienza dedicata all'interno di ChatGPT pensata per domande su salute e benessere, con una separazione specifica per i dati sanitari. Permette di collegare in modo sicuro informazioni sanitarie personali come cartelle cliniche elettroniche e dati da app di benessere (es. Apple Health, MyFitnessPal, ecc.) in modo che l'AI possa usare quel contesto per dare risposte più rilevanti e personalizzate. I dati e le conversazioni in questa area sono isolati dai normali chat e non vengono usati per addestrare i modelli di base.

In parole semplici: non è solo “fare domande di salute al chatbot”, ma avere un ambiente con privacy rinforzata e connessioni ai tuoi dati salutistici.

2) ChatGPT Salute è destinato a utenti generali interessati a gestire e comprendere meglio la propria salute e benessere, non a medici o personale sanitario professionale. È particolarmente utile a chi vuole: *i.* capire meglio i propri esami clinici o risultati di laboratorio; *ii.* prepararsi a visite mediche con domande utili; *iii.* interpretare trend su attività, dieta, sonno, ecc., dai dati di app collegate; *iv.* avere consigli pratici su stile di vita basati sui propri dati; *v.* esplorare opzioni assicurative o scenari di cure in modo informato.

Importante: non è pensato per fare diagnosi o prescrivere trattamenti, né per sostituire un medico. Rimane uno strumento di supporto informativo e di preparazione, da usare insieme ai professionisti sanitari.

3)

| Aspetto | ChatGPT (standard) | ChatGPT Salute/Health |
|------------------------------------|--|---|
| Uso dei dati di salute | Non può collegare cartelle cliniche o app di benessere | Può connettere dati sanitari personali per risposte più contestuali. |
| Privacy e sicurezza | Conversazioni normali, dati usati secondo le policy generali | Isolamento totale dei dati sanitari, crittografia dedicata e non usati per addestrare modelli. |
| Contestualizzazione delle risposte | Risposte generiche su salute basate su conoscenze generali | Risposte basate sul contesto personale (es. risultati recenti, trend da app). |
| Obiettivo | Rispondere a domande generiche (anche sanitarie) | Supportare gestione quotidiana della salute, preparazione a visite, comprensione di dati personali. |
| Medici coinvolti | Nella creazione generale del modello | Sviluppato con feedback di centinaia di medici (per maggiore accuratezza nelle risposte). |

In breve: ChatGPT Salute è più sicuro, più personalizzato e meglio strutturato per il contesto sanitario rispetto a una semplice chat di domande.

L'AI ha mosso i primi passi nell'ambito biomedico anni fa, con gli strumenti di machine learning applicati all'analisi dei dati, ma con la crescente diffusione degli strumenti di AI generativa, dei modelli di linguaggio e la nascita dei chatbot, che ne hanno semplificato l'utilizzo da parte degli utenti, è entrata a tutti gli effetti nella nostra vita, rappresentando quella rivoluzione tecnologica che ha il potenziale di cambiare in maniera drastica il nostro futuro, a patto di saperla gestire nel modo appropriato, di capire come utilizzarla nel modo più giusto perché possa davvero dare una spinta al nostro lavoro e fornirci quella marcia in più per crescere come essere umani intelligenti. Così come negli anni 90 del secolo scorso internet ha cambiato drasticamente le nostre vite (e il cui valore non può essere sminuito dagli utilizzi sbagliati che in alcuni casi ne sono stati fatti), offrendo accesso ad una quantità di informazioni che ha aumentato il potenziale di chi l'ha saputo utilizzare in maniera intelligente, così, se usata nel modo giusto, con spirito critico e consapevolezza dei limiti e dei rischi associati, l'AI può aumentare il potenziale umano piuttosto che ridurlo.

L'AI è entrata in ambito sanitario e di ricerca soprattutto come elemento di supporto alla diagnostica, nella redazione di referti medici, nell'imaging medico, fornendo supporto analitico, ma il suo impiego è destinato ad aumentare. In un contesto delicato come quello sanitario e di ricerca, la crescente integrazione dell'AI richiede un utilizzo consapevole che permetta di governare piuttosto che subire la rivoluzione tecnologica a cui stiamo assistendo e di cui tutti noi facciamo parte. L'uso consapevole richiede la conoscenza di aspetti fondamentali strettamente connessi all'utilizzo dell'AI, che consistono nel **prestare attenzione agli aspetti etici e normativi**, così come la necessità di **formazione** in questo ambito e l'importanza di continuare a **coltivare le competenze tecnico/scientifiche necessarie per essere in grado di valutare l'output fornito dalla macchina**. Mantenendo l'attenzione su questi fattori fondamentali è possibile utilizzare l'AI e beneficiare al massimo di ciò che può dare, per potenziare – e non annientare – l'intelligenza naturale.

Sebbene la rapidità di crescita e di integrazione dell'AI porti con sé dei rischi, legati al fatto che non sempre le leggi che ne regolamentano l'utilizzo (soprattutto in contesti delicati come quello sanitario), o la formazione vadano allo stesso passo, la normativa europea (European AI Act) e Italiana si stanno adeguando, regolamentando numerosi aspetti chiave, tra cui la privacy dei dati (ottemperanza con i requisiti del GDPR) e la sicurezza –intesa come prevenzione e protezione da attacchi informatici–, la valutazione dei numerosi strumenti di AI disponibili –per assicurarne gli standard di qualità necessari per l'impiego in ambito sanitario e l'aderenza a determinati requisiti quando, uscendo dall'ambito della ricerca, vengono integrati nel contesto sanitario–, la trasparenza riguardo al loro utilizzo, l'importanza di informare il paziente nel caso in cui strumenti di AI vengano impiegati nel percorso diagnostico.

In ogni caso, è fondamentale ricordare che nonostante l'integrazione di questi strumenti, il potere decisionale rimane sempre nelle mani del medico e del ricercatore, che esercita il suo diritto/dovere di supervisione, che deve conservare lo spirito critico sull'output, che deve continuare a coltivare le proprie competenze per poter conservare questo spirito critico, e la responsabilità giuridica.

Referenza: Attitudes toward the use of ChatGPT to seek oncological information: a qualitative study. *Ilaria Durosini, Marianna Agnese Masiero, Milija Strika, Davide Mazzoni, Gabriella Pravettoni*. *Front Psychol* 2025. doi: 10.3389/fpsyg.2025.1644323.

What's new from IEO researchers?

Le informazioni in codice nelle modificazioni post-traduzionali degli istoni – Un nuovo strumento computazionale per decifrarle.

Le modificazioni post-traduzionali degli istoni (hPTM) sono delle modificazioni chimiche delle proteine istoniche associate al DNA che giocano un ruolo chiave nella biologia cellulare, modulando la struttura della cromatina, l'espressione genica e i processi cellulari. Le PTM sono solitamente studiate tramite spettrometria di massa –che permette di rilevarle e quantificarle–, attraverso l'utilizzo di protocolli ottimizzati abbinati a specifiche analisi computazionali.

“Con l'espansione continua del linguaggio del codice istonico –commenta Tiziana Bonaldi, Group Leader presso il Dipartimento di Oncologia Sperimentale di IEO– il nostro gruppo si è chiesto se la natura intrinsecamente obiettiva (priva di *bias*) dell'analisi per spettrometria di massa (MS) potesse essere sfruttata in modo più efficiente per rilevare e profilare in maniera sistematica molte più 'lettere' di questo codice, spesso osservate in modo fortuito, ma raramente esplorate. Questo obiettivo è stato perseguito attraverso lo sviluppo di un nuovo framework bioinformatico in grado di rendere la loro identificazione più completa, automatizzata e affidabile”.

In uno studio recente, condotto da Alessandro Vai, dottorando computazionale nel gruppo Bonaldi, in collaborazione con Alexey Nesvizhskii (University of Michigan) e Andrea Graziadei (Human Technopole), i ricercatori riportano lo sviluppo di un nuovo strumento

computazionale –HiP-Frag– per l'identificazione di nuove hPTM, meno comuni e meno abbondanti, nei dati di spettrometria di massa (MS). L'applicazione di questo strumento ai dati di MS di linee cellulari e campioni clinici di tumore al seno ha permesso di identificare nuove hPTM, confermandone l'utilità.

Avere una conoscenza approfondita delle hPTM permette di comprendere la regolazione dinamica dell'espressione genica e dei processi cellulari, che è cruciale per definire le alterazioni associate alla malattia. Nel cancro, le hPTM sono spesso alterate ed infatti ampiamente studiate come biomarcatori prognostici, diagnostici e predittivi. Acetilazione e metilazione della lisina sono le hPTM più diffuse e le prime ad essere state descritte. Più recentemente, ne sono state descritte altre, meno comuni (come le acilazioni della lisina, monoaminilazioni della glutammina –ovvero serotonilazione e dopaminilazione– e glicazione). Pur avendo un ruolo fondamentale nella regolazione genica, queste nuove hPTM sono ancora poco studiate, soprattutto per via della mancanza di strumenti analitici adeguati. HiP-Frag risponde a questa problematica permettendo l'identificazione di hPTM note e nuove nell'intero proteoma dei campioni analizzati.

Le nuove hPTM si trovano spesso sugli stessi siti già noti per essere modificati da altre hPTM come acetilazioni e metilazioni, indicando che la loro presenza possa contribuire a regolare in maniera precisa l'espressione genica, dotando le cellule della capacità di rispondere a stimoli diversi con maggiore precisione e accuratezza, suggerendo un loro potenziale ruolo chiave –quando alterate– in un contesto patologico. Sebbene siano

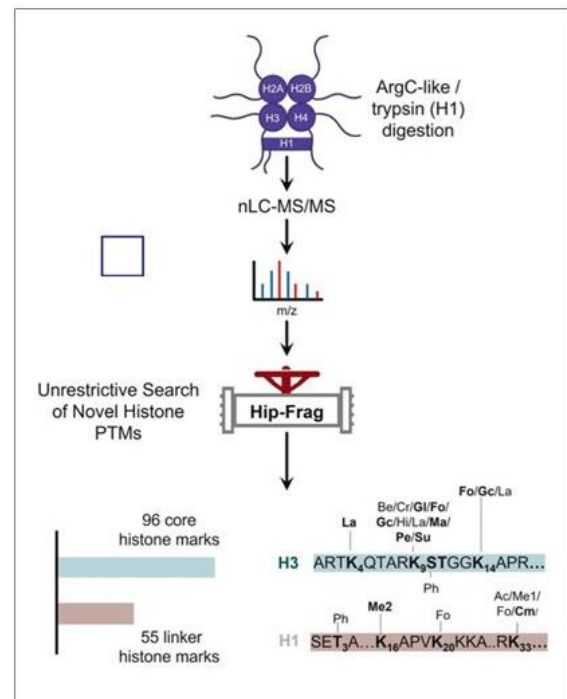


Figure from Vai et al. 2025 (an open access [article](#) under the [CC BY](#) license.)

necessarie ulteriori miglorie e ottimizzazioni delle tecniche di preparazione dei campioni per rendere più solidi i risultati ottenuti, dato che modifiche clinicamente rilevanti potrebbero essere piccole e quindi difficili da identificare, HiP-Frag rappresenta un nuovo utile strumento di ricerca, per scoprire l'epigenoma istonico ancora sconosciuto.

TELL ME MORE!

Come funziona HiP-Frag? In breve, HiP-Frag (*Histone PTMs Analysis with FragPipe*) integra (in quattro fasi successive) tre diversi approcci analitici dei dati di MS: *i.* la cosiddetta **ricerca chiusa**, *ii.* la **ricerca aperta** e *iii.* la ricerca **DMO (detailed mass offset search)**. Questi approcci sono implementati in FragPipe, uno strumento computazionale all'avanguardia sviluppato dal gruppo del prof. A. Nesvizhskii.

“In una ricerca chiusa, –spiega Alessandro Vai, primo autore del lavoro– le sequenze peptidiche vengono identificate confrontando uno spettro di massa sperimentale con un elenco predefinito di spettri teorici generati da un database proteico. Ogni possibile corrispondenza viene valutata in base alla somiglianza tra lo spettro sperimentale e quello teorico, e il peptide con il punteggio più alto viene assegnato allo spettro. Tuttavia, l'identificazione dei peptidi modificati utilizzando questo approccio richiede la generazione di spettri teorici per ogni possibile combinazione di peptidi e modifiche. Per le proteine ipermodificate come gli istoni, questo numero diventa estremamente elevato, rendendo l'analisi computazionalmente proibitiva quando si considerano modifiche oltre l'acetilazione e la metilazione. I metodi di ricerca aperta affrontano questa limitazione consentendo il rilevamento delle modifiche peptidiche senza generare esplicitamente spettri teorici per ogni peptide, riducendo sostanzialmente le esigenze computazionali. Questo vantaggio, tuttavia, comporta una minore sensibilità. Il DMO rappresenta un compromesso tra ricerche chiuse e aperte, consentendo l'analisi di grandi insiemi di potenziali modifiche pur mantenendo un'elevata sensibilità. HiP-Frag combina queste tre strategie per massimizzare la scoperta di hPTM. Le ricerche

chiuse e aperte vengono prima utilizzate per identificare le proteine contaminanti non istoniche e gli artefatti chimici introdotti durante la preparazione dei campioni, riducendo le fonti di interferenza nei dati. Alla luce di questi fattori, il DMO rappresenta il passaggio chiave per individuare con elevata sensibilità le reali modifiche biologiche”.

I risultati ottenuti con HiP-Frag sono anche indipendenti dal tipo di protocollo usato per la preparazione dei campioni, restituendo lo stesso risultato con campioni preparati secondo protocolli diversi.

HiP-Frag per l'identificazione di nuovi marcatori tumorali istonici. Gli autori hanno valutato il potere di questo strumento nell'identificare hPTM applicando HiP-Frag a dati di MS acquisiti da campioni di linee cellulari di cancro al seno e tessuti clinici. I profili di MS acquisiti sono stati confrontati con dataset di hPTM note e comuni. Tra le hPTM identificate, il 62% non è mai stato descritto prima. Ad esempio, hanno identificato la glicerolazione della lisina, una hPTM piuttosto frequente, che gioca un ruolo probabilmente nella dinamica della cromatina e nella regolazione genica. Quando HiP-Frag era applicata ad altri dataset precedentemente pubblicati di hPTM, la frequenza delle varie PTM identificate era paragonabile a quella rilevata utilizzando HiP-Frag, confermandone la validità.

Infine, quando si sono focalizzati in maniera specifica sull'analisi dell'istone H1, che ha un ruolo chiave nel definire la struttura della cromatina (pur non essendo un istone *core*), in un dataset di MS di campioni clinici di tumore al seno (luminal-A e TNBC), HiP-Frag ha identificato diverse hPTMs, tra cui nove che non erano mai state descritte prima.

Referenza: Breaking Boundaries in Histone Modification MS-Based Detection: A Tailored Search Strategy for Unrestricted Identification of Novel Epigenetic Marks. *Alessandro Vai, Roberta Noberini, Andrea Graziadei, Daniel A Polasky, Fengchao Yu, Alexey I Nesvizhskii, Tiziana Bonaldi.* Mol Cell Proteomics 2025. doi: 10.1016/j.mcpro.2025.101080.

What's new from IEO researchers?

Tumore al seno nelle giovani: più cura ormonale dimezza metastasi e recidive.



Un nuovo risultato della ricerca IEO è stato appena pubblicato sul *Journal of Clinical Oncology*. Lo studio, coordinato dal nostro Istituto, dimostra che nelle giovani pazienti in premenopausa, con carcinoma mammario ormonopositivo la prosecuzione della terapia endocrina adiuvante oltre i cinque anni standard dimezza il rischio di metastasi a distanza e riduce di circa il 40% il rischio di recidiva, senza aumentare gli effetti collaterali gravi.

Il lavoro nasce dalla collaborazione tra IEO e l'Harvard University di Boston ed è stato guidato dal Dott. Carmine Valenza, medico della Divisione Sviluppo di Nuovi Farmaci per Terapie Innovative e attualmente ricercatore ad Harvard e al Dana-

Farber Cancer Institute di Boston. Per IEO, oltre alla Divisione Sviluppo di Nuovi Farmaci, diretta dal Vicedirettore Scientifico IEO Giuseppe Curigliano, è stata coinvolta la Divisione di Senologia Medica IEO, diretta dal Dott. Marco Colleoni, con il gruppo di ricerca coordinato dalla Dott.ssa Elisabetta Munzone, Direttrice dell'Unità di Ricerca in Senologia Medica.

«Questo risultato rappresenta una vera pietra miliare nel carcinoma mammario nelle pazienti giovani, ancora poco rappresentate negli studi clinici», afferma il Prof. Curigliano, confermando il ruolo di leadership di IEO nella ricerca oncologica internazionale (Leggi il [comunicato stampa](#)).

TELL ME MORE!

La somministrazione di terapia endocrina in un contesto adiuvante (Tamoxifen per un periodo di 5 anni dopo la resezione chirurgica) si è dimostrata efficace nell'aumentare la sopravvivenza delle pazienti giovani con tumore al seno positivo al recettore degli ormoni rispetto alle pazienti non trattate. L'aggiunta di soppressori della funzione ovarica (*luteinizing hormone-releasing hormone agonist*, LHRHa) alla terapia a base di tamoxifen ha mostrato un ulteriore beneficio in termini di sopravvivenza. Nelle pazienti giovani esiste però un

rischio non trascurabile di recidiva distante (25% a 15 anni), sottolineando la necessità di definire strategie adeguate per queste pazienti, per ridurre la recidiva ed ottimizzare l'esito della terapia. Questo studio ha valutato i benefici di una terapia endocrina prolungata in pazienti giovani (prima della menopausa) con tumore al seno positivo al recettore degli ormoni, senza metastasi distanti, ma in presenza di cellule tumorali a livello dei linfonodi regionali (stadio pT-qualsiasi, pN1-3, cM0), che non erano ancora entrate in menopausa

al termine dei 5 anni di terapia endocrina adiuvante in combinazione con LHRHa.

L'analisi retrospettiva ha valutato l'efficacia di questo approccio terapeutico sulla manifestazione di recidiva con malattia invasiva in 501 pazienti (<40 anni di età) con tumore al seno, che avevano completato la terapia endocrina prolungata (287) rispetto a quelle trattate solo per cinque anni (con terapia endocrina –AI o tamoxifen– più LHRHa).

Efficacia. I risultati hanno mostrato una notevole riduzione del rischio di recidiva con malattia invasiva nel caso in cui la terapia endocrina veniva

estesa oltre il periodo standard (ovvero oltre i 5 anni). I benefici apparivano inoltre più evidenti negli stadi più avanzati della malattia, sebbene siano necessari studi ulteriori per confermare quest'ultima osservazione.

Tossicità. I ricercatori non hanno osservato differenze in termini di eventi avversi (come quelli associati ad effetti deleteri a lungo termine della terapia di soppressione ovarica) tra i due gruppi di pazienti, sebbene studi ulteriori, con un follow-up più lungo, siano fondamentali per poter trarre delle conclusioni definitive in questo senso.

Referenza. Extended Endocrine Therapy Following 5 Years of Adjuvant Luteinizing Hormone-Releasing Hormone Agonist in Premenopausal Patients With Node-Positive, Hormone Receptor-Positive Breast Cancer: A Cohort Study. *Carmine Valenza, Yue Zheng, Monica Milano, Dario Trapani, Elisa Giordano, Lorenzo Guidi, Pier Paolo Maria Berton Giachetti, Laura Boldrini, Grazia Castellano, Jalissa Katrini, Bianca Malagutti, Gabriele Antonarelli, Fabio Conforti, Eleonora Pagan, Vincenzo Bagnardi, Gregory J Kirkner, Claudia Sangalli, Kate E Dibble, Marco Colleoni, Meredith M Regan, Elisabetta Munzone, Giuseppe Curigliano, Ann H Partridge.* J Clin Oncol 2026. doi: 10.1200/JCO-25-01660.

What's new from IEO researchers?

La metformina per contrastare la progressione del glioblastoma – risultati di studi preclinici.

L'eterogeneità tumorale e la notevole abilità di invadere i tessuti circostanti rendono il glioblastoma (GBM) un tumore difficile da trattare. Le cellule staminali di glioblastoma (GSC) sono la sottopopolazione di cellule tumorali dotate di capacità di self-renewal, che di fatto alimentano la progressione del tumore e la recidiva, rappresentando quindi un target promettente per eradicare il GBM.

In un articolo recente, gli autori, tra cui Saverio Minucci –Group Leader al dipartimento di oncologia sperimentale di IEO e professore all'Università di Milano–, grazie anche alla collaborazione con il gruppo di Giuliana Pelicci, hanno mostrato che le GSC possono essere colpite con la metformina: interagendo direttamente e bloccando l'attività di una proteina espressa sulla superficie delle GSC –CLIC1–, la metformina ostacola la crescita del tumore. I ricercatori hanno rivelato i meccanismi coinvolti, che includono il pathway PP2A-GSK3beta-MCL1, lo stress ossidativo delle cellule tumorali e necessitano dell'attività della proteina CLIC1: CLIC1 sostiene la produzione di specie reattive dell'ossigeno (ROS) e, di conseguenza, la progressione del ciclo cellulare, determina l'inibizione del pathway PP2A-GSK3beta-MCL1 a valle, sostenendo la proliferazione delle cellule tumorali. Al contrario, la metformina inibisce l'attività di CLIC1, causando la ridotta produzione di ROS, ostacolando la progressione del ciclo cellulare e al contempo attivando la via PP2A-GSK3beta-MCL1, riducendo infine la crescita del tumore.

Le GSC sono in grado di adattare il loro metabolismo –passando dalla glicolisi alla fosforilazione ossidativa– in risposta alle condizioni del microambiente tumorale e sostenere la crescita del GBM. In questo lavoro, gli autori identificano un nuovo target terapeutico –CLIC1– per contrastare la progressione del GBM interferendo proprio con la capacità di adattamento delle GSC: essendo necessaria per il metabolismo della cellula tumorale, per la proliferazione e la morte cellulare, la proteina CLIC1 ha un ruolo strategico per la progressione del GBM. Il legame diretto della metformina a CLIC1 induce una cascata di eventi che coinvolge CLIC1, l'attività mitocondriale (e la generazione di ROS) ed infine la proliferazione del GBM: interferendo con la generazione di ROS e quindi con il metabolismo delle GSC e con la via PP2A-GSK3β-MCL1, la metformina compromette la sopravvivenza della cellula tumorale, ritarda la progressione del ciclo cellulare e riduce la crescita tumorale, sia *in vitro* che *in vivo*.

Sebbene CLIC1 sia sovraespressa sulla membrana cellulare in molti tumori solidi, tra cui il GBM, è poco espressa sulla membrana delle cellule sane, rendendola un eccellente potenziale target terapeutico. La metformina è un farmaco ampiamente utilizzato in ambito clinico, originariamente sviluppato come farmaco antidiabetico. Gli effetti antitumorali sono oggi oggetto di studio, e questo lavoro suggerisce fortemente un eventuale riposizionamento della metformina per il trattamento del glioblastoma.

La metformina contro i tumori.

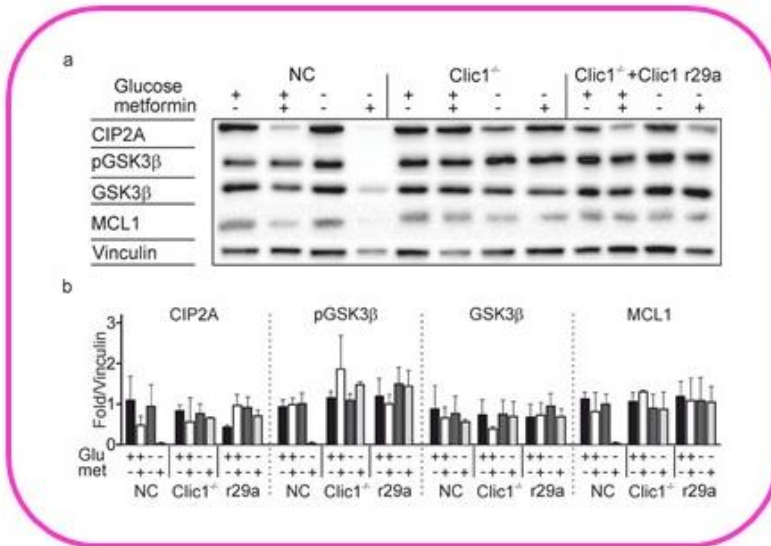
Gli effetti antitumorali della Metformina sono oggi oggetto di studio. I ricercatori IEO hanno precedentemente identificato, in modelli preclinici di malattia, un effetto sinergico del trattamento con Metformina e dell'ipoglicemia causata da digiuno intermittente, nel bloccare la crescita tumorale, definendo anche il meccanismo molecolare responsabile (e identificando la proteina PP2A quale elemento chiave). Più recentemente, gli effetti della metformina sono stati analizzati in un contesto clinico, rivelando i metaboliti influenzati dal trattamento e i pathway molecolari coinvolti, in pazienti in sovrappeso sopravvissute al tumore al seno, che hanno una maggiore probabilità di manifestare recidiva, e in cui questo trattamento potrebbe ridurre il rischio di recidiva.

TELL ME MORE!

La morte delle GSC indotta da metformina richiede la presenza di CLIC1 sulla membrana delle cellule tumorali. Utilizzando colture bidimensionale e tridimensionali di GBM –sia isolate dai pazienti che

tumorali che esprimevano la forma mutata R29A-CLIC1 non rispondevano al trattamento con metformina. L’inibizione di CLIC1 da parte di uno specifico anticorpo monoclonale riduceva la proliferazione cellulare proprio come la metformina o la delezione di CLIC1, dimostrando che l’effetto della metformina era mediato da CLIC1.

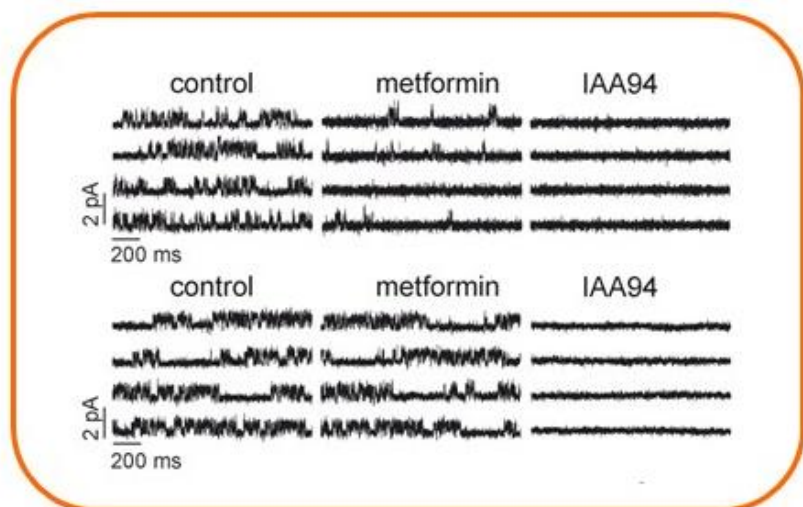
Il trattamento con metformina in condizioni di basso glucosio. Studi precedenti hanno mostrato, in altri tipi di tumore, che in condizioni di basso glucosio la metformina induce la morte cellulare, agendo sul pathway CIP2A-GSK3β-MCL1. In questo lavoro, gli autori hanno mostrato che, in condizioni di basso glucosio, la morte cellulare indotta da metformina richiede la presenza della proteina CLIC1 sulla membrana cellulare. L’inibizione di CLIC1 aveva infatti gli stessi effetti della metformina sull’asse CIP2A-GSK3β-MCL1 e, in assenza di



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linee cellulari–, gli autori hanno valutato gli effetti della metformina sulla proliferazione cellulare del GBM: il trattamento con metformina riduceva in maniera significativa la proliferazione cellulare. Gli effetti della metformina sulla proliferazione cellulare erano mediati dalla presenza della proteina CLIC1 sulla membrana cellulare. CLIC1 è una proteina che, in seguito a segnali di stress, migra dal citoplasma alla membrana plasmatica, dove costituisce un canale ionico che media il flusso di cloro tra l'interno e l'esterno della cellula. L’attività di CLIC1 è stata precedentemente associata all’ossidazione cellulare. Gli autori hanno mostrato che la delezione di CLIC1 (tramite CRISPR-Cas9) riduceva in maniera significativa la proliferazione delle cellule tumorali e la ri-espressione di CLIC1wt, o di una forma mutata (R29A-CLIC1, in cui uno dei due residui carichi nel dominio transmembrana di CLIC1, l’arginina 29, è sostituito con un residuo di alanina), ripristinava la proliferazione cellulare. Studi precedenti hanno dimostrato che la mutazione R29A previene il legame della metformina e infatti le cellule

CLIC1, la metformina non attivava l’asse CIP2A-GSK3β-MCL1 e non induceva la morte cellulare. **Sia la delezione di CLIC1 che il trattamento con metformina rallentano la progressione del ciclo cellulare nel GBM.** Studi precedenti hanno mostrato il coinvolgimento di CLIC1 nella progressione del ciclo cellulare (nello specifico, nella transizione G1/S). Esaminando la progressione del ciclo cellulare nelle cellule di GBM trattate con metformina, gli autori hanno osservato che sia le cellule di GBM trattate con metformina sia le



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cellule prive di CLIC1 mostravano un rallentamento della progressione del ciclo cellulare.

La metformina e l'ossidazione cellulare. La metformina è nota ridurre l'ossidazione cellulare, attraverso l'inibizione della fosforilazione ossidativa. Gli autori hanno osservato, nelle cellule di GBM, una riduzione della fosforilazione ossidativa sia in seguito al trattamento con metformina che nelle cellule prive di CLIC1 (non è stato osservato alcun effetto della metformina nelle cellule prive di CLIC1, in cui la fosforilazione ossidativa era già inibita dalla perdita di CLIC1). Il trattamento con metformina riduceva la generazione di specie reattive dell'ossigeno (ROS) nelle cellule di GBM; la produzione di ROS non era però influenzata dalla metformina nelle cellule prive di CLIC1, indicando che CLIC1 giocava un ruolo critico nella morte cellulare indotta da metformina e mediata dai ROS.

La metformina lega uno specifico residuo aminoacidico di CLIC1. I loro risultati hanno anche confermato il legame di CLIC1 all'arginina 29 nel dominio transmembrana di CLIC1, mostrando che la mutazione R29A preveniva il legame della metformina alla proteina. Esperimenti di elettrofisiologia (sia registrazioni di whole cell che di singolo canale in configurazione outside-out) hanno mostrato una ridotta attività di CLIC1 nelle cellule che esprimevano CLIC1 trattate con metformina. Diversamente dal noto inibitore di CLIC1 IAA94, il legame della metformina a CLIC1 era

irreversibile. La metformina induceva inoltre una riduzione dell'espressione di CLIC1 sulla membrana cellulare, forse dovuta alla riduzione dei livelli di ossidazione osservati in seguito al trattamento con metformina. Analisi approfondite del legame della metformina a CLIC1 hanno rivelato un ruolo chiave del residuo E81 nel sito di legame della metformina, mentre R29, che interagiva debolmente con la metformina, probabilmente contribuiva alla stabilizzazione strutturale del complesso proteico formato dalle varie unità di CLIC1.

La metformina riduce la crescita del GBM in due diversi modelli preclinici in vivo. Per confermare gli effetti osservati *in vitro* in un contesto *in vivo*, gli autori hanno utilizzato un modello di zebrafish. Il trattamento con metformina riduceva la proliferazione delle cellule tumorali iniettate in embrioni di zebrafish trattati con metformina, mentre non aveva alcun effetto né sulle cellule prive di CLIC1 né sulle cellule che esprimevano la forma mutata (R29A-CLIC1). I risultati raccolti nei modelli di zebrafish sono stati ulteriormente confermati in modelli murini trapiantati con cellule GBM: in questi animali la somministrazione di metformina (nell'acqua) induceva una concentrazione misurabile di metformina nel cervello e riduceva la capacità invasiva del tumore, mentre non aveva alcun effetto nel caso in cui le cellule tumorali trapiantate erano prive di CLIC1.

Referenza: Chronic administration of metformin exerts cytostatic and cytotoxic effects via the PP2A-GSK3 β -MCL-1 pathway by inhibiting the tmCLIC1 membrane protein in glioblastoma-initiating cells. Francesca Cianci, Ivan Verduci, Riccardo Cazzoli, Gaetano Cannavale, Guido Rey, Marina Veronesi, Beatrice Balboni, Matteo Ranucci, Luca Maria Giovanni Palloni, Federico Ballabio, Noemi Barsotti, Giorgia Ailuno, Alice Balboni, Sara Baldassari, Gabriele Caviglioli, Carlotta Tacconi, Carlo Camilloni, Stefania Giroto, Federica Barbieri, Alessandro Fantin, Andrea Cavalli, Massimo Pasqualetti, Tullio Florio, Saverio Minucci & Michele Mazzanti. Journal of Experimental & Clinical Cancer Research 2025. doi: 10.1186/s13046-025-03577-3.

What's new from IEO researchers?

Studio Clinico NO-CUT.

Una svolta importante nella cura del tumore del retto arriva con la pubblicazione su *The Lancet Oncology* dei risultati dello studio clinico NO-CUT, che dimostrano come sia possibile ottenere una remissione completa del tumore senza ricorrere alla chirurgia in un paziente su quattro, grazie ad un innovativo protocollo neoadiuvante che comprende la



chemioterapia seguita dalla chemio-radioterapia. Lo studio inoltre ha valutato il ruolo della biopsia liquida (ricerca del DNA tumorale circolante nel sangue) dimostrandone il valore prognostico.

Tra i centri coinvolti un ruolo chiave è stato svolto dallo IEO, con la guida di Maria Giulia Zampino, Medico con Incarico di Alta Specializzazione della Divisione di Oncologia Medica Gastrointestinale e Tumori Neuroendocrini diretta da Nicola Fazio.

Lo IEO ha partecipato allo studio attraverso il lavoro integrato del proprio team multidisciplinare, che ha coinvolto oncologi, radioterapisti, chirurghi, radiologi, endoscopisti, patologi, biologi e professionisti dedicati alla ricerca traslazionale.

Un risultato che apre nuove possibilità terapeutiche e conferma l'importanza della collaborazione interdisciplinare tra centri clinici e gruppi di ricerca altamente specializzati.

----- TELL ME MORE! -----

Sulla base di studi retrospettivi precedenti, a sostegno di una gestione non chirurgica della malattia, gli autori hanno valutato l'efficacia, a livello delle metastasi distanti, di un approccio non chirurgico –ovvero un approccio “no-cut”, nessuna chirurgia– al tumore rettale in pazienti selezionati che mostravano una risposta clinica completa alla terapia neoadiuvante (chemioterapia e chemioradioterapia). Questo studio prospettico, multicentrico, di fase II ha incluso 179 pazienti con tumore rettale (*mismatch repair proficient/microsatellite stable*, pMMR/MSS) in stadio II-III. Tutti i pazienti hanno ricevuto terapia neoadiuvante; al termine del trattamento, i 47 pazienti che hanno mostrato una risposta clinica completa sono stati sottoposti a sorveglianza, mentre gli altri pazienti, in cui la risposta al trattamento neoadiuvante era solo parziale, sono stati trattati chirurgicamente (i pazienti sotto

sorveglianza che successivamente sono andati incontro a recidiva locale, sono stati sottoposti ad intervento chirurgico).

Efficacia. L'efficacia dell'approccio “no-cut” è stata valutata in termini di recidiva (distante e locale): tra i pazienti nel gruppo “no-cut” (sottoposti a sorveglianza), la sopravvivenza in assenza di recidiva distante era del 95% (ad un followup mediano di 35 mesi), a supporto dell'eccellente controllo della malattia con questo approccio. La recidiva locale (a due anni) si manifestava nel 15% dei pazienti del gruppo “no-cut” e nell'11% dei pazienti sottoposti a chirurgia.

Biopsia liquida. Nell'ambito di un'analisi esplorativa, è stata inoltre valutata la presenza di DNA tumorale circolante (ctDNA) prima (per 114 pazienti) e dopo (per 111 pazienti) la terapia neoadiuvante, al fine di ottenere informazioni sul valore del ctDNA nel prevedere la probabilità di

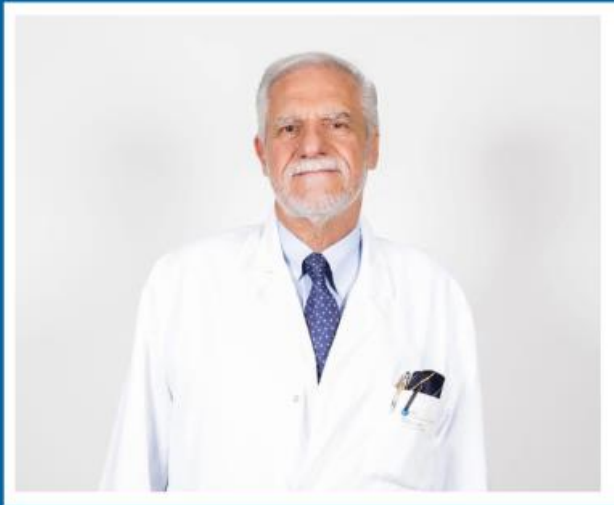
risposta clinica completa alla terapia neoadiuvante, e la correlazione con il manifestarsi della recidiva. Questa è stata la prima analisi di questo tipo in pazienti con tumore rettale. I risultati hanno mostrato una riduzione del ctDNA in seguito alla terapia neoadiuvante: prima del trattamento neoadiuvante, il tasso di rilevamento del ctDNA era del 95% (95% nei pazienti in stadio III, 88% nei pazienti in stadio II, 97% nei pazienti che manifestavano recidiva), che si riduceva a 24% dopo la terapia, raggiungendo l'8% in quelli che mostravano risposta clinica completa (valore

predittivo del ctDNA). La presenza di ctDNA nel sangue al termine della terapia neoadiuvante appariva anche avere un valore prognostico: tra i pazienti del gruppo no-cut, la presenza di ctDNA nel sangue dopo la terapia neoadiuvante correlava con l'aumento della recidiva distante (ma non locale); inoltre, la percentuale di pazienti che, dopo il periodo di sorveglianza, non necessitavano di ulteriori interventi chirurgici era maggiore tra coloro in cui il ctDNA veniva completamente eliminato in seguito alla terapia neoadiuvante.

Referenza. Total neoadjuvant therapy followed by non-operative management or surgery in stage II-III rectal cancer (NO-CUT): a multicentre, single-arm, phase 2 trial. Alessio Amatu, Giorgio Patelli, Maria Giulia Zampino, Francesca Bergamo, Stefania Mosconi, Federica Tosi, Davide Ciardiello, Sara Lonardi, Giorgia Negrini, Daniela Sibio, Marianna Alessandra Gerardi, Sara Galuppo, Francesco Romeo Filippone, Pietro Carnevali, Simona Borin, Pierluigi Pilati, Elia Poiasina, Erica Bonazzina, Lorenzo Gervaso, Enzo Mammano, Francesco Bracco, Luca Bergamaschi, Gaya Spolverato, Matteo Origi, Uberto Fumagalli Romario, Gianluca Mauri, Nicola Fazio, Edoardo Forti, Giuseppe De Roberto, Chiara Cristofori, Cesare Burti, Luigi Asmundo, Luigi Funicelli, Gaetano Ramondo, Pietro Andrea Bonaffini, Sara Mariano, Luca Lazzari, Silvia Ghezzi, Claudio Isella, Daniela Cantarella, Maria Costanza Aquilano, Luca Bottiglieri, Emanuela Bonoldi, Massimiliano Mutignani, Valter Torri, Enzo Medico, Alberto Bardelli, Silvia Marsoni, Angelo Vanzulli, Mauro Filippo Palazzi, Giovanni Carlo Ferrari, Katia Bencardino, Andrea Sartore-Bianchi, Salvatore Siena. *Lancet Oncol* 2025. doi: 10.1016/S1470-2045(25)00542-X.

News, initiatives and events from the IEO world!

Heine H. Hansen Award 2026.



Premio Heine H. Hansen (HHH) Award 2026



La European Society for Medical Oncology (ESMO) e la International Association for the Study of Lung Cancer (IASLC) annunciano che Filippo de Marinis è il destinatario dell'Heine H. Hansen (HHH) Award 2026.

Il suo contributo incarna pienamente lo spirito di questo prestigioso premio, che celebra l'eccellenza nella ricerca, l'innovazione clinica e una dedizione costante al miglioramento dell'esito clinico dei pazienti affetti da tumore del polmone.

Negli anni alla direzione della Divisione di Oncologia Toracica dello IEO, il Prof. de Marinis è sempre stato un punto di riferimento nazionale e internazionale per l'oncologia polmonare e in particolare per le terapie innovative. In questi anni ha contribuito allo sviluppo di un programma integrato dedicato alla prevenzione, diagnosi, trattamento e ricerca sulle neoplasie toraciche. Il suo lavoro ha avuto un ruolo centrale nell'avanzamento della ricerca clinica sul tumore del polmone, rendendo la sua divisione un centro di riferimento per i principali studi clinici internazionali e per collaborazioni con gruppi di ricerca di primo piano. Nel corso della sua carriera, de Marinis ha contribuito in modo significativo allo sviluppo di nuove strategie terapeutiche per il carcinoma polmonare non a piccole cellule (NSCLC), il carcinoma polmonare a piccole cellule e altri tumori toracici, partecipando e contribuendo alla definizione di studi che hanno influenzato gli attuali standard di cura.

In qualità di membro delle più importanti società scientifiche nazionali e internazionali, è ampiamente riconosciuto il ruolo di de Marinis nel promuovere la collaborazione multidisciplinare e l'avanzamento della pratica clinica basata sull'evidenza nel trattamento del tumore del polmone.

News, initiatives and events from the IEO world!

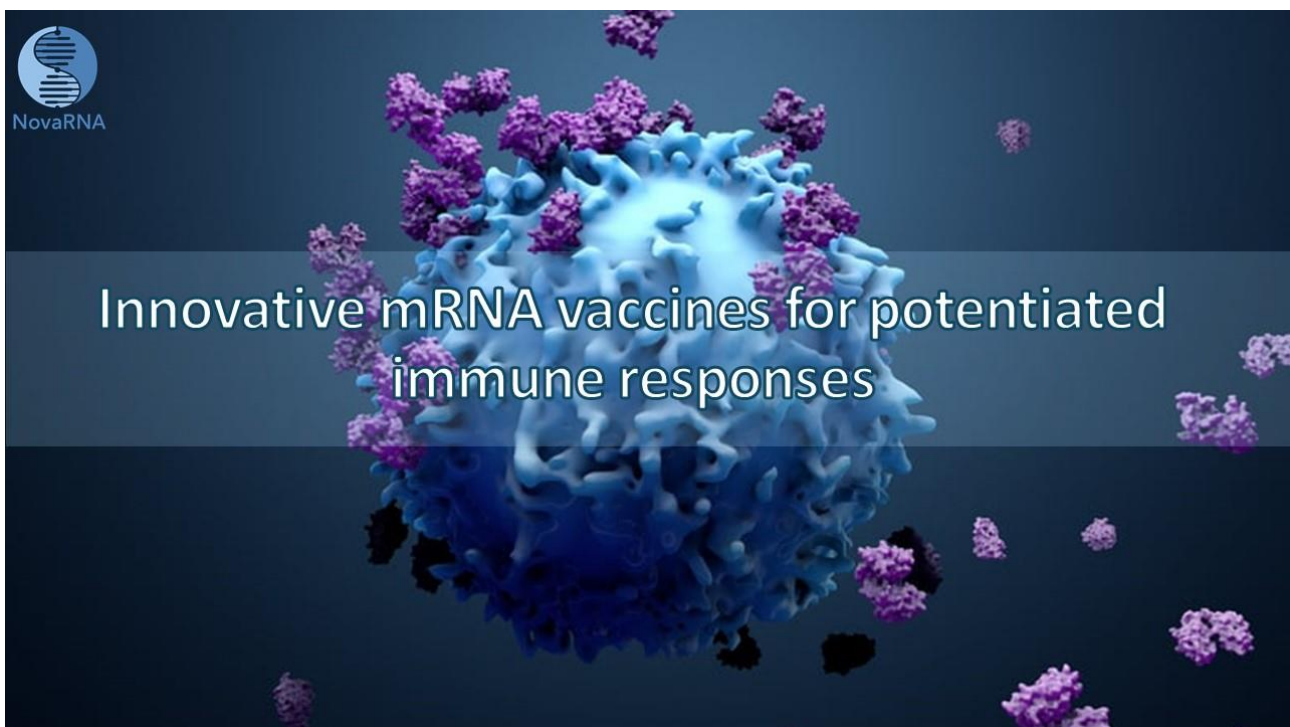
Una nuova cura per le aritmie più gravi.



Un'importante collaborazione tra Monzino e IEO apre nuove prospettive nel trattamento delle aritmie ventricolari maligne. I risultati di STRA-MI-VT, primo studio italiano e tra i primi al mondo sull'uso della radioterapia stereotassica in un'unica seduta, mostrano un controllo delle aritmie superiore all'80%, con risultati migliori rispetto alle tecniche tradizionali. Un traguardo reso possibile dal lavoro congiunto dei cardiologi del Monzino e dei radio-oncologi IEO, guidati rispettivamente dal Dott. Corrado Carbuicchio –Direttore Unità Operativa per il trattamento delle Aritmie Ventricolari Monzino, Ideatore e Principal Investigator dello Studio– e dalla Prof.ssa Barbara Jerezek –Direttrice della Divisione di Radioterapia IEO–, che conferma il valore dell'integrazione tra competenze cardiologiche e oncologiche.

News, initiatives and events from the IEO world!

Il progetto NovaRNA selezionato per il programma *Accelerator* di PerfeTTO.



A Dicembre 2023, finanziato dal Ministero della Salute attraverso i fondi del PNRR, è stato creato il primo network di uffici di trasferimento tecnologico in Italia –PerfeTTO–, per promuovere la cultura del trasferimento tecnologico, supportando attività di trasferimento tecnologico al fine di aumentare lo sfruttamento dei risultati della ricerca in ambito industriale.

Recentemente, il progetto NovaRNA di IEO e Università di Milano si è distinto tra i progetti candidati della seconda edizione del programma TT Accelerator, organizzato all'interno del network PerfeTTO, per il suo forte

potenziale innovativo e l'impatto traslazionale ed è stato selezionato (primo in classifica) per far parte del programma dedicato TT *Accelerator* organizzato dal network PerfeTTO, che fornirà mentoring, formazione e supporto strategico ai progetti di ricerca più promettenti sviluppati dalle istituzioni parte del network.

La tecnologia sviluppata nell'ambito del progetto NovaRNA, guidato da Stefano Persano –ricercatore senior in IEO– sotto la supervisione di Pier Giuseppe Pelicci e Saverio Minucci –entrambi group leader di IEO e professori dell'Università di Milano–, sostenuti da IEO-TT –l'ufficio di trasferimento tecnologico di IEO guidato da Marzia Fumagalli–, e in conproprietà tra IEO e Università di Milano, è una piattaforma innovativa per potenziare la risposta immunitaria ai vaccini tumorali a RNA.

Gli attuali vaccini tumorali a RNA sono generalmente in grado di indurre una risposta del sistema immunitario mediata da anticorpi, mentre l'attivazione dei linfociti T citotossici rimane limitata. Questo è principalmente legato ad un processo chiave dell'attivazione del sistema immunitario, ovvero l'espressione, da parte di specifiche cellule immunitarie (le cellule presentanti l'antigene), delle proteine tumorali (gli antigeni) codificate dalle molecole di RNA del vaccino, che è limitata con i vaccini a RNA convenzionali; questo meccanismo è necessario per un'attivazione robusta e duratura delle cellule immunitarie citotossiche (i linfociti T CD8+).

La piattaforma NovaRNA si pone l'obiettivo di risolvere questo problema attraverso un duplice approccio: da un lato, l'eliminazione di quelle modificazioni chimiche delle molecole di RNA (solitamente introdotte nella preparazione dei vaccini) che, pur incrementando la tollerabilità al trattamento (riducendo l'immunità innata), aumentano in maniera significativa i costi di produzione e la complessità tecnica, impattando di conseguenza sull'accessibilità al trattamento; dall'altro, focalizzandosi su specifiche regioni della molecola di RNA (*untranslated regions*, UTR), al fine di aumentare la scarsa espressione della proteina tumorale antigenica.

Migliorando l'espressione della proteina antigenica e riducendo la complessità tecnica, il risultato dell'approccio NovaRNA è una tecnologia più semplice, con tempi e costi di produzione ridotti, che potrebbe aprire la strada a una nuova generazione di vaccini a RNA, in ambito oncologico, con lo sviluppo di vaccini per altri tipi di tumore, così come contro altri agenti patogeni.

Iniziato ufficialmente il 14 gennaio, il programma TT *Accelerator* rappresenta una notevole opportunità di mandare avanti il progetto NovaRNA e accelerare il suo percorso verso applicazioni real-world.

“La durata del TT *Accelerator* è di 6 mesi e alla conclusione è previsto un incontro di business matching – commentano i membri di IEO TT–. Si tratta di un percorso che permette di approfondire aspetti del progetto dal punto di vista del trasferimento tecnologico, con l'obiettivo di trasformare risultati innovativi in opportunità di business da presentare a investitori e a potenziali partner industriali”.

Congratulazioni all'intero team –scienziati e membri dell'ufficio di trasferimento tecnologico– per questo eccellente risultato. Sfruttiamo al massimo questa opportunità!

----- TELL ME MORE! -----

I vaccini a RNA funzionano istruendo il sistema immunitario a riconoscere delle specifiche proteine tumorali –antigeni– ed uccidere le cellule (tumorali) che le esprimono. Le cellule presentanti l'antigene (APC) giocano un ruolo chiave, esprimendo le proteine codificate dalle molecole di RNA e attivando la risposta del sistema immunitario. Il livello di espressione delle proteine tumorali antigeniche è quindi critico per un'efficiente risposta del sistema immunitario contro il tumore.

Per aumentare l'espressione della proteina antigenica, l'approccio NovaRNA si concentra sulle regioni UTR, che sono note influenzare la stabilità del trascritto, l'efficienza di traduzione, la localizzazione intracellulare, e l'interazione con

fattori cellulari. Nello specifico, attraverso uno screening, i ricercatori hanno identificato le combinazioni di UTR in grado di aumentare l'espressione della proteina antigenica da parte delle APC, e la presentazione dell'antigene mediata dal complesso MHC-1, potenziando così la risposta del sistema immunitario (mediata dai linfociti T citotossici CD8+), risolvendo così un problema comune a molte piattaforme di vaccini, ovvero la scarsa espressione della proteina antigenica. In modelli preclinici *in vivo* di melanoma, l'approccio NovaRNA ha determinato un notevole aumento della risposta immunitaria dei linfociti T rispetto agli RNA impiegati dalle piattaforme convenzionali, riducendo in maniera significativa la mortalità per tumore.

News, initiatives and events from the IEO world!

Partecipa al workshop SEMM "The Proteomics Revolution: Advancing Science and Society".

Dal 29 Giugno al 1 Luglio 2026, Milano ospiterà il workshop scientifico, organizzato dalla Scuola Europea di Medicina Molecolare (SEMM), "The Proteomics Revolution: Advancing Science and Society".

L'evento si pone l'obiettivo di rafforzare la comunità proteomica mondiale, creando un ambiente interattivo e interdisciplinare.

Dottorandi, ricercatori giovani ed esperti, dal mondo accademico e farmaceutico, si riuniranno per promuovere la discussione scientifica, creare nuove collaborazioni o consolidare quelle esistenti. La natura interdisciplinare dell'evento faciliterà il confronto tecnico e scientifico e il trasferimento delle innovazioni tecnologiche in applicazioni nel mondo reale.

I talk, di leader nel campo della proteomica da Italia, Germania, Israele, USA, Austria, Canada, Olanda, UK, Spagna, Danimarca, affronteranno numerosi argomenti, tra cui il ruolo della proteomica nella salute e nella malattia, dall'identificazione di marcatori di malattia a meccanismi e terapia; l'impiego della proteomica spaziale per decifrare l'informazione spaziale dei proteomi e la loro dinamica nelle cellule e nei tessuti; l'utilizzo di approcci di proteomica per descrivere le signaling cellulari e l'innovazione tecnologica e computazionale che guida la "rivoluzione proteomica". Inoltre, discussioni e tavole rotonde rappresenteranno un momento per discutere sugli investimenti per il futuro della proteomica, sull'*empowerment* della prossima generazione di ricercatori proteomici e i *bias* nel design sperimentale, sia nella scienza di base che nella medicina.

"Il workshop nasce dall'idea di una vera e propria rivoluzione della proteomica, un campo in cui biologia, tecnologia e analisi computazionale stanno trasformando il modo in cui comprendiamo la salute e la malattia.– commenta Tiziana Bonaldi, professore associato di biologia sperimentale all'Università degli Studi di Milano, group leader all'Istituto Europeo di Oncologia (IEO) e membro del comitato organizzativo– Questo incontro vuole riflettere la direzione futura della disciplina e, allo stesso tempo, valorizzare la qualità e l'energia della comunità proteomica italiana in un contesto internazionale. Lo vedo come un passo naturale verso HUPO 2027 a Milano e come un'opportunità concreta per la nuova generazione di scienziati di contribuire a definire il futuro del settore. Pur rivolgendosi a ricercatori in tutte le fasi della carriera, il workshop mette al centro i giovani scienziati. Il programma è pensato per favorire visibilità, confronto e networking, offrendo spazi dedicati al dialogo, con esperti affermati, e alla discussione su sfide, opportunità e percorsi professionali. Un formato raccolto e un contesto informale completano l'esperienza, creando un ambiente ideale per costruire relazioni scientifiche durature".

Non perdere l'opportunità di far parte di un ambiente dinamico e beneficiare delle interessanti discussioni all'hotel Quark a Milano. La partecipazione è limitata a 120 persone registrate, quindi non perdere tempo! Assicurati un posto al workshop "The Proteomics Revolution: Advancing Science and Society".

| Deadlines | |
|---|-------------------|
| Abstract submission deadline | February 28, 2026 |
| Chosen participant will be notified by | March 15, 2026 |
| Registration deadline | March 30, 2026 |
| REGISTRATION FEES (in euros) | |
| Graduate Student/PhD Student/Post-doc | € 350,00 |
| Academic/Principal Investigator | € 450,00 |
| Industry | € 732,00 |
| For further details, check the event website here | |

Consulta il sito web del workshop per i dettagli: <https://www.proteomicsrevolution2026.net/>
Per qualsiasi richiesta riguardo all'evento: Sabrina Frata (Event Management & Organizing Secretariat, Fondazione SEMM ETS) events@semm.it.

News, initiatives and events from the IEO world!

Al via l'attività del nuovo blocco operatorio di IEO 3!

A meno di due mesi dall'Inaugurazione del Building IEO 3, è entrato ufficialmente in funzione, senza alcun disservizio verso i pazienti, il nuovo blocco operatorio. In soli cinque giorni, l'intera piastra robotica – composta da quattro sale robotiche affiancate– e quattro



sale (delle otto previste) dedicate alla chirurgia open sono già operative a pieno regime, con oltre 100 procedure chirurgiche, di cui più del 20% in robotica. Nelle prime due settimane di attività, il nuovo blocco operatorio ha già accolto quasi 300 pazienti, di cui circa il 30% operati in chirurgia robotica. Le sale operatorie sono ambienti altamente tecnologici, che integrano in modo intelligente apparecchiature e dispositivi, assicurando più elevati standard di efficienza, sicurezza e precisione e coniugando l'innovazione tecnologica con l'umanizzazione degli spazi, offrendo al contempo comfort a pazienti e operatori. Anche l'architettura e il design dell'area recovery –luce naturale, pannelli serigrafati e retroilluminati e scelte cromatiche studiate– contribuiscono a ridurre l'ansia e a migliorare il benessere emotivo, offrendo una sensazione di calma e protezione in un momento particolarmente delicato del percorso di cura.

«In IEO l'ambiente è parte integrante del processo terapeutico.– sottolinea Silvia Oldazzi, Direttrice Strategia e Sviluppo Piano Industriale –Il nuovo blocco consentirà inoltre di aumentare l'efficienza, permettendo di effettuare più interventi e conseguentemente ridurre i tempi di attesa».

«Il benessere del paziente guida da sempre ogni nostra scelta –aggiunge Gabriella Pravettoni, Direttrice della Divisione di Psiconcologia –IEO 3 integra alla *patient experience* le possibilità di cura offerte oggi dalle nuove tecnologie, dando agli insegnamenti del nostro fondatore, Umberto Veronesi, il respiro del futuro».



Grazie a questa combinazione di tecnologia, efficienza organizzativa e attenzione alla persona, IEO 3 rappresenta un *unicum* in Italia per un centro oncologico monospecialistico e conferma l'impegno del nostro Istituto nell'innovazione al servizio della salute.

Scopri di più, leggi il [Comunicato Stampa!](#)

What's new in science?

Hydroxychloroquine to reduce recurrence by inhibiting cancer cell autophagy.

Despite the remarkable advances of the past decades in breast cancer treatment, the metastatic disease still remains a challenge for many patients. Indeed, although early diagnosis and timely treatment increase remarkably the chances of cure, many patients, while initially responding to therapy, and despite the benefits deriving from adjuvant (post-surgery) therapy, later recur with incurable metastatic disease. Recurrence is due to the presence of the so-called minimal residual disease (MRD), namely the persistence of cancer cells that managed to survive treatment and, by remaining in a dormant state for month or even years after surgical resection of primary tumors, eventually fuel disease relapse.

Previous preclinical *in vivo* studies showed that in murine breast cancer models, recapitulating key traits of the human counterpart, residual dormant cancer cells display altered mTOR signaling, and dormant residual breast cancer cells deploy autophagy mechanisms to survive the therapeutic stress and fuel recurrence.

To evaluate whether by specifically acting on the biological mechanisms underlying the survival of dormant recurring cells, MRD can be eradicated, eventually decreasing disease recurrence, researchers investigated the effects of mTOR signaling and autophagy inhibitors both in *in vivo* preclinical disease models and in the frame of a prospective clinical trial.

Preclinical *in vivo* clearing of dormant recurrent cells. Firstly, researchers evaluated, in *in vivo* preclinical breast cancer models with MRD (namely, displaying disseminated tumor cells), the effects on breast cancer recurrence of the dual inhibition of mTOR signaling and autophagy through the combined administration of everolimus (EvE) and hydroxychloroquine (HCQ), respectively. EvE is a FDA-approved treatment against breast cancer, commonly administered in the advanced disease stage, and HCQ is an approved treatment for autoimmune diseases (with a more favorable toxicity profile compared to chloroquine, CQ).

Confirming previous studies exploiting Rapamycin, inhibition of the mTOR pathway by EvE reduced recurrence, both in chronically and transiently (to be easily translated to the clinical setting) treated disease models; the extent of reduction of recurrence was dependent on treatment duration. In addition, autophagy inhibition, through CQ or HCQ, slightly reduced recurrence, both when the two drugs were administered alone and when were administered along with mTOR inhibitors. The dual inhibition of mTOR pathway and autophagy only weakly reduced further tumor recurrence, indicating that the two inhibitors likely acted on different mechanisms: On one side, mTOR inhibitors reduced residual cancer cell proliferation, limiting metastasis growth; on the other side, autophagy inhibitors decreased survival of dormant tumor cells, thus synergizing in reducing disease recurrence.

Alex, can you write few words about autophagy?

Autophagy is a “recycling” process of the cell that degrades damaged organelles and proteins to maintain energy balance and survival under stress. In cancer, it plays a dual role. Early in tumor development, autophagy can suppress cancer by limiting DNA damage and inflammation. Once a tumor is established, however, cancer cells often exploit autophagy to survive nutrient deprivation, hypoxia, and therapy-induced stress. This makes autophagy both a protective mechanism and a therapeutic target: inhibiting it can sensitize tumors to treatment, while activating it may prevent malignant transformation.

Indeed, quantification of the number of residual tumor cells after EvE and HCQ revealed that, despite the greater effect of mTOR inhibitors, both EvE and HCQ decreased the number of residual cancer cells, which correlated with treatment duration. Notably, under treatment with autophagy inhibitors, some cancer cells resumed proliferation, increasing recurrence, which did not occur under dual inhibition of mTOR pathway and

autophagy, further sustaining the concept that the two mechanisms contributed differently to the metastatic disease.

Interestingly, a correlation was found between the number of residual cells at the end of treatment and recurrence-free survival: Lower numbers of dormant cells correlated with longer recurrence-free survival, indicating that recurrence is indeed due to the MRD.

Autophagy and mTOR inhibition in a clinical setting – the CLEVER trial. Based on the results collected within the preclinical study, the authors evaluated the efficacy of the combined inhibition of mTOR signaling and autophagy on disease recurrence in breast cancer survivors. In the frame of the trial, patients (who had undergone surgery for primary breast cancer, either of the TNBC or ER+/HER2- subtype, and resulted positive for disseminated tumor cells within 5 years from initial cancer diagnosis) were randomized to receiving either *i.* HCQ (15 patients), *ii.* EvE (15 patients), *iii.* HCQ+EvE (8 patients), *iv.* 3-month surveillance followed by HCQ+EvE treatment (15 patients).

Toxicity. Although in some patients, both in the monotherapy arms and in the combination therapy arms, drug dosage was adjusted along the study, no grade 4 toxicity was observed. However, some patients experienced grade 1, 2 and 3 adverse events. Overall, the two drugs appeared both safe, either administered alone or in combination.

Quantification of disseminated tumor cells. The number of disseminated tumor cells decreased in all treatment arms. However, the decrease was greater with HCQ and EvE combination therapy than in HCQ- or EvE- only treatment arm. In some patients who, at the end of the treatment cycle, were still positive for disseminated tumor cells, the additional therapy cycles further reduced the number of disseminated cells.

Efficacy. Recurrence-free survival was greater for those patients who, at the end of treatment, showed undetectable disseminated cancer cells.

Although the study showed only a slight further effect of autophagy inhibition on the number of residual tumor cells as compared to mTOR inhibitor EvE, results

strongly point to the existence of two different mechanisms of disease recurrence. On one side, mTOR inhibitors act on tumor cell *proliferation* (for instance, delaying proliferation of cells exiting dormancy and resuming proliferation, “ready to” fuel metastasis colonization), thus reducing disease recurrence. On the other side, autophagy inhibitors act on maintenance of dormancy, interfering with the mechanism that cancer cells deploy to survive the therapeutic stress, by inducing autophagy and remaining dormant. This study demonstrates that *intercepting* recurrence by interfering with the biological mechanism underlying cancer cell dormancy is feasible, to prevent –rather than treat– disease relapse.

Although the combined administration of both inhibitors likely eradicates the minimal residual disease, significantly reducing disease recurrence, further studies are needed to disentangle the actual contribution of the different cell mechanisms to cancer relapse. Anyway, if confirmed, the therapeutic efficacy of these combination treatment appears promising. Further ongoing studies have been investigating the durability of the observed effects on disease recurrence.

Alex, can you write few words about mTOR signaling in cancer?

mTOR is a central regulator of cell growth, metabolism, and survival, integrating signals from nutrients, growth factors, and cellular stress. In cancer, mTOR signaling is frequently hyperactivated, driving uncontrolled proliferation, enhanced protein synthesis, and metabolic reprogramming. Tumors use mTOR to support their high energy and biosynthetic demands. Because of this, mTOR is a major therapeutic target: inhibiting its activity can slow tumor growth and increase sensitivity to other treatments.

“this study demonstrates that intercepting recurrence by interfering with the biological mechanism underlying cancer cell dormancy is feasible, to prevent –rather than treat– disease relapse”

References: **1)** Targeting dormant tumor cells to prevent recurrent breast cancer: a randomized phase 2 trial. *Angela DeMichele, Amy S. Clark, Emily Shea et al.*, Nature Medicine 2025. doi: 10.1038/s41591-025-03877-3. **2)** Intervening on dormancy to prevent breast cancer recurrence. *Tanja Fehm & Hans Neubauer.* Nature reviews clinical oncology 2025. doi: 10.1038/s41571-025-01087-x.

What's new in science?

CART cells for the treatment of pediatric neuroblastoma – encouraging results from a phase 1/2 clinical trial.

Neuroblastoma is the most common tumor in childhood. Although a deeper understanding of the biology of this tumor has enabled an improved disease management, especially by allowing for a more accurate estimate of the risk of disease, its high heterogeneity limits efficacy of the current therapies. Previous studies have shown positive results in neuroblastoma patients upon treatment with monoclonal antibodies targeting the GD2 protein (in combination with chemotherapy). However, the disease often relapsed at the end of treatment. In this scenario, CART cells offer the advantage of a more durable response. A previous paper reported the promising preliminary results of a phase 1/2 clinical trial, showing positive clinical outcome in five pediatric patients with neuroblastoma resistant to previous lines of therapy, after GD2-CART cell-based treatment (namely, infusion of CART cells engineered to target specifically tumor cells expressing the GD2 protein). More recently, the authors reported the final results of this clinical trial, in a larger 35-patient cohort, assessing treatment safety, tolerated dose, and efficacy.

The final results confirmed those of the interim analysis: In patients with lower disease burden receiving the optimal dose of CART cells, overall response rate was almost 80%, about 50% achieved complete response, and long term (5-year) survival was almost 70%.

Moreover, the authors identified key aspects to be considered for achieving greater therapy response, such as isolation of T cells to be engineered from the patients before treatment initiation, for highest viability and antitumor activity of CART cells. The long term persistence of CART cells (for over 1 year) in treated patients suggests that this approach may allow for a long term disease control, thus possibly preventing recurrence. Furthermore, their results strongly suggest that CART cell infusion at earlier disease phases (namely, not after two lines of prior therapy) is critical for optimal therapy efficacy.

Although treatment-related toxicity was not negligible, symptoms were those commonly related to cell-based therapy – though stronger, likely due to the greater CART cell activity – and overall manageable. Finally, no T cell-related malignancies were observed after infusion.

Encouraged by the positive clinical outcome of patients within the current study, in which the treatment allowed to induce durable remission in some patients with high risk relapsing/refractory neuroblastoma, an international phase II trial is under development, to corroborate the results collected in the context of larger patient cohorts and at earlier time points (after first line therapy) to maximize the chances of patient cure.

“the final results confirmed those of the interim analysis: In patients with lower disease burden receiving the optimal dose of CART cells, overall response rate was almost 80%, about 50% achieved complete response, and long term (5-year) survival was almost 70%. Encouraged by the positive clinical outcome of patients within the current study, an international phase II trial is under development, to corroborate the results collected in the context of larger patient cohorts and at earlier time points to maximize the chances of patient cure”

TELL ME MORE!

The 35 patients included in the study were children with metastatic disease who already received previous lines of therapy. T cells were isolated from patients and engineered for ensuing re-infusion. Engineered cells were viable and endowed with

strong antitumor activity (as shown by their killing activity in *in vitro* assays).

Toxicity. Treatment-associated toxicity was not negligible, yet manageable. Some patients experienced grade 2, 3 and even 4 adverse events.

Toxicity manifested mostly as hematologic toxicity and excessive inflammatory response (cytokine release syndrome –CRS– whose severity was not linked to the disease status). While no link was observed between inflammatory molecules in the blood and response to treatment, it did correlate with CRS severity. Notably, these CART cells were engineered to express, in addition to the GD2-targeted protein, a so-called “suicide gene”, namely a gene that, when induced by treatment with a specific compound (rimiducid), killed CART cells expressing it, thus allowing to control CART cell viability/death in case of manifestation of severe, life-threatening CART-cell treatment-related adverse events. In case of severe toxicity, patients were treated with anti-inflammatory drugs and the compound to activate the “suicide gene”, obtaining a rapid decrease of CART cell number and symptom amelioration. CART cells surviving suicide gene induction were not killed even after additional drug administration, however their persistence did not associate with toxicity.

Efficacy. Researchers observed overall 31% of patients experiencing complete response, 26% achieving partial response, and 6% of patients showing only minor response. 15% of the patients showed progressive disease despite CART cell infusion, 19% achieved a stable disease. Some patients (23% at 1 year, 38% at 5 years), after

initially responding to the treatment, relapsed. CART cells persisted in the blood over 12 months in about 60% of the patients. Survival was around 50% at 1 year, and around 30% at 5 years.

When they analyzed in more detail a patient subpopulation with low disease burden who received the optimal CART cell dose, they observed an overall greater response rate, with 50% of them achieving a complete response and almost 70% 5-year survival. However, even in this population, the duration of response did not appear to be strongly correlated with CART persistence, pointing towards the involvement of other factors to fully explain the effects observed.

Notably, long term (5-year) survival was associated with the number of therapy lines prior to CART cell infusion, with 1-2 therapy lines associated with better long term survival as compared to those who had already received 3 or more treatment cycles. In these patients, survival at 5 years was almost 90% (as compared to around 40% in those treated after failure of >3 prior lines of therapy). Moreover, when cells to be engineered were collected at diagnosis rather than after previous treatments, 5-year survival was significantly better (being 100% vs 33%).

After infusion, CART cells expanded in all patients for about 2 weeks and then persisted months after infusion.

What's new in science?

Bispecific antibodies for the treatment of follicular lymphoma: Results of the EPCORE FL-1 phase III clinical trial.

Follicular lymphoma (FL) is a non-Hodgkin Lymphoma. Patients are usually treated with chemo-immunotherapy and, in case of relapse, they are administered a combination of Lenalidomide and Rituximab (R2). However, complete response is observed in about 50% of patients only, highlighting the need for new and more effective therapeutic strategies.

Therefore, previous studies have assessed, in the frame of a (phase 1b/2) clinical trial, efficacy of a triple combination with Rituximab, Lenalidomide and Epcoritamab (R3), in FL patients refractory to conventional therapy. Epcoritamab is a bispecific antibody binding both CD20 protein (on B cells) and CD3 protein (on T cells), leading to T cell-mediated death of malignant B cells. The combination of Epcoritamab with Rituximab and Lenalidomide showed strong and durable response.

More recently, efficacy and safety of this new combination were evaluated, for the first time, in the context of a phase III (EPCORE FL-1) clinical trial, in comparison with R2 treatment, showing 83% strong and durable complete response rate and 79% reduced risk of disease progression. Although the *ad interim* analysis did not allow to thoroughly evaluate long term effects of the treatment, especially in terms of survival (due to the relatively short followup duration; a crucial aspect in this disease), results showed longer time to the successive anti-cancer treatment and lower number of disease-related deaths, both in the low risk as well as in the high risk population. However, the overall higher incidence of adverse events in the R3 group as compared to the R2 group requires careful analysis of risk/benefits as well as optimized management of adverse events. Yet, the results of this trial showed a superior efficacy of this chemotherapy-free triple combination as compared to the R2 therapy, in refractory FL patients, with higher complete response rate, reduced risk of disease progression, along with a manageable safety profile, thus proposing Rituximab-Lenalidomide-Epcoritamab as the new standard of care for these patients, offering them a new, more effective therapy option, devoid of the burdensome side effects linked to chemotherapy. Finally, from a research point of view, future translational studies –focused on the identification of biomarkers of response, mechanisms of resistance, and the role of the minimal residual disease– and clinical studies –aimed at defining the rationale for evaluating the efficacy of new therapeutic combinations, with immunotherapy or other emerging therapies– may allow for patient selection and hence optimization of clinical efficacy.

“the results of this trial showed a superior efficacy of this chemotherapy-free triple combination Rituximab-Lenalidomide-Epcoritamab. From a research point of view, future translational studies –focused on the identification of biomarkers of response, mechanisms of resistance, and the role of the minimal residual disease– and clinical studies –aimed at defining the rationale for evaluating the efficacy of new therapeutic combinations, with immunotherapy or other emerging therapies– may allow for patient selection and hence optimization of clinical efficacy”

TELL ME MORE!

EPCORE FL-1 was a randomised, phase III clinical trial involving 189 research centers in 30 different countries, in Africa, Asia, Australia, Europe, North and South America. The trial enrolled stage II, III, IV patients. Epcoritamab was administered subcutaneously; Rituximab (inducing complement-

dependent cytotoxicity and natural killer cell-mediated antibody-dependent cellular cytotoxicity and macrophage phagocytosis) and Lenalidomide (increasing activation of both T and NK cells) were administered systemically. This paper collects the results of the second (planned) *ad interim* analysis

(at May 2025) and involved 488 patients. The study will continue to analyse long term followup data. Enrolled patients were randomized to receive either R2 (245 patients) or R3 (243 patients) drug combination. Almost all participants had previously received first line therapy including anti-CD20 antibodies plus chemotherapy; 37% were refractory to anti-CD20 antibodies.

Efficacy. Objective response rate (ORR, 95% vs 79%), progression-free survival (PFS, 79% reduced risk of disease progression or death), complete response rate (83% vs 50%) were all significantly greater in the R3 group as compared to R2, including both high- and low- risk population.

Safety. Grade 3 or higher/severe adverse events

were more frequently observed in the R3 group than in the R2. Anyway, no new adverse effects were noted (all were known for being associated with administration of the three drugs in monotherapy). Fatal adverse events were observed in 2% of patients in the R3 group vs 4% in the R2 group. 19% of the patients in the R3 group discontinued treatment due to treatment-related adverse events, vs 12% in the R2 group. Importantly, a specific regimen (increasing doses of R2 over three therapy cycles, each followed by full doses of Epcoritamab) allowed to reduce the incidence and severity of cytokine release syndrome, which resulted to be mild and reversible. Quality of life was preserved.

References: **1)** Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial. *Lorenzo Falchi, Marcel Nijland, Huiqiang Huang et al.*, Lancet 2025. doi: 10.1016/S0140-6736(25)02360-8. **2)** A step forward in the treatment of relapsed or refractory follicular lymphoma. *Laura Magnano, Andrea Rivero.* Lancet 2025. doi: 10.1016/S0140-6736(25)02436-5.

What's new in science?

Gut microbiota modulation of anti-tumor immune response – mechanistic insights.

Several studies have shown the regulatory effect of the gut microbiome on immune checkpoint inhibitor (ICI)-based immunotherapy efficacy. The underlying mechanisms are still not completely known; however, increasing evidence suggest, on one side, the involvement of the release in the blood of microbiota-derived metabolites, in turn influencing the anti-tumor immune response; on the other side, the so-called “tumor mimicry”, in which molecules expressed on the surface of gut microorganisms may mimic tumor-specific proteins and directly modulate and instruct the immune system into attacking such tumoral protein-expressing cancer cells. IEO researchers have previously shown that some bacterial peptides, such as Flagellin of the *Lachnospiraceae* species (Flach), closely resemble some melanoma proteins and are preferentially expressed on tumors of patients responding to immunotherapy. Moreover, they also showed that T cells are more reactive against Flach peptides isolated from the blood of patients responding to therapy, and, *in vitro*, induce a greater expansion on intratumoral T cells and have a greater tumor cell killing ability, demonstrating their ability in potentiating the antigen-specific antitumor immune response against melanoma, which may be exploited for therapeutic purposes.

“a specific gut microorganism –SFB– modulates the immune system, increasing ICI efficacy in countering the growth of tumors expressing antigen proteins in common with SFB gut microorganism”

----- Main finding.-----

In a recent paper, researchers showed that a specific gut microorganism –SFB– modulates the immune system, increasing ICI efficacy in countering the growth of tumors expressing antigen proteins in common with SFB gut microorganism; immune cells “activated” by the gut bacterium infiltrate the tumor where, upon ICI treatment, become pro-inflammatory. The gut microorganism- and ICI- elicited remodelling of the tumor immune microenvironment promotes the recruitment and activation/proliferation of cytotoxic T cells that counter tumor growth, hence demonstrating that gut microbiota species can be exploited to modulate T cell activity and enhance anti-tumor immune system efficacy.

----- Details.-----

The authors engineered a melanoma cell line, to express a protein of a gut bacterium –SFB– (lysates of these engineered cells effectively activated T cells *ex vivo*, demonstrating the reliability of the model).

ICI efficacy in SFB-colonized mice. Engineered melanoma cells were then transplanted in recipient mice, whose gut was colonized by the gut microorganism SFB, and treated with ICI (anti-PD1). While ICI treatment impaired growth of transplanted engineered melanoma cells in SFB-colonized mice, increasing mouse survival, no effect of ICI was observed neither in mice transplanted with non-engineered melanoma cells, nor in mice lacking SFB in the gut. Moreover, surviving mice rejected re-transplanted engineered melanoma cells even in absence of ICI treatment, demonstrating that the immune system had acquired memory against the specific SFB protein expressed by engineered melanoma cells.

Notably, tumor growth was remarkably reduced in tumor-bearing, ICI-treated mice especially if SFB was administered in the early phases of tumorigenesis (that is, short after tumor cell transplantation). The same SFB-induced enhancement of ICI efficacy was observed in other two (colon and lung) tumor models.

Intratumor CD8 T cells in SFB-colonized, ICI-treated mice. Since ICI therapy works by potentiating T-cell mediated antitumor immune system activity (through the removal of a “brake” to T cell activity), they characterized intratumor T cells isolated from engineered (and not) tumors grown in ICI-treated mice colonized –or not– by SFB bacteria. First, in SFB-colonized mice, intratumoral CD8 T cells were more numerous than regulatory T cells (Tregs) as compared to non-engineered tumors and engineered tumors isolated from SFB-lacking mice (no changes in T CD8/Treg ration was seen in the healthy intestine of ICI-treated mice). Moreover, CD8 T cells isolated from engineered tumors grown in ICI-treated SFB-colonized mice displayed higher effector function (that is, there was a higher frequency of CD8 T cells producing inflammatory cytokines such as IFN γ , TNF α).

Intratumor CD4 T cells in SFB-colonized, ICI-treated mice. Tumors from SFB-colonized mice exhibited a greater proportion of CD4 T cells specific for the transplanted engineered tumors, characterized by a more pro-inflammatory phenotype, producing high levels of IFN γ and TNF, as compared to tumors isolated from SFB-lacking mice, contributing to the remodelling of the immune tumor microenvironment and the enhanced responsiveness to ICI therapy.

In the other (non-melanoma) tumor types, T cell composition was comparable, with SFB promoting accumulation inside the tumor of CD4 T cells with a particular IFN γ -producing pro-inflammatory phenotype.

CD4 and CD8 T cells work together to enhance ICI response. Their data indicated that SFB gut colonization induced the increase of both CD8 T cells and pro-inflammatory CD4 T cells inside the tumor, which together enhanced ICI response. Indeed, *in vivo* depletion of either CD4 or CD8 T cells impaired ICI response. Notably, while CD8 T cell depletion had only a modest effect on CD4 T cells proportion in the tumor, in CD4 T-depleted mice, CD8 T cells were less active, showing that CD8 T cells require tumor-specific CD4 T cells for their full antitumor activity. Single cell transcriptomic analysis revealed that tumor-infiltrating T cells from SFB-colonized and SFB-lacking mice were transcriptionally different.

Gut-to-tumor migration of CD4 T cells. SFB colonization elicited the migration of SFB-specific CD4 T cells from the gut (intestinal lamina propria) to the tumor; once in the tumor, they acquired a different, pro-inflammatory phenotype sustaining ICI response.

Tumor mimicry only works for some gut microorganisms. Finally, researchers observed that the effect on tumor growth was specific for SFB bacteria, because when tumor-bearing mice were instead colonized with another bacterium (*Helicobacter hepaticus*, Hh) ICI efficacy on the growth of tumors (engineered with a Hh-specific protein) was not affected, despite the induced expansion of Hh (and tumor)-specific CD4 T cells and migration to the tumor. However, Hh-specific CD4 T cells exhibited a less pro-inflammatory phenotype (producing lower amounts of IFN γ and TNF), and intratumoral CD8 T cells were unaffected.

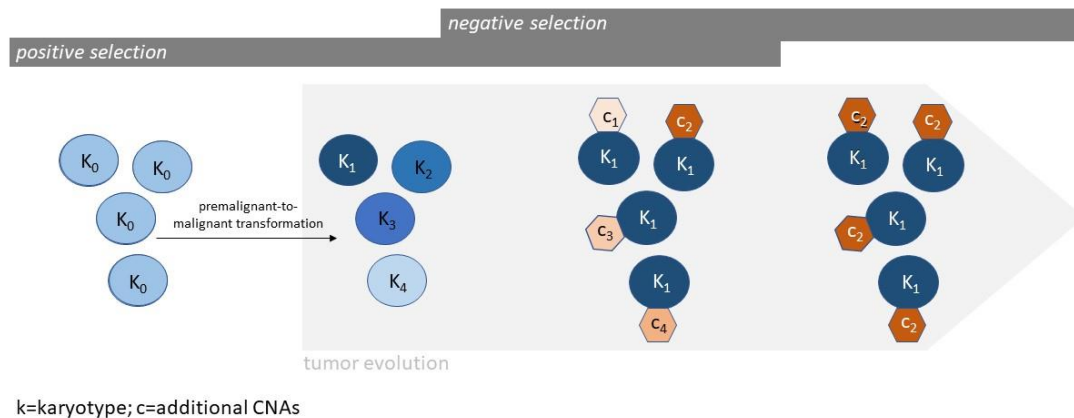
Conclusions.

Gut microbiota modulation of the response to ICI therapy has been demonstrated both preclinically and clinically. This work proposes a mechanistic explanation underlying the observed clinical effects, showing that by mimicking tumor-specific antigen proteins, some gut microorganisms are capable of instructing the immune system, inducing an immune remodeling of the tumor microenvironment towards a more pro-inflammatory antitumor immunity that sustains ICI efficacy. These results are in line with clinical observations showing that ICI efficacy correlates with the presence of specific microbiome species in the gut. Interestingly, by demonstrating that gut microbiota and ICI synergize within a narrow time window, the authors suggest the importance of the right timing in microbial antigen exposure for therapy efficacy.

Reference: Microbiota-induced T cell plasticity enables immune-mediated tumour control. Tariq A Najar, Yuan Hao, Yuhao Hao, Gabriela Romero-Meza, Alexandra Dolynuk, Emma Almo, Dan R Littman. Nature 2026. doi: 10.1038/s41586-025-09913-z.

What's new in science?

Aneuploidy in tumor evolution – colorectal cancer.



The altered number of chromosomes (aneuploidy) is a widespread feature of many tumors. Cells can manage a certain degree of aneuploidy, by deploying specific coping mechanisms; in this case, aneuploidy can confer a growth advantage to tumor cells, resulting into new acquired traits that sustain cell survival and proliferation. However, if these coping mechanisms are not sufficient, resulting in excessive genomic alterations, aneuploidy can represent a threat to cell viability. Indeed, the aneuploid status of cancer cells is dynamic, evolving during tumor progression, as a result of positive and negative selective forces: during tumor evolution, some genomic alterations are positively selected –and maintained–, some are negatively selected – and lost.

Main finding.

Researchers exploited colorectal cancer –frequently aneuploid– as a disease model to track the evolution of the cells' altered genome during tumor progression, from precancerous lesions (adenomas) to malignant transformation, to metastases. Their results showed that after an initial significant genomic alteration, during the premalignant-to-malignant transformation, the karyotype of colorectal cancer cells remains overall stable during the following tumor progression – until metastases. However, additional genomic alterations acquired by tumor cells are progressively selected (through negative selection), reducing intratumor genetic heterogeneity, because during tumor progression cancer cells with the most advantageous set of alterations (that is with the genomic alterations conferring them an advantage over other cells) are selected, survive, proliferate and support tumor growth.

Details.

The authors analyzed (by whole genome sequencing) genomic alterations in patient-derived, spatially distinct regions of precancerous lesions, early tumor lesions and stage II/III tumors.

Quantification of aneuploidy degree. Genome alterations (specifically, copy number alterations, CNA) were lower (8.5%) in pretumoral lesions and higher in tumoral (27.2%) lesions. Gains were more abundant than losses. Cell populations (subclones) characterized by a specific CNA were larger in adenomas than in tumor lesions, suggesting that, once acquired an advantageous CNA differentiating them from the other cells, aneuploid cells expand (as a cell clone), sustain tumor progression, and eventually gain additional alterations producing further smaller cell populations (subclones). As the tumor progresses, these subpopulations/subclones become less numerous than in early cancer, and intratumor heterogeneity decreases.

Emergence of CNAs. In the initial phases of tumor development, CNA emergence sustained premalignant-to-

malignant transformation that, under selection forces, generated aneuploid cancer cells with a proliferation advantage.

A core karyotype. After malignant transformation, all cellular subpopulations within the tumor mass (cellular clones) had a “core” karyotype, which remained overall stable during the ensuing tumor progression; however, few of them harbored additional (subclonal) CNAs contributing to (subclonal) intratumor heterogeneity.

Evolving tumors are high fitness cell populations shaped by positive and negative selection. Under *positive* selection, CNAs constantly accumulated (CNA accrual *did not* proceed through bursts of CNAs accumulating during tumor evolution until shaping the “most fit”, or “winning” malignant karyotype – as it has been described, instead, in breast cancer) but, during tumor evolution, the acquired CNAs were negatively selected until the definition of a karyotype with the highest fitness.

The action of positive selection on CNA acquisition was previously proposed and further demonstrated in this study (through the analysis of scDNAseq in cell lines and patient-derived organoids).

To demonstrate the action of *negative* selection on the shaping of the “final” karyotype, the authors hypothesized that each evolving tumor represents the optimal condition in terms of fitness, namely equipped with all the traits that, under the specific selective pressure of a particular tumor microenvironment, result in tumor cell survival and proliferation. To test that, they developed a mathematical model, which indeed supported their hypothesis: Negative selection shaped the “winning” karyotype (with the highest fitness, at population level), with the right number and type of CNAs. Indeed, by using this model they found that *i.* if mutations occurred in a growing tumor, with no negative selection, tumor intratumor heterogeneity increased; *ii.* in case of negative selection, the number of different CNAs decreased and tumor intratumor heterogeneity was reduced. These results were validated by single cell sequencing data.

Tumor evolution during metastatic dissemination and treatment. During metastatic dissemination, cancer cells, with their unique pattern of CNAs that equipped them to survive and grow in the primary tumor, face novel (strong) negative selective pressure (in the bloodstream and in the new organ colonization), which may select the CNA pattern (karyotype) for the new organ colonization. Therefore, the authors compared metastasis and primary tumor samples and observed that, even after metastatization, tumor cells maintained their “core” karyotype but, within metastases, there were also small cell subpopulations (cellular subclones) characterized by specific CNA patterns. Space- and time- resolved analyses revealed that, despite maintaining a stable core karyotype, the acquisition of sets of additional CNAs varied remarkably across the different patients and samples analyzed. However, overall, differences were more evident between primary vs metastatic samples (possibly to survive in the new organ) than among metastases, and between different sampling time points than at the same time point. Interestingly, treatment did not have a significant effect on the CNA pattern, suggesting that survival to treatment is more likely to be related to other mechanisms, such as gene expression-related cell plasticity.

----- Conclusions.-----

The tumor is a cell population (at high fitness) shaped by positive and negative selection forces from the tumor microenvironment during progression, which determine survival and proliferation of a cancer cell/cell subpopulation with a given set of genomic alterations. Therapy does not significantly impact on the selection of the cancer cell subpopulation (clone) with specific genomic features, indicating that cancer cell survival during treatment may be more likely related to other mechanisms, such as gene expression-related cell plasticity.

Reference: Negative Selection Maintains Grossly Altered but Broadly Stable Karyotypes in Metastatic Colorectal Cancer. William C H Cross #, Salpie Nowinski #, George D Cresswell #, Maximilian Mossner #, Abhirup Banerjee #, Bingxin Lu #, Marc J Williams, Georgios Vlachogiannis, Laura J Gay, Ann-Marie Baker, Christopher Kimberley, Frederick J H Whiting, Hayley L Belnoue-Davis, Pierre Martinez, Maria Traki, Viola Walther, Kane Smith, Javier Fernandez-Mateos, Erika Yara-Romero, Erica A Oliveira, Salvatore Milite, Giulio Caravagna, Chela T James, George Elia, Alison Berner, Chang-Ho Ryan Choi, Pradeep Ramagiri, Ritika Chauhan, Nik Matthews, Jamie Murphy, Anthony Antoniou, Susan K Clark, Miriam Mitchison, Jo-Anne Chin Aleong, Enric Domingo, Inmaculada Spiteri, Stuart A C McDonald, Darryl Shibata, Miangela M Laclé, Lai Mun Wang, Morgan Moorghen, Ian P M Tomlinson, Marco Novelli, Marnix Jansen, Alan Watson, Nicola Valeri, Nicholas A Wright, John A Bridgewater, Manuel Rodriguez-Justo, Chris P Barnes, Hemant M Kocher, Simon J Leedham, Andrea Sottoriva, Trevor A Graham. Cancer Discov 2026. doi: 10.1158/2159-8290.CD-24-0813.

What's new in science?

Data and specimen sharing – good or bad? The importance of the context.

In the past decades, cancer patient outcome has remarkably improved. Research made it possible. The joint work of researchers in the public and private sector, in profit and non-profit institutions, sharing the common goal of improving patient health through the in-depth understanding of tumor biology and the mechanisms underlying drug efficacy, along with the bidirectional and structured, regulated sharing of data and specimens, led to remarkable advances in cancer research.

In US, regulated data sharing has started in the early 2000s when researchers were required to share data collected in the frame of research projects involving government funding. Later on, other funding agencies requested applicants to include a “data sharing” section when submitting a grant application. European bodies such as EMA have started publishing the clinical data submitted by the pharmaceutical companies to support their regulatory applications, in order to avoid duplication of clinical trials, foster innovation, allowing for re-assessment of clinical data by academics and researchers, as well as to build public trust and confidence in EMA's scientific and decision-making processes¹.

Similarly, concerning patients' specimens often collected within clinical trials for diagnostic purposes, academic and non-academic research institutions are encouraged to ensure responsible custody of specimens (and associated data) on behalf of the study participants, while ensuring access to procedures and samples in compliance with participants' will.

Despite some difficulties in the actual implementation of data and specimen sharing practices, mainly regarding ownership –of data and samples– by the clinical study sponsor, several stories exist documenting the successful collaboration –within and between private sector and academia– in clinical research, where proper data and sample sharing in the frame of large collaborative groups has allowed to gather critical scientific/clinical information, to advance translational and clinical research, to define novel therapeutic strategies and new medical devices, for the identification of biomarkers informing treatment choices and refining clinical trial design.

In preclinical research, data sharing has become the routine, through the development of publicly available databases of harmonized omic data and clinical trial information. In the clinical context, how to overcome existing obstacles and maximize the clinical output of current translational/clinical research effort, by properly valuing patients' contribution (in terms of data and specimens) and accelerate scientific advance? In other words, how can all the stakeholders work together for clinical research? A series of practical guidelines have been recently proposed, which include ensuring that clinical trials (even when industry-initiated) have co-leadership of pharma, academics, patients and regulatory experts, empowering all in the study design, in order to guarantee the interests of study participants and future patients, and maximize the use of both samples and data. In this regard, a plan for data (and specimen) sharing should be cooperatively drafted at the time of trial design. Increasing data sharing would enable to reach the statistical significance that may be lost in individual studies (*i.*). The greater involvement of patients in clinical study design may contribute to maximize data sharing; indeed, patients could actively request data sharing for further secondary studies, while maintaining compliance with laws and regulations, and ensuring privacy (*ii.*). Post-approval sharing of harmonized data requested as a regulatory requirement for the approval of a new drug/medical device may allow for further analyses in patient subgroups, for instance in biomarker-based defined patient subgroups with greater treatment-derived benefits, which could expedite drug approval and reimbursement (*iii.*). Standardization of specimen collection and procedures (prospectively stated at the moment of trial design), as well as data harmonization, are also needed for effective sharing (*iv.*). Disclosure/sharing of (both positive and negative) clinical trial results, as it routinely occurs for raw data from preclinical studies, would allow also to maximize patients' benefits derived from clinical research (*v.*). Finally, in the Artificial Intelligence (AI) era,

data sharing for the training of AI algorithms becomes extremely important to allow for the development of robust tools for the benefits of patients, the healthcare system, and society in general (*vi.*).

Aligning all stakeholders' interests for an effective data/specimen sharing is not an easy task. However, the benefits deriving from that, for the people who in the first place provided their own information and samples, makes this task an ethical duty. An effective collaboration and communication, driven by the common goal of improving patients' health, can certainly lead to establishing the framework required to make this happen.

Reference: Enhancing Clinical Cancer Research Through Sharing of Data and Biospecimens. *Hans Wildiers, Virginie Adam, Seamus O'Reilly, Josephine Van Cauwenberge, Amal Arahmani, Carlos L Arteaga, Philippe L Bedard, Judith Bliss, Panayota Bousis, Etienne Brain, Marc Buyse, Carmela Caballero, David Cameron, Fatima Cardoso, Eva Carrasco, Ana Casas, Boon Chua, Giuseppe Curigliano, Angela DeMichele, Laura Esserman, Giuseppe Floris, Matthew P Goetz, Theodora Goulioti, Benjamin Haibe-Kains, Christine Hodgdon, Michail Ignatiadis, Marleen Kok, Denis Lacombe, Barbro Linderholm, Sherene Loi, Christopher J Lord, Mairead MacKenzie, Julia Maues, Lydie Meheus, Judy Needham, Patrick Neven, Heather Parsons, Martine Piccart, Lajos Pusztai, Evangelia Razis, Shigehira Saji, Eva Schumacher-Wulf, Gabe S Sonke, Tania Spanic, Ian F Tannock, Andrew Tutt, Ander Urruticoechea, Laura van 't Veer, Ines Vaz-Luis, Gustavo Werutsky, Douglas Yee, Khalil Zaman, Christine Desmedt.* JAMA Oncol 2025. doi: 10.1001/jamaoncol.2025.5376.

What's new from IEO researchers?

The Wnt signal from the microenvironment regulating cell division.

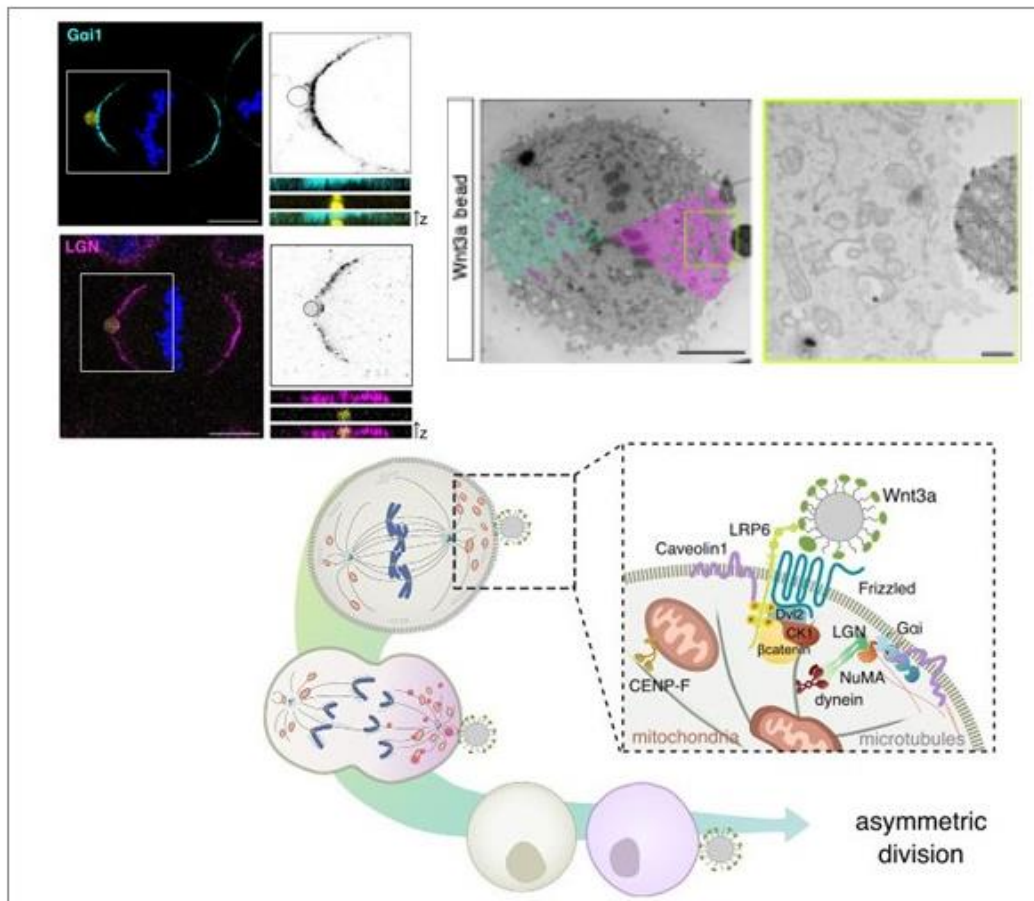


Figure adapted from Eli, Rauso et al., 2025 (an open access [article](#) under the [CC BY](#) license)

Physiologically, stem cell self-renewal occurs by asymmetric division of stem cells, leading to the generation of two daughter cells with different fates: One maintaining stemness traits and another one undergoing differentiation. Asymmetric cell division requires the asymmetric partitioning of intracellular components inside the cell, the specific positioning of the dividing cell in respect to the microenvironment, the right orientation of the mitotic spindle (the critical cellular structure whose assembly and alignment is required for proper cell division). Key extracellular factors in this process are the Wnt proteins. Wnt is secreted in the microenvironment, binds its receptor on stem cells membrane and activates the signaling leading to the establishment of asymmetry/cell polarity. Wnt signaling involves the activation of the Frizzled receptor, LRP6/LRP5 coreceptors, β -catenin stabilization (through the Wnt-inhibited GSK β -dependent β -catenin degradation), expression of Wnt target genes, in parallel to the modulation of cell polarity, cell adhesion and cytoskeleton reorganization. Wnt signaling (specifically, Wnt3a) has also been linked to the orientation of cell division.

In a recent paper by Eli, Rauso et al., the authors, headed by Marina Mapelli –Group leader at the department of experimental oncology of IEO–, dissected the molecular mechanisms underlying Wnt-regulated oriented cell division: Their results revealed that Wnt3a induces spindle orientation by promoting the assembly of the protein complex constituted by NuMA/ β -Catenin/LRP6 coreceptor. This Wnt-induced process relies on

caveolin and the actin-binding protein MACF1, and triggers a local actin rearrangement that sustains oriented cell division. Moreover, they showed that the spatially defined Wnt signals also induce an asymmetric distribution of mitochondria inside the dividing cell, with the ensuing enrichment, upon division, of mitochondria –as well as β -catenin– in one of the daughter cells. By dissecting the molecular players in oriented cell division, the authors demonstrated that oriented cell division results from the integration of two different signals: The one mediating cell adhesion and the one mediating spindle orientation. This involves membrane proteins and components of the cytoskeleton, translating localized chemical cues into different forces, whose balance ensures the correctly oriented cell division.

The definition of this mechanism both in stem cells and in a transformed cancer cell line indicates that the same process may be relevant both in development and in a disease context.

“Collectively –says Marina Mapelli, last author of the study– our findings support a conceptual frameshift in the principles governing Wnt-mediated self-renewal in vertebrate systems, whereby local niche signals orchestrate asymmetric distribution of cellular components, including mitochondria, to promote asymmetry in daughter cell fate and metabolic potential. Given that Wnt signaling is highly deregulated in most intestinal cancers, the connection between Wnt activation, metabolism and cell identity might eventually pave the way to the development of new therapeutic strategies.”

-----TELL ME MORE!-----

Localized Wnt signals and molecular factors for spindle orientation. By using HeLa cells (a patient-derived cell line of cervical cancer) and Wnt-bound microbeads, the authors found that localized Wnt signals (namely, Wnt3a niches artificially generated by immobilizing Wnt3a on the microbeads) were sufficient for asymmetric oriented cell division. Specifically, this occurred through the local rearrangement of actin cytoskeleton and the ensuing assembly of the spindle. The forces modulating spindle orientation acted together with adhesion forces, modulating the final orientation of the spindle. Molecularly, spindle orientation in response to localized Wnt3a

“by dissecting the molecular players in oriented cell division, the authors demonstrated that oriented cell division results from the integration of two different signals: The one mediating cell adhesion and the one mediating spindle orientation. This involves membrane proteins and components of the cytoskeleton, translating localized chemical cues into different forces, whose balance ensures the correctly oriented cell division”

signals and the alignment to the substrate required other players such as LRP6, β -catenin, Dvl1 and Dvl2. Wnt-regulated gene expression, instead, did not affect the oriented cell division. Wnt-induced spindle orientation was also regulated by the NuMA/LGN/Gai complex. Indeed, these proteins were enriched and localized at the contact site between the Wnt-microbeads and the cell membrane and, when these proteins were lost, Wnt-induced spindle orientation was disrupted. NuMA complex-modulated spindle orientation occurred through the recruitment of the microtubule motors dynein/dynactin at locally restricted areas (that is, the Wnt-microbead/cell

contact sites); this was crucial for the generation of the pulling forces correctly positioning/orienting the spindle.

Proteomic analyses identify other players in spindle orientation. After establishing a novel protocol for the specific proteomic analysis of Wnt-proximal cell areas (to identify membrane and cytoplasmic proteome components locally recruited at the site of Wnt3a activation), the authors found that other proteins were recruited at the cell membrane by

the localized Wnt signals, together with the NuMA/LGN/Gai complex. Indeed, a number of proteins appeared enriched at the Wnt-microbead/cell contact sites, such as the kinases CK1 α and CK2 α , β -catenin, caveolins, R-spondin-3, the PP2A phosphatase regulator PPP2R1A, the transmembrane proteoglycan syndecan-1, Gai1 and Gai3, NuMA, and the microtubule depolymerase Kif2A, the myosin-1 family members myosin1B, myosin1C and MACF1. These proteins were involved in cell processes such as mitotic progression, actin organization, membrane dynamics. Notably, these analyses showed that also RNA-binding proteins and mitochondrial components were recruited at the Wnt3a-contact site. Although these proteins did not contribute to the orientation of cell division, their enrichment suggests that they may be asymmetrically

partitioned and contribute to daughter cell fate asymmetry.

Wnt signal transduction at the cell membrane.

Further investigation of the other factors involved in transducing the Wnt-initiated signal to spindle positioning revealed the Wnt-induced recruitment of caveolin, in turn ensuring Wnt-dependent spindle orientation –through NuMA/LGN/Gai/dynein/dynactin–, the myosin-linked regulation of both actin and microtubule cytoskeleton –strengthening cell adhesion–, the involvement of the MACF1 protein (which was found, indeed, enriched at Wnt/cell contact sites), and the Wnt-activated CK1 α kinase.

Asymmetric partitioning of mitochondria.

Importantly, the localized Wnt3a signals polarized mitochondria distribution, resulting in the enrichment of mitochondria at the Wnt-microbead/cell contact sites and, upon cell division,

in the daughter cell, through the transport of mitochondria on microtubules, promoted by the protein CENP-F. Wnt3a-induced polarization of mitochondria in epithelial cells represents a major finding of this study.

Wnt3a signals-induced molecular mechanisms in asymmetric division of mouse embryonic stem cells.

The authors showed that, similar to what they observed in HeLa cells, Wnt-induced cell polarization and asymmetric division –with a Wnt proximal (β -catenin enriched) pluripotent cell and a Wnt distal cell undergoing differentiation– also occurred in mouse embryonic stem cells (mESCs). Likewise, mitochondrial density was modulated by Wnt signals, becoming enriched at Wnt-microbead/cell contact sites. LRP6 also appeared crucially involved in the asymmetric distribution of mitochondria, as LRP6 depletion interfered with asymmetric distribution of mitochondria.

Reference: Localized Wnt-signaling promotes asymmetric NuMA-dependent oriented divisions and unequal apportioning of mitochondria. *Susanna Eli, Greta Rauso, Paola Ghezzi, James L. A. Szczerkowski, Michela Bruzzi, Francesca Rizzelli, Fabiola Iommazzo, Alessia Loffreda, Francesco Castagna, Federico Donà, Chiara Gaddoni, Ambra Dondi, Mattia Marenda, Simona Rodighiero, Pierre Tournier, Zeno Lavagnino, Dario Parazzoli, Nils C. Gauthier, Simone Tamburri, Diego Pasini, Shukry James Habib & Marina Mapelli.* Nature communications 2025. doi: 10.1038/s41467-025-65775-z.

What's new from IEO researchers?

Defining a healthy gut microbiome through the evaluation of nutrition and common health-related markers.

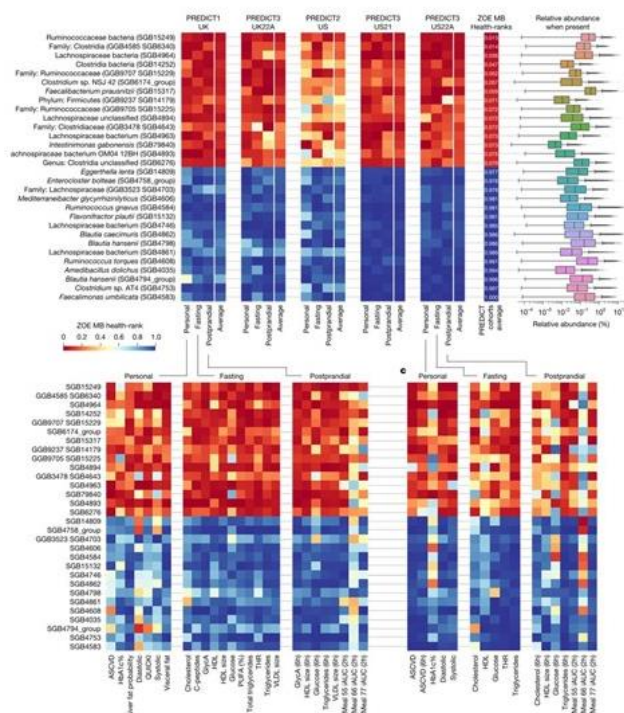


Image from Asnicar et al., 2025 (an open access [article](#) under the [CC BY](#) license)

Numerous studies have demonstrated the link between human health and the gut microbiome composition. A healthy dietary regimen, with high consumption of plant-based food and low consumption of processed food, is commonly advised to reduce the risk of chronic diseases, and the gut microbiota represents a link and underlying mechanistic reason for this recommendation. Moreover, previous studies found that the gut microbiome profile distinguishes omnivore, vegetarian and vegan dietary regimens, and highlighted that while the omnivore microbiome (strongly driven by a red meat-containing diet) negatively correlates with human health –in particular, cardiometabolic health–, vegan diet-related microbiome profile positively correlates with cardiometabolic health. Being the diet a modifiable factor, both for prevention and treatment, research efforts have been dedicated to the understanding of the link between gut microbiome, nutrition and health, showing that a change in dietary habits can modify the gut microbiome composition, in turn influencing human health. In this scenario, “precision

nutrition” aims at identifying the specific factors that modulate the interaction between diet and host health in each human being. However, this is complicated by the high inter-individual variability of the gut microbiome, which is shaped by a number of factors. IEO researchers previously investigated the link between gut microbiome and coffee consumption, showing that this is characterized by the presence of a specific gut bacterial species – *Lawsonibacter asaccharolyticus* –, demonstrating the causal link between coffee and this gut microorganism (as coffee stimulated in vitro bacterial growth), unraveling the

IEO researchers previously exploited metagenomic approaches to analyze, at high resolution, the microbiome species involved in the process of benign-to-malignant transformation, demonstrating that the presence of typically oral species in the gut are associated with colorectal cancer, and that species-level analyses of the gut microbiome can distinguish quite accurately cancer patients from healthy subjects, as well as the different tumor stages. Moreover, they previously demonstrated that the abundance of a specific eukaryotic gut microorganism –*Blastocystis*– is related to the diet, is anticorrelated with body weight, increases after dietary intervention improving diet quality, and is positively correlated with cardiometabolic health, strongly suggesting a potentially active and beneficial role of *Blastocystis* in human health. They previously showed a pivotal role of *Blastocystis* in this scenario, especially in the context of cardiometabolic health, and data suggest an enrichment in healthy vs disease individuals in several pathological conditions, including colorectal cancer, suggesting a favorable role of specific gut microorganisms, such as *Blastocystis*, in human health.

metabolites enriched in coffee consumers, and providing a link between a specific gut microorganism and a specific food item.

In a paper recently published in *Nature*, researchers, coordinated by Nicola Segata –Group leader at the dept of experimental oncology of IEO and professor at the University of Trento– leveraged the knowledge on the link between healthy diet and human health on one side (that is, a healthy diet is linked to human health), and the link between diet and gut microbiome, revealing the existence of a direct and actionable nutrition-microbiome-health axis, and the gut microbiome species correlated with a healthy diet and human health. Amid the numerous hurdles in defining the composition of a healthy microbiome, by approaching the problem from a different perspective, the authors asked “what are the gut microbiome species that correlate with human health, such as a healthy diet or markers of human health?”. With this approach, by analyzing metagenomic data of around 34.000 people –thus overcoming issues linked to the high variability of the gut microbiome– paired with dietary data and health markers (such as biochemical and anthropometric data), they ranked the (top 50) microbiome species most strongly correlating with human health, in a dataset that, due to its heterogeneity, can be easily generalizable, not only in geographical terms (although it refers anyway to a western lifestyle), but also to different pathological conditions. Moreover, abundance of these species proved to be modifiable through dietary changes, making it an interesting target for therapeutic intervention, with predictable results.”

“amid the numerous hurdles in defining the composition of a healthy microbiome, by approaching the problem from a different perspective, the authors asked ‘what are the gut microbiome species that correlate with human health, such as a healthy diet or markers of human health?’ ”

----- TELL ME MORE! -----

The authors assembled the largest dataset containing metagenomic gut microbiome data along with dietary information and anthropometric measures of over 34.000 US and UK individuals. Their analysis revealed a strong association between microbiome composition, biochemical markers of health (e.g. blood glucose levels, triglycerides,...), anthropometric factors (e.g. body mass index, BMI), and nutrition (e.g. healthy eating habits such as that measured based on the diversity of plant-based foods in the diet).

Next, they analyzed in greater detail the specific microbiome species associated with either **health markers** or a **healthy diet**, and ranked the microbiome species most strongly correlating (or anticorrelating) with health markers or markers of a healthy diet. Interestingly, the species associated (that is, at the top of the ranking) with health markers were also associated with healthy diet markers. Since the BMI is an anthropometric factor frequently used to identify patients with higher risk of disease, they also analyzed the correlation between microbiome species and **BMI**, showing

that the microbiome species highly correlated with good human health anticorrelated with BMI and *viceversa*.

Notably, the identified species, associated with *i.* health markers, *ii.* healthy BMI, *iii.* healthy diet, were differentially abundant in healthy control cohorts vs their matched disease cohorts; namely, the species most strongly correlated with health were more abundant in controls than in disease subjects, and *viceversa*.

Interestingly, the top ranked microbiome species could be also used to distinguish the single control individuals from the diseased individuals.

Finally, by exploiting data of controlled dietary intervention clinical trials, they investigated how diet changes affected abundance of the ranked microbiome species, demonstrating that some species were significantly impacted by the dietary intervention aimed at improving diet by either prebiotic administration or personalized dietary program: Some favorable species increased while some unfavorable species decreased after the same intervention.

Reference: Gut micro-organisms associated with health, nutrition and dietary interventions. Francesco Asnicar, Paolo Manghi, Gloria Fackelmann, Gabriel Baldanzi, Elco Bakker, Liviana Ricci, Gianmarco Piccinno, Elisa Piperni, Katarina Mladenovic, Federica Amati, Alberto Arrè, Sajaysurya Ganesh, Francesca Giordano, Richard Davies, Jonathan Wolf, Kate M Bermingham, Sarah E Berry #, Tim D Spector #, Nicola Segata #. *Nature* 2025. doi: 10.1038/s41586-025-09854-7.

What's new from IEO researchers?

Fecal microbiota transplantation in clinical trial: renal cancer, lung cancer and melanoma.

Despite the remarkable success of immune checkpoint inhibitor (ICI)-based immunotherapy, some patients experience disease progression; in that case, alternative therapeutic options are limited. Increasing scientific evidence indicates that the gut microbiome may influence ICI efficacy. For instance, antibiotics use, by disrupting the gut microbiome, has been shown to reduce ICI efficacy; specific microbiome species have been associated with therapy response, with preclinical studies showing the effects of fecal microbiota transplantation (FMT) on ICI response, and clinical studies showing benefits of FMT in ICI-resistant patients (especially in melanoma), with no serious adverse events.

In the frame of the phase II (randomized, placebo-controlled) **TACITO** clinical study, whose results were recently published in *Nature Medicine*, researchers, including Nicola Segata –Group leader at the department of experimental oncology of IEO and full professor at the University of Trento– who coordinated the microbiome analysis, evaluated efficacy of FMT (from complete responders) in improving response to the combination treatment with the anti-PD1 pembrolizumab and the VEGFR inhibitor axitinib in patient with metastatic renal cell carcinoma (mRCC).

From a clinical point of view, the study showed that FMT (from complete responders) was safe –in agreement with findings of previous studies–, and improved efficacy of therapy, increasing the objective response rate (ORR), which was 52% in the FMT group and 32% in the placebo group, and progression-free survival (PFS), which was 24 months in the FMT group and 9 months in the placebo group. Treatment efficacy was especially significant in the intermediate/poor prognosis group, in which immune system-regulating therapies have usually stronger effects.

From a microbiological perspective, the study highlighted that the acquisition, after FMT, of some “beneficial” microbial species, such as *Blautia wexlerae* (a short-chain fatty acids (SCFAs)-producing bacterium, already associated with response to neoadjuvant chemotherapy in patients with rectal cancer, and anti-inflammatory effects), was associated with better clinical outcome. Furthermore, the

loss of “detrimental” species, such as *Akkermansia massiliensis* (which is different from *Akkermansia muciniphila* that has been previously associated with response to ICI) correlated with better clinical outcome. Interestingly, *Akkermansia* strains are not easily replaced by other *Akkermansia* strains, suggesting that patients with adequate abundance of *A. muciniphila* before FMT could have not been colonized by the detrimental *A. massiliensis*, and the combination of beneficial (*A. muciniphila* and *B. wexlerae*) strains along with the loss of a detrimental strain (*A. massiliensis*) may contribute to the clinical success of FMT.



Nicola Segata

In the frame of a different phase II, multicenter, clinical trial –FMT-LUMINate–, whose results were published in the same issue of Nature Medicine, researchers (including Nicola Segata) evaluated safety and efficacy of FMT (from healthy donors) in improving efficacy of ICI-based immunotherapy in the treatment of lung cancer (with anti-PD1) and melanoma (with anti-PD1 and anti-CTLA4).

From a clinical perspective, the FMT-LUMINate results demonstrated the efficacy of FMT in increasing response to two different ICI, in two different tumor types, reporting an ORR of 80% in lung cancer –higher than ever demonstrated (usually ranging between 39 and 46%)–, and 75% ORR in melanoma (commonly ranging between 50 and 58% with ipilimumab and nivolumab).

Mechanistically, their results suggested that clinical efficacy was linked to the depletion of specific deleterious bacteria rather than engraftment of specific donor-derived species, which was parallel to systemic changes such as the reduced levels of some metabolites of the tryptophan pathway (such as quinolinic acid and kynurenic acid) in the blood, and changes at the immune system level, with increased numbers of cytotoxic CD8+ T cells and decreased number of regulatory T cells (Tregs), as well as increased levels of pro-inflammatory molecules, highlighting the greater immune response in post-FMT ICI-treated responders. Interestingly, the effects on circulating molecules was the result of depletion of distinct microbial species in lung cancer and melanoma patients, converging on the same biochemical processes. In the TACITO trial as well, the depletion of some detrimental gut microbial species after FMT (only in the FMT group and not in the placebo group) correlated with clinical outcome. Similar results were obtained re-analyzing data from other previously published trials, underlining the validity of this observation across tumor types (and geographic regions – Asia, Europe, North America). In addition, through preclinical *in vivo* experiments, researchers showed the onset of ICI resistance upon introduction in recipient animals of the detrimental species depleted in post-FMT responders, providing further mechanistic evidence of the harmful effect of these bacterial species on ICI-FMT clinical efficacy.

Although some toxicity (observed in the FMT-LUMINate trial), associated with the presence of *Prevotella*, observed upon the administration of both anti-PD1 and anti-CTLA4 in melanoma patients requires attention, both these studies support the efficacy of FMT in the context of ICI-based immunotherapy, in different tumor types, and provide important mechanistic pieces of information to explain the processes underlying the observed clinical results.

----- TELL ME MORE! -----

The TACITO trial.

The study enrolled 50 patients with metastatic RCC. All patients received pembrolizumab and axitinib (P+A) and were randomly assigned to receive FMT from renal cancer patients who had a complete response to ICI therapy (complete responders). Efficacy was evaluated in terms of number of patients free of disease at 12 months, median progression-free survival (PFS), objective response rate (ORR). FMT-induced microbiome changes and safety were evaluated as well.

Efficacy. Although the study suggests that the effects may be more evident at longer time points (that is, over 12 months), the results show an improved response to ICI in FMT-treated patients (FMT group) as compared to the control group, receiving P+A and a placebo instead of FMT (placebo group). Median PFS was improved in patients receiving FMT (being 24 months) vs those in the placebo group (9 month). Cancer-related deaths were more frequent in the placebo group (50%) vs the FMT group (26%). Overall survival was

longer (though not significantly) in the FMT group (41 months) vs placebo (28 months). The number of patients who did not progress or die at the data cut off were more in the FMT group than in the placebo (71% vs 38%). ORR was 52% in the FMT vs 32% in the placebo. Complete response was observed in 2 patients of the FMT group and in none of the placebo group.

Post-hoc analysis. A *post-hoc* analysis (that is, not originally included in the study design) evaluated efficacy in those patient subgroups in which P+A treatment was usually more effective (namely, in patients with poor or intermediate prognosis) vs those with good prognosis (in which P+A was usually less effective). In the intermediate/poor prognosis patient subgroup, differences in the FMT vs placebo groups were more evident, with median PFS being 18.8 months in the FMT group vs 5.5 in the placebo, 12-month PFS being 63% in the FMT vs 27% in the placebo, and OS being 41 months in the FMT vs 21.5 months in the placebo. ORR was

50% in the FMT vs 8% (1 patient) in the placebo group.

Safety. The treatment was overall well tolerated, and adverse events were rare. No treatment-related deaths were observed and no infection upon FMT. However, adverse events related to P+A were more frequent (28%) in the FMT group than in the placebo group (16%).

Microbiome changes. Stool samples were collected and analyzed by metagenomic approaches, at high resolution, at different time points during the study. Before FMT, donors and recipients had similar microbiomes, in terms of overall diversity (that is, number of different species), but the specific microbiome composition (namely the different types of microorganisms) of the donors was different, and especially enriched in *Bifidobacterium adolescentis* species, *Akkermansia massiliensis*, and lacking *Akkermansia muciniphila* (which was instead abundant in recipients). However, after 4-week treatment, the diversity (in terms of number of different microbiota species in the gut, “richness”) increased in the FMT group (while no increase was seen in the placebo group, confirming that FMT was microbiologically successful). Moreover, many species were not present at all before FMT but appeared after FMT. Importantly, after FMT some species disappeared. Overall, FMT resulted in a remodelling of the microbiome favoring clinical response.

The number of donor strains engrafting the gut's recipients was not related to the clinical outcome. However, a close inspection of the specific strains acquired or lost after FMT revealed a correlation between the acquisition of a particular strain (*Blautia wexlerae*) and longer PFS, and acquisition of a yet-to-be-described species (SGB14845) of the *Oscillospiraceae* family inversely correlated with PFS. Importantly, the loss of *Ruminococcus bromii* was associated with a shortened PFS, while loss of *Escherichia coli* strain or an uncharacterized *Clostridium* species was linked to longer PFS.

The FMT-LUMINate trial.

The trial enrolled 20 lung cancer patients (non-small cell lung cancer, NSCLC, if they had no actionable mutations) and 20 melanoma patients (irrespective of BRAF-V600 mutation). NSCLC patients were treated with FMT and ICI (anti-PD1); melanoma patients were treated with FMT and ICI (anti-PD1 and anti-CTLA4). The FMT source were multiple (10 for lung cancer, 6 for melanoma)

healthy donors (differently from the TACITO trial in which donors were complete responders). Almost all patients were in stage IV.

Efficacy. FMT efficacy in increasing ICI response was calculated in terms of ORR, PFS at 1 year, OS at 1 year, disease control and duration of response. In NSCLC, ORR was 80% (as compared to 39-46% usually observed with ICI treatment), disease control rate was 95%, PFS and OS at 1 year were 65% and 100% respectively. In melanoma, ORR was 75% (as compared to the 50-58% commonly observed in ipilimumab- and nivolumab- treated patients), disease control rate was 75%, PFS and OS at 1 year were 58% and 79% respectively. Overall, the combination of FMT and ICI showed clinical efficacy in both NSCLC and melanoma.

Safety. Adverse events induced by FMT administration (occurring prior to ICI therapy) were minimal (35% of patients manifested grade 1 adverse events); however, adverse events (although no grade 3 or higher) were observed in 85% of FMT+ICI treated NSCLC patients. In melanoma patients, FMT+ICI caused adverse events in 95% of the patients, with 60% of them experiencing grade 3 and one patient manifesting grade 4 adverse events. 70% of melanoma patients discontinued treatment due to toxicity. Anyway, FMT+ICI treatment was considered safe by an external committee, with adverse events deemed in line with known ICI toxicity profile (although FMT may have caused an earlier onset of adverse events as compared to the usual ICI-only treatment).

Microbiome changes. The majority of patients experiencing more severe adverse events received microbiome from the same donor, which was enriched in specific species (including *Prevotella* species). However, the same microbiome did not induce severe adverse events neither in previous monotherapy treated patients (anti-PD1 only, no anti-CTLA4), nor in lung cancer patients of this study. Yet, these data underline the importance of donor selection.

Despite the donor effect on toxicity, no donor effect was observed in terms of efficacy. Nevertheless, when microbiome changes were analyzed in detail in relation to clinical

Alpha (α) diversity measures the number of species (richness) and their relative abundances (evenness). **Beta** (β) diversity measures the differences in microbial composition between samples.

outcome, the data showed that while pre-FMT microbiome diversity –both alpha and beta– was not different between responders and non-responders, post-FMT beta diversity (but not alpha diversity) was differently associated with responders and non-responders, both in melanoma and NSCLC patients: The shifts in microbiota composition correlated with response to therapy.

Overall, after FMT the microbiome of the recipient became similar to that of the donor, with an overall similar number of species engrafting after FMT in responders and non-responders. However, analyses at the level of the single species showed an enrichment of beneficial bacteria in responders (such as *Faecalibacterium prausnitzii*, *Gemmiger formicilis* and *Akkermansia muciniphila*, in lung cancer patients, *Bacteroides eggertii*, *Bacteroides faecis* and *Alistipes senegalensis* in melanoma patients, and species previously linked to ICI response), and enrichment of deleterious bacterial species in non-responders (such as *Streptococcus vestibularis* and *Fusobacterium nucleatum*).

Importantly, responders showed a larger loss (after vs before FMT) of some species as compared to non-responders, both in lung cancer and melanoma patients. The most depleted species

were known to be detrimental. The findings obtained by metagenomic analyses were validated by other approaches (qPCR). Moreover, to further strengthen the correlation observed between loss of some bacterial species and clinical outcome, culturomics experiments were performed: Counting the number of species lost (that is, impossible to be cultured) from post- vs pre- FMT stool samples from responders and non-responders confirmed indeed a more evident loss of detrimental species in responders than in non-responders. Moreover, new analyses of published metagenomic data from FMT experiments further confirmed these findings, suggesting that the depletion of pre-existing species during FMT-induced microbiome remodeling may be more critical for the therapeutic response than the engraftment of specific donor-derived species. These data were further validated in preclinical *in vivo* models: When recipient animals, that already received favorable species, were administered the detrimental species isolated from responders (which in patients were lost after FMT, thus basically those that, when lost, conferred response to ICI), the response to ICI was impaired, confirming that detrimental species loss was required for therapy response.

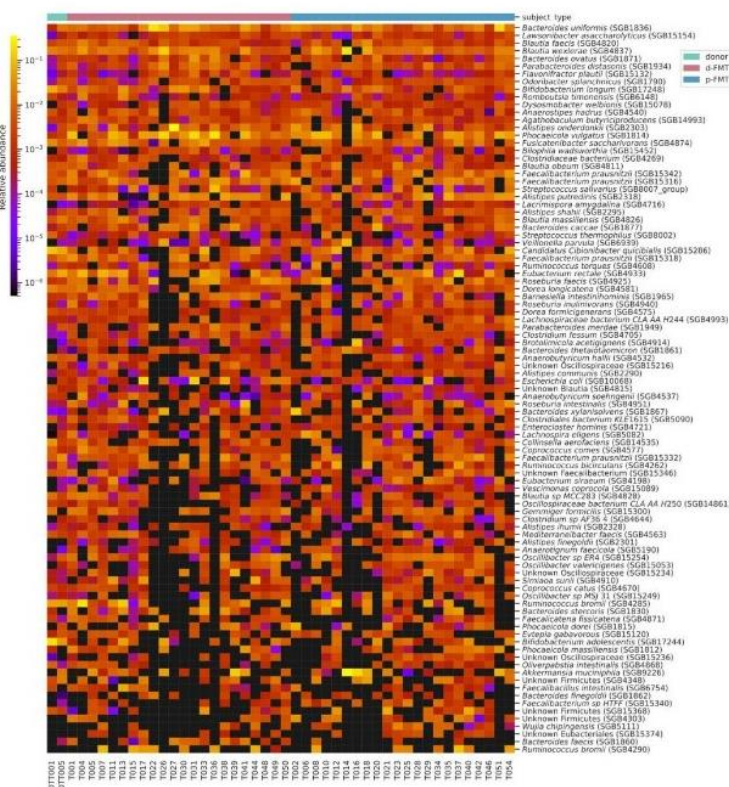


Image from Porcari, Ciccarese, Heidrich et al., *Nature Medicine* 2026
(an open access [article](#) under the [CC BY NC ND](#) license)

Mechanistic study. To determine how the loss of detrimental bacterial species observed in responders after FMT influence the response to therapy, the authors evaluated induced systemic changes by metabonomic analyses in blood samples. They found in non-responders (which did not show bacterial loss) an increased amount of metabolites of the tryptophan pathway (that is, quinolinic acid and kynurenine), which have been previously associated with ICI resistance. Metabonomic analyses of stool samples showed instead a decrease of these metabolites in responders; this was the result of the loss of distinct species in lung cancer and in melanoma patients (meaning that, different bacterial species loss, as evidenced by their metagenomic analyses, converged on the tryptophan pathway). Moreover, proteomic analyses revealed a higher proportion of circulating inflammatory markers after FMT in responders. These patients

also showed changes at the level of immune system, with enrichment of cytotoxic CD8 T cells and reduction of Tregs, suggesting that the persistence of deleterious species may sustain an

immunosuppressive metabolic and systemic immune environment that compromises ICI response.

References: 1) Fecal microbiota transplantation plus pembrolizumab and axitinib in metastatic renal cell carcinoma: the randomized phase 2 TACITO trial. Serena Porcari#, Chiara Ciccarese#, Vitor Heidrich#, Debora Rondinella, Gianluca Quaranta, Andrea Severino, Daniela Arduini, Sebastiano Buti, Giuseppe Fornarini, Francesca Primi, Luciano Stumbo, Diana Giannarelli, Giulia Claire Giudice, Alessandra Damassi, Julio Rodrigo Giron Berríos, Michal Punčochář, Thomas B Barbazuk, Gianmarco Piccinno, Federica Pinto, Federica Armanini, Francesco Asnicar, Giovanni Schinzari, Lisa Derosa, Guido Kroemer, Maurizio Sanguinetti, Luca Masucci, Antonio Gasbarrini, Giampaolo Tortora, Giovanni Cammarota, Laurence Zitvogel, Nicola Segata#, Roberto Iacovelli#, Gianluca Ianiro#. *Nat Med* 2026. doi: 10.1038/s41591-025-04189-2. **2)** Fecal microbiota transplantation plus immunotherapy in non-small cell lung cancer and melanoma: the phase 2 FMT-LUMINate trial. Sreya Duttagupta#, Meriem Messaoudene#, Sebastian Hunter, Antoine Desilets, Rahima Jamal, Catalin Mihalciuiu, Wiam Belkaid, Nicolas Marcoux, Marine Fidelle, Deborah Suissa, Mayra Ponce, Mallia Geiger, Julie Malo, Gianmarco Piccinno, Michal Punčochář, Alysé Filin, Vitor Heidrich, Diana Rusu, Babacar Mbaye, Sylvere Durand, Imen Ben Aissa, Vadim Puller, Raynald de Lahondès, Normand Blais, Mustapha Tehfe, Scott Owen, Karl Bélanger, Seema Nair Parvathy, Benjamin Shieh, Jacques Raphael, John Lenehan, Daniel Breadner, Jeffrey Rothenstein, Nicholas Rozza, Jade Maillou, Somayeh Nili, Diogjena Katerina Prifti, Federica Pinto, Federica Armanini, Seunghee Kim-Schulze, Thomas U Marron, Guido Kroemer, Lisa Derosa, Laurence Zitvogel, Michael Silverman, Nicola Segata, Saman Maleki Vareki, Bertrand Routy, Arielle Elkrief. *Nat Med* 2026. doi: 10.1038/s41591-025-04186-5.

What's new from IEO researchers?

A new drug combination against aggressive lymphoma? Results of preclinical studies.

Diffuse large B-cell lymphoma (DLBCL) is a group of B cell malignancies, which includes Double hit lymphoma (DHL, characterized by chromosome rearrangements involving Myc and BCL2 genes) and double-expressor lymphoma (DEL, characterized by Myc and BCL2 mutations without chromosome rearrangements). Both tumors are highly aggressive and lack effective treatment.

Myc overexpression makes cancer cells vulnerable to specific drugs inhibiting mitochondrial processes: Tigecycline (inhibiting mitochondrial ribosomes) and IACS-010759 (IACS, inhibiting mitochondrial electron chain complex). Moreover, combining either IACS or tigecycline with venetoclax (a specific BCL2 inhibitor) displayed strong antitumor effects in preclinical tumor models.

Previous studies by Amati's team revealed the mechanisms underlying IACS antitumor efficacy in Myc-overexpressing cells, involving cell oxidation (generation of reactive oxygen species, ROS). These results suggest that pharmacologically

exacerbating oxidative stress in these cells that, due to Myc overexpression, already have a higher basal oxidation level as compared to healthy cells, may contribute to increase cancer cell death, hence enhancing the antitumor effects of these drugs. Indeed, IEO researchers previously showed that the antitumor efficacy of IACS can be further potentiated by the combination with other pro-oxidant compounds, such as high doses of vitamin C. However, preclinical and clinical studies revealed a non-negligible toxicity associated with IACS administration.

Leveraging the understanding of the processes involved, gained through the mechanistic studies, can the effects of tygeicline or IACS be further enhanced?

In a recent study, IEO researchers jointly coordinated by Bruno Amati –PI at the dept of experimental oncology of IEO– and Giulio Donati –staff scientist in Amati's group–, exploited the mechanistic understanding of these drugs' antitumor efficacy and focused on a *triple* drug combination: The

administration of venetoclax-tygeicline-vitaminC significantly reduced tumor growth (more effectively than



Amati Lab

“leveraging the understanding of the processes involved, gained through the mechanistic studies, can the effects of tygeicline or IACS be further enhanced?”

the single or double drug treatment), increasing survival, without the toxicity observed under IACS treatment. Moreover, the enhanced efficacy of the triple combination suggests that administering these drugs together may allow to reduce the dosage while maintaining the same efficacy, thus possibly reducing drug-related side effects, overall paving the way to new clinical testing.

TELL ME MORE!

The authors showed, in preclinical *in vitro* models, that combining oxidation-inducing drugs such as IACS or tygecicline along with venetoclax or vitamin C increased their cytotoxic effects. *In vivo*, the triple combination significantly delayed tumor growth. Importantly, antitumor efficacy was also visible when the drugs were administered at lower dosages than those commonly used in double combination.

Since IACS administration has been previously linked to neurotoxicity, researchers focused on

tygecicline, and further testing in *in vivo* preclinical models demonstrated the antitumor effects of the venetoclax-tygecicline-vitaminC combination –as well as the double tygecicline and venetoclax combination–, which resulted in reduced tumor burden and increased survival. Interestingly, while IACS alone induced neurotoxicity, it did not when administered together with vitamin C or venetoclax, suggesting a putative protective effect of the drug combination (which would however require further investigation).

Reference: Combinatorial targeting of MYC/BCL2-associated vulnerabilities in high-grade B-cell lymphoma. *Giulio Donati, Paola Nicoli, Federica Miele, Paola Podini, Giorgia Dina, Angelo Quattrini, Bruno Amati*. Br J Haematol 2025. doi: 10.1111/bjh.70249.

What's new from IEO researchers?

Employing ChatGPT in the medical field – the users' perspective.

In the past decade, Artificial Intelligence (AI) has entered our everyday life. In the biomedical sector as well, AI-based tools have been increasingly employed, for different tasks. ChatGPT is a free, user-friendly chatbot, developed by OpenAI, largely used by the population.

In a recent study by Durosini et al., IEO researchers led by Gabriella Pravettoni –head of the Applied Research Division for Cognitive and Psychological Science at the European Institute of Oncology– investigated people feelings about exploiting this tool to get further information and clarifications after receiving a cancer diagnosis. The goal of this study was to identify potential improvement points, towards the widespread employment of such technology in the healthcare.

While emphasizing the need for healthcare professional consultation, the study acknowledged the added value of the chatbot in providing additional medical information, thus contributing to reassure people, although aspects such as data privacy, security, and compliance with the GDPR, as well as ethical and legal issues (linked to responsibility in case of errors or negative outcome) must be addressed to increase users' trust in the chatbot. Moreover, while underlining the limitations of the chatbot and the need for medical consultation, the study highlighted the useful informative role of chatGPT in the care process.

Finally, from participants' answers emerged the importance of the human interaction between patients and their doctors in the complex, emotionally burdensome, path of cancer patients, from the initial diagnosis and throughout the whole treatment; in this context, the role of the physician cannot be replaced by a chatbot, as refined and accurate it may be.



Gabriella Pravettoni

----- TELL ME MORE! -----

The study involved 74 healthy participants; about 70% of them had a high education level. Participants were invited to read an *ad hoc*-created scenario in which a user inquired ChatGPT to get medical information after receiving a cancer diagnosis. The chat with ChatGPT included further explanation of the medical terms in the clinical report and the possible future steps in the care process. After reading the user-chatGPT chat, the participants were asked about their feelings and potential concerns related to the use of ChatGPT for medical (specifically, oncological) purposes. Then, the authors analyzed the participants' answers: Briefly, if a participant expressed concern

about the reliability of information provided by ChatGPT, they considered (and grouped) his/her feelings as being linked to "distrust"; if a participant expressed anxiety about the possibility of people using ChatGPT excessively, or in the wrong way, they considered his/her feelings as "fear"; if a participant expressed positive emotions such as increased tranquility when receiving additional information and clarifications, they considered his/her feelings as "calmness", and so on.

Both positive and negative emotions were reported by the participants: Fear, distrust and uncertainty, as well as trust and satisfaction related to the usefulness of such tools.

Concerns about the use of ChatGPT for this purpose was mostly related to the impossibility to understand the “chain of thoughts” leading to the chatbot answers (that is, the so-called, yet unresolved “black box issue” contributing to people distrust), as well as privacy issues regarding the personal data provided to the AI chatbot. Moreover, while concern about the reliability of the information collected was expressed (highlighting the need of better understanding the source of the information), the possibility of accessing, through the chatbot, a huge amount of information generated positive feelings. Interestingly, some participants proposed that the use of AI-based tools could help health professionals in decreasing their workload, by reducing the time needed to provide thorough yet understandable information to the patients who, thanks to the chatbot, may already have a basic understanding of some

medical concepts.

Other concerns were expressed in terms of fear of users using ChatGPT “in the wrong way”, such as for self-diagnosis, without medical consultation (although the chatbot clearly encouraged the user in seeking medical advice), and the possibility that these chats may generate anxiety (linked to excessive use and hypochondriacal thoughts). On the other hand, other participants expressed positive thoughts about the usefulness of integrating the information provided by the clinicians.

Finally, despite the importance of further emphasizing that the chatbot cannot replace physicians’ expertise, and medical consultation remains mandatory, participants underlined a number of positive aspects, considering chatbots a useful support tool to be integrated —rather than replaced— into traditional medical consultation.

OpenAI is about to release ChatGPT Health, to respond to the growing use by the population of ChatGPT for health issues as well as address criticalities linked to data privacy and safety, with a tool designed and developed together with clinicians ([ChatGPT Health](#)).

Alex, can you briefly explain 1) what is ChatGPT Health, 2) who are the intended end-users, 3) what are the differences/improvements compared to the current ChatGPT version?

Sure, here is a brief and clear explanation of ChatGPT health (the ChatGPT version dedicated to health):

1) ChatGPT Health is a dedicated experience within ChatGPT designed for health and wellness–related questions, with a specific separation for health data. It allows users to securely connect personal health information such as electronic medical records and data from wellness apps (e.g., Apple Health, MyFitnessPal, etc.), so the AI can use that context to provide more relevant and personalized responses. Health data and conversations in this space are isolated from regular chats and are not used to train the base models.

In simple terms: it’s not just “asking health questions to a chatbot,” but having a privacy-enhanced environment with connections to your personal health data.

2) ChatGPT Health is designed for general users who want to better understand and manage their health and wellbeing, not for doctors or healthcare professionals. It is especially useful for people who want to: *i.* better understand medical test results or lab reports; *ii.* prepare for doctor visits with more informed questions; *iii.* interpret trends from connected apps (activity, diet, sleep, etc.); *iv.* receive practical lifestyle guidance based on their own data; *v.* explore care or insurance options in a more informed way.

Important: it is not intended to provide diagnoses or prescribe treatments, nor to replace a healthcare professional. It is a support and information tool, meant to be used alongside clinicians.

3)

| Aspect | Standard ChatGPT | ChatGPT Health |
|--------------------|---|---|
| Use of health data | Cannot connect medical records or wellness apps | Can securely connect personal health data for more contextual responses |

| | | |
|-------------------------------|--|---|
| Privacy & security | General data handling policies | Full isolation of health data, dedicated encryption, and no use for model training |
| Response context | General, non-personalized health information | Responses based on your personal context (e.g., recent results, app-based trends) |
| Primary goal | Answer general questions (including health-related ones) | Support day-to-day health management, preparation for medical visits, and understanding personal data |
| Clinical input | General model development | Developed with feedback from hundreds of physicians to improve reliability in health-related answers |

In short: ChatGPT Health is more secure, more personalized, and more purpose-built for health use cases than simply asking health questions in standard ChatGPT.

AI made its first steps in the biomedical field years ago, with the machine learning tools applied to data analysis. However, with the increasing diffusion of generative AI tools, natural large language models, and the launch of chatBOTS, that simplified end-users' usage, it effectively entered our lives, representing the technological revolution that holds the potential to drastically change our future, as long as we are able to handle it properly, understand how to exploit it correctly to make it boost our work and provide the additional fuel to grow as intelligent human beings. Similar to what happened in the 90s of the past century, with internet diffusion that drastically changed our lives (and whose value cannot be considered diminished by the wrong use that sometimes has been done with it), allowing access to a huge amount of information that enhanced the potential of those who used it smartly, AI can increase the human potential rather than reduce it, if used correctly and critically, with awareness of its associated limits and risks.

AI entered the health and research field especially as a supportive tool for diagnosis, medical report writing, medical imaging, providing analytical support, but its usage is destined to increase. In a sensitive context such as that of health and research, the growing integration of AI requires an aware usage, enabling to rule rather than being ruled by the technological revolution we are witnessing and we are all part of. The aware use requires knowledge of critical aspects tightly linked to the AI employment, which include ***paying attention to ethical and legal aspects***, as well as the need for ***training*** in this field, and the importance of continuing to ***nurture technical/scientific skills required to be able to evaluate the output provided by the machine***. By keeping an eye on these critical factors, AI can be leveraged to make the best out of it, to potentiate –rather than weaken– natural intelligence.

Although the rapid growth and integration of AI brings with it some risks, linked to the fact that laws regulating its use (especially in delicate contexts such as the sanitary context) or training do not always proceed at the same pace, European (European AI act) and Italian laws are following, regulating several key aspects, including data privacy (GDPR compliance) and safety –intended as prevention and protection from cyberattacks–, evaluation of numerous available AI tools –to ensure the high standards needed for the employment in the clinical setting and adherence to specific requisites when, out of the research setting, are integrated in the clinics–, transparency regarding their usage, the importance of informing the patients in case AI tools are employed in the diagnostic path.

Anyway, it is critical to remember that, despite the integration of these tools, the final decision remains always in the clinician's and researcher's hands, who has the right/duty of supervision, who must maintain his/her critical assessment of the output, and legal responsibility.

Reference: Attitudes toward the use of ChatGPT to seek oncological information: a qualitative study. *Ilaria Durosini, Marianna Agnese Masiero, Milija Strika, Davide Mazzone, Gabriella Pravettoni*. *Front Psychol* 2025. doi: 10.3389/fpsyg.2025.1644323.

What's new from IEO researchers?

The secret code of the histone post-translational modifications – A new computational tool for the decryption.

Histone post-translational modifications (hPTMs) are chemical modifications of DNA-associated histone proteins playing a key role in cell biology, modulating chromatin structure, gene expression and cell processes. hPTMs are commonly studied by mass spectrometry (MS) –which allows for hPTM detection and quantification–, through the exploitation of optimized protocols coupled with specific computational pipelines for data analysis.

“As the language of the histone code continues to expand —explains Tiziana Bonaldi, Group leader at the department of experimental oncology of IEO— our group asked whether the inherently unbiased nature of MS could be exploited more efficiently to systematically detect and profile many more “letters” of this code — often serendipitously observed but rarely explored— by developing a novel bioinformatic framework able to make our discovery more comprehensive, automated, and reliable.”

In a recent study carried out by Alessandro Vai, computational PhD student in Bonaldi's team, in collaboration with Alexey Nesvizhskii (University of Michigan) and Andrea Graziadei (Human Technopole), the researchers report the development of a novel computational tool –HiP-Frag– for the identification of novel, less common and less abundant, hPTMs in MS data. The application of this tool to MS data of breast cancer cell lines and clinical samples enabled to identify novel hPTMs, confirming the utility of the tool.

Having a thorough knowledge of histone PTMs allows to understand the dynamic regulation of gene expression and cell processes, which is crucial to define disease-related alterations. In cancer, histone PTMs are often altered and, indeed, largely explored as prognostic, diagnostic and predictive biomarkers. Lysine acetylation and methylation are the most widely distributed hPTMs and the first to be described. More recently, other less common PTMs have been described (such as K-acylations, glutamine monoamination –like serotonylation and dopamination–, and glycation). However, despite being critically involved in gene regulation, these new and less abundant hPTMs are still poorly explored, mainly due to the lack of adequate analytical tools. HiP-Frag addresses this issue, allowing for the identification of known and new hPTMs in the whole sample proteome.

Notably, the newly identified hPTMs often decorate the same sites already known to be modified by other PTMs such as acetylations and methylations, indicating that they could contribute to fine tune gene expression, equipping cells with the ability to respond to different stimuli with higher precision and accuracy, suggesting their potential key role –when altered– in disease. Although further optimization of sample preparation techniques is mandatory to further strengthen the results collected, as clinically relevant changes may be small,

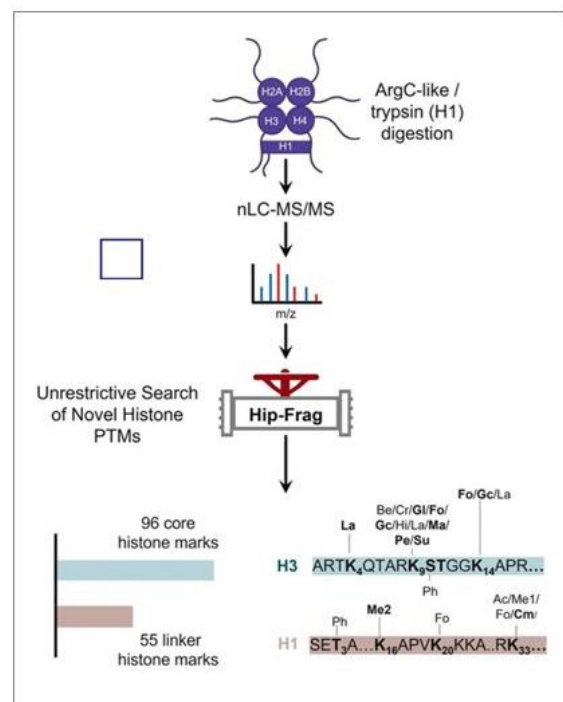


Figure from Vai et al. 2025 (an open access [article](#) under the [CC BY](#) license.)

and thus hard to detect, HiP-Frag represents a useful new tool for research purposes in the discovery setting, allowing to uncover the still under-explored and unknown histone epigenome.

----- TELL ME MORE! -----

How does HiP-Frag work? Briefly, HiP-Frag (Histone PTMs Analysis with FragPipe) combines (in four successive phases) three different approaches to MS data analysis: *i.* the so-called **closed search approach**, *ii.* the so-called **open search** and *iii.* the **detailed mass offset search (DMO)**. These approaches are implemented in FragPipe, a state-of-the-art tool developed by the group of prof. Nesvizhskii.

“In a closed search, —explains Alessandro Vai, first author of the paper— peptide sequences are identified by comparing an experimental mass spectrum with a predefined list of theoretical spectra generated from a protein database. Each possible match is scored based on the similarity between the experimental and theoretical spectra, and the highest-scoring peptide is assigned to the spectrum. However, identifying modified peptides using this approach requires generating theoretical spectra for every possible combination of peptides and modifications. For hypermodified proteins like histones, this number quickly becomes extremely large, making the analysis computationally impractical when considering modifications beyond acetylation and methylation. Open search methods address this limitation by allowing the detection of peptide modifications without explicitly generating theoretical spectra for each peptide, substantially reducing computational demands. This advantage, however, comes at the cost of lower sensitivity. DMO represents a compromise between closed and open searches, enabling the analysis of large sets of potential modifications while maintaining high sensitivity.

HiP-Frag combines these three strategies to maximize hPTM discovery. Closed and open searches are first used to identify non-histone contaminant proteins and chemical artifacts introduced during sample preparation, reducing sources of interference in the data. Accounting for these factors allows DMO to serve as the key step for the sensitive detection of genuine biological modifications.”

The results obtained by using HiP-Frag were also protocol-independent, giving the same results when run on samples prepared with different protocols).

HiP-Frag for the identification of novel tumoral histone marks. The authors evaluated the power of this tool in identifying hPTMs by applying HiP-Frag to MS data acquired from samples of breast cancer cell lines and clinical tissues. The acquired MS profiles were compared with datasets of common and known hPTMs. Among the identified hPTMs, 62% were never been described. For instance, they identified K-glyceroylation as a quite frequent PTM, playing a putative role in chromatin dynamics and gene regulation. Notably, when HiP-Frag was applied to other previously published datasets of hPTMs, the frequency of the identified PTMs was comparable, confirming its validity.

Finally, when they focused specifically on the analysis of histone H1, having a crucial role in chromatin structure (despite being a non-core histone) in a MS dataset of clinical breast cancer samples (luminal-A and TNBC), HiP-Frag identified several hPTMs, including nine which have never been described.

Reference: Breaking Boundaries in Histone Modification MS-Based Detection: A Tailored Search Strategy for Unrestricted Identification of Novel Epigenetic Marks. *Alessandro Vai, Roberta Noberini, Andrea Graziadei, Daniel A Polasky, Fengchao Yu, Alexey I Nesvizhskii, Tiziana Bonaldi.* Mol Cell Proteomics 2025. doi: 10.1016/j.mcpro.2025.101080.

What's new from IEO researchers?

Breast cancer in young women: Longer hormone-based therapy halves the risk of metastases and recurrence.



A new result of IEO research has been recently published in the *Journal of Clinical Oncology*. The study, coordinated by our institute, demonstrates that in young premenopausal patients with hormone-positive breast cancer, prolonged adjuvant endocrine therapy over the standard 5 years halves the risk of distant metastases and reduces the risk of recurrence by 40%, with no increase in severe adverse events.

The work, resulting from the collaboration between IEO and Harvard University in Boston, has been coordinated by Carmine Valenza, clinician of the IEO Division of New Drugs for Innovative Therapies and currently researcher at Harvard and

Dana-Farber Cancer Institute in Boston. Among IEO researchers, in addition to the New Drug Division headed by the IEO vice-scientific director Giuseppe Curigliano, were also involved the Medical Senology Division, directed by Marco Colleoni, with the research group coordinated by Elisabetta Munzone, director of the research unit in Medical Senology.

“This result represents an actual milestone for young breast carcinoma patients, who are still under-represented in clinical trials” states Giuseppe Curigliano, confirming IEO leadership role in the international cancer research landscape (read the [press release](#). Italian only).

----- TELL ME MORE! -----

Administration of endocrine therapy in the adjuvant setting (Tamoxifen for 5 years after surgical resection) proved effective in increasing survival of young patients with hormone-positive breast cancer as compared to untreated patients. The addition of suppressors of ovarian function (*luteinizing hormone-releasing hormone agonist*, LHRHa) to tamoxifen-based therapy showed further benefits in terms of survival. However, in young patients a non-negligible risk of distant recurrence persists (25% at 15 years), underlining the need to define proper strategies for these

patients, to reduce relapse and optimize therapy outcome.

This study evaluated the benefits of prolonged endocrine therapy in young pre-menopausal patients with hormone receptor-positive breast cancer, without distant metastases, but with node-positive disease (that is, cancer cells at the regional lymph nodes; pT-any, pN1-3, cM0), who were not menopausal yet at the end of the 5-year adjuvant treatment with endocrine therapy and LHRHa.

The retrospective analysis assessed efficacy of this therapeutic approach on the relapse with invasive

disease in 501 patients (<40 years of age) with breast cancer, who had completed prolonged endocrine therapy (287) as compared to those treated for 5 years only (with endocrine therapy – Aromatase Inhibitor, AI– plus LHRHa).

Efficacy. The results showed a significantly reduced risk of relapse with invasive disease when endocrine therapy was prolonged over the 5-year standard therapy. Beneficial effects appeared more

evident in advanced disease stage, though further studies are needed to confirm this observation.

Toxicity. No differences were observed in terms of adverse events (such as the detrimental effects related to the long-term administration of ovarian function suppressors) between the two research groups, although, to draw final conclusions, further studies, with longer follow-ups, are needed.

Reference. Extended Endocrine Therapy Following 5 Years of Adjuvant Luteinizing Hormone-Releasing Hormone Agonist in Premenopausal Patients With Node-Positive, Hormone Receptor-Positive Breast Cancer: A Cohort Study. *Carmine Valenza, Yue Zheng, Monica Milano, Dario Trapani, Elisa Giordano, Lorenzo Guidi, Pier Paolo Maria Berton Giachetti, Laura Boldrini, Grazia Castellano, Jalissa Katrini, Bianca Malagutti, Gabriele Antonarelli, Fabio Conforti, Eleonora Pagan, Vincenzo Bagnardi, Gregory J Kirkner,, Claudia Sangalli, Kate E Dibble, Marco Colleoni, Meredith M Regan, Elisabetta Munzone, Giuseppe Curigliano, Ann H Partridge.* J Clin Oncol 2026. doi: 10.1200/JCO-25-01660.

What's new from IEO researchers?

Metformin to counter glioblastoma progression – results of preclinical studies.

Tumor heterogeneity and a highly invasive behavior make glioblastoma (GBM) a hard-to-treat tumor. Glioblastoma stem cells (GSCs) are the cancer cell subpopulation endowed with self-renewal ability, *de facto* fueling tumor progression and relapse, hence representing a promising target to eradicate GBM.

In a recent paper, the authors, including Saverio Minucci –Group Leader at the department of experimental oncology of IEO and professor at the University of Milan–, and thanks to the collaboration with Giuliana Pelicci's group, have shown that GSCs can be targeted with metformin: By directly interacting and blocking the activity of a protein expressed on the cell surface of GSCs –CLIC1–, metformin counters tumor growth. They unraveled the underlying mechanism, involving the PP2A-GSK3beta-MCL1 pathway, oxidative stress of cancer cells, and requiring CLIC1 protein: CLIC1 sustains the production of reactive oxygen species (ROS) and the ensuing cell cycle progression, leads to the inactivation of the downstream PP2A-GSK3beta-MCL1 pathway, supporting cancer cell proliferation. Conversely, metformin inhibits CLIC1 activity, causing a decreased ROS production, countering cell cycle progression, and at the same time activating the PP2A-GSK3beta-MCL1 pathway, ultimately reducing tumor growth.

GSCs are able to adapt their metabolism –switching between glycolysis and oxidative phosphorylation– in response to tumor microenvironment conditions and sustain GBM growth. In this work, the authors identify a new therapeutic target –CLIC1– to counter GBM progression by interfering with GSC adaptability: Being required for cancer cell metabolism, proliferation and death, CLIC1 protein has a strategic role for GBM progression. The direct binding of metformin to CLIC1 triggers a stress cascade of events involving CLIC1, mitochondrial activity (and ROS generation) and ultimately GBM proliferation: By interfering with ROS generation and thus with GSC metabolism and the PP2A-GSK3beta-MCL1 pathway, metformin damages cancer cell survival, delays cell cycle progression and reduces tumor growth, both *in vitro* and *in vivo*.

Notably, while being overexpressed on the cell membrane of many solid tumors, including GBM, CLIC1 is poorly expressed on the membrane of healthy cells, making it an optimal potential therapeutic target. Metformin is a drug largely employed in the clinical setting, initially developed as an anti-diabetic drug. Its antitumor effects are under investigation, and this work strongly suggests a potential repositioning of metformin for GBM treatment.

Metformin against cancer.

Metformin antitumoral effects are currently under investigation. IEO researchers have previously identified, in preclinical disease models, a synergistic effect of metformin administration and low glucose, caused by intermittent fasting, in blocking tumor growth, defining also the underlying molecular mechanism (and identifying PP2A protein as a key player). More recently, metformin effects have been analyzed in a clinical setting, revealing the metabolites affected by the treatment and the involved molecular pathways, in overweight breast cancer survivors, who are at higher risk of disease relapse, in which this treatment may reduce the risk of recurrence.

TELL ME MORE!

Metformin-induced GSC death needs CLIC1 expression on tumor cells. By employing *in vitro* 2D and 3D GBM cultures –both patient-derived and cell lines–, the authors evaluated the effects of metformin on GBM cell proliferation: Metformin treatment significantly reduced cell proliferation. Importantly, they found that metformin effects on

cell proliferation were mediated by the presence of CLIC1 protein on the cell membrane. CLIC1 is a protein that, upon stress stimuli, moves from the cell cytoplasm to the cell membrane, where it constitutes an ion channel mediating chloride flux. CLIC1 activity has been previously demonstrated to be linked with cell oxidation. The authors showed

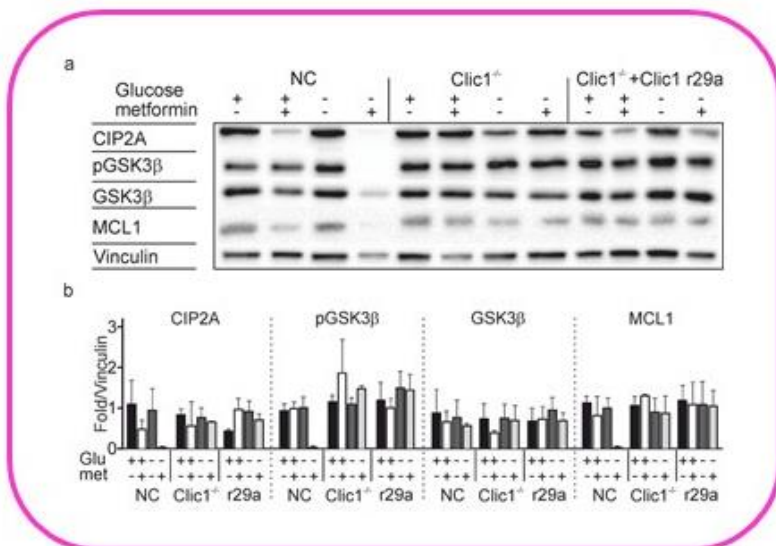
that (CRISPR-Cas9-mediated) CLIC1 deletion resulted in a significantly reduced cancer cell proliferation, and re-expression of either wtCLIC1 or a mutated CLIC1 form (R29A-CLIC1, in which one of the two residues of CLIC1 transmembrane

progression (specifically, in the G1/S transition). Assessment of GBM progression through the cell cycle in metformin-treated cells revealed that both metformin-treated GBM cells and CLIC1-lacking cells displayed delayed cell cycle progression.

Metformin and cell oxidation.

Metformin has been previously demonstrated to reduce cell oxidation, through the inhibition of oxidative phosphorylation. Indeed, the authors observed reduced oxidative phosphorylation both upon metformin treatment and in CLIC1-lacking cells (no effect of metformin was observed in CLIC1-lacking cells, in which oxidative phosphorylation was already inhibited by CLIC1 loss). Metformin treatment resulted in reduced ROS generation in GBM cells; however, ROS generation was unaffected by metformin treatment in CLIC1-lacking cells, indicating that CLIC1 was crucially involved in metformin-induced, ROS-mediated cell death.

Metformin binds to a specific aminoacidic residue of CLIC1. Their results also confirmed metformin specific binding to arginine 29 in CLIC1 transmembrane domain, showing that R29A mutation prevented metformin binding to the protein. Consistently, electrophysiology experiments (both whole cell recordings and single cell outside-out experiments) showed reduced CLIC1 activity in metformin-treated CLIC1-expressing cells. Differently from the known CLIC1 inhibitor IAA94, metformin binding to CLIC1 was



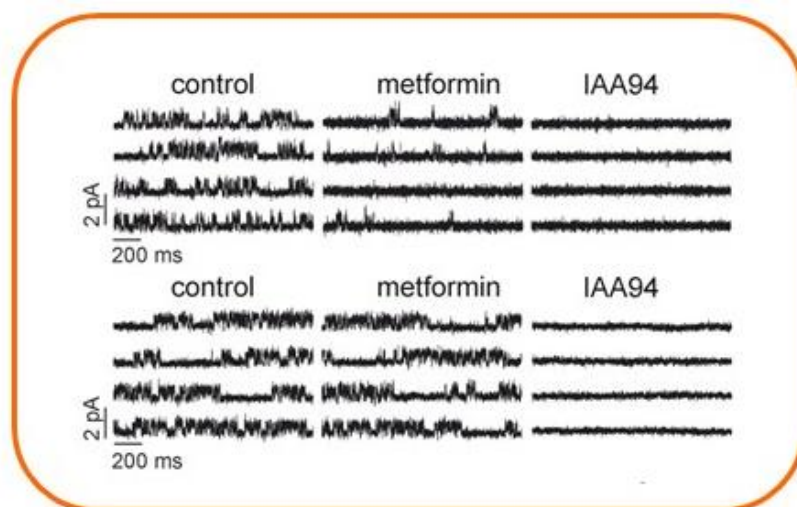
Adapted from Cianci et al., 2025 (an open access [article](#) under the [CC BY](#) license.)

domain, arginine 29, is replaced by an alanine) rescued cancer cell proliferation. Notably, R29A mutation was previously shown to prevent metformin binding; consistently, R29A-CLIC1-expressing cancer cells failed to respond to metformin treatment. CLIC1 inhibition by a specific monoclonal antibody reduced cell proliferation, mirroring the effects of metformin and CLIC1 deletion, further demonstrating that metformin effect was indeed mediated by CLIC1.

Metformin treatment in low-glucose conditions.

Previous studies showed, in other tumor types, that in low glucose conditions, metformin induces cell death via the CIP2A-GSK3β-MCL1 axis. In this work, the authors showed that in low glucose, metformin-induced cell death required CLIC1 on the plasma membrane. Notably, CLIC1 inhibition mirrored metformin effect on the PP2A-GSK3β-MCL1 pathway and, in the absence of CLIC1, metformin failed to activate the CIP2A-GSK3β-MCL1 axis and to induce cell death.

Both CLIC1 deletion and metformin treatment delay GBM cell cycle progression. Previous studies showed CLIC1 involvement in cell cycle



Adapted from Cianci et al., 2025 (an open access [article](#) under the [CC BY](#) license.)

irreversible. Notably, metformin treatment induced a reduction of CLIC1 expression on the cell membrane, likely due to the reduced oxidation level observed upon metformin treatment. In-depth analysis of metformin binding to CLIC1 revealed a key role of E81 residue in the metformin binding site, while R29, weakly interacting with metformin, likely contributed to the structural stabilization of the protein complex constituted by the different CLIC1 units.

Metformin reduces GBM growth in two *in vivo* preclinical models. To confirm the effects observed *in vitro* in an *in vivo* context, the authors used a

zebrafish model. Metformin treatment reduced proliferation of tumor cells injected in zebrafish embryos treated with metformin, while had no effect neither on CLIC1-lacking cells nor R29A-CLIC1-expressing cells. Results collected in zebrafish models were further confirmed in murine models transplanted with GBM cells: Tumor-carrying mice administered metformin (in drinking water) showed measurable metformin concentration in the brain and reduced tumor invasion, whereas no effect of metformin was seen when CLIC1-lacking GBM cells were transplanted in recipient mice.

Reference: Chronic administration of metformin exerts cytostatic and cytotoxic effects via the PP2A-GSK3 β -MCL-1 pathway by inhibiting the tmCLIC1 membrane protein in glioblastoma-initiating cells. Francesca Cianci, Ivan Verduci, Riccardo Cazzoli, Gaetano Cannavale, Guido Rey, Marina Veronesi, Beatrice Balboni, Matteo Ranucci, Luca Maria Giovanni Palloni, Federico Ballabio, Noemi Barsotti, Giorgia Ailuno, Alice Balboni, Sara Baldassari, Gabriele Caviglioli, Carlotta Tacconi, Carlo Camilloni, Stefania Girotto, Federica Barbieri, Alessandro Fantin, Andrea Cavalli, Massimo Pasqualetti, Tullio Florio, Saverio Minucci & Michele Mazzanti. Journal of Experimental & Clinical Cancer Research 2025. doi: 10.1186/s13046-025-03577-3.

What's new from IEO researchers?

The NO-CUT clinical trial.

The research results of the NO-CUT study recently published in *The Lancet Oncology* represent a turning point in the treatment of rectal cancer, demonstrating that a complete tumor remission is possible without surgery in 1 over 4 patients, thanks to an innovative neoadjuvant protocol including chemotherapy followed by chemo-radiotherapy.



Moreover, the study evaluated the role of liquid biopsy (circulating tumor DNA in the blood), demonstrating its prognostic value.

Among the research centers involved, IEO played a key role, with Maria Giulia Zampino, clinician of the Division of Medical Gastrointestinal Oncology and Neuroendocrine Tumors headed by Nicola Fazio.

IEO joined the study through the integrated effort of its multidisciplinary team, involving oncologists, radiotherapists, surgeons, radiologists, endoscopists, pathologists, biologists, and translational research professionals.

This result paves the way to new therapeutic opportunities and further confirms the importance of an interdisciplinary collaboration among clinical and research centers.

----- TELL ME MORE! -----

On the basis of previous retrospective studies, supporting a no-surgery disease management, the authors evaluated efficacy, on distant metastases, of a non-surgical approach –namely, “no-cut” approach– to rectal cancer in selected patients showing complete clinical response after neoadjuvant (chemotherapy and chemoradiotherapy) therapy. This prospective, phase II, multicenter study included 179 patients with (mismatch repair proficient/microsatellite stable, pMMR/MSS) stage II–III rectal cancer. All patients received neoadjuvant therapy; at the end of the treatment, the 47 patients showing a complete clinical response underwent surveillance while the other patients, in which the clinical response to neoadjuvant therapy was only partial, were surgically treated (patients under surveillance who later relapsed with localized

disease were then subjected to surgery).

Efficacy. Efficacy of the no-cut approach was evaluated in terms of (distant and local) relapse: Among those in the “no-cut” (surveillance-only) group, distant relapse-free survival was 95% (at 35 months of median followup), supporting its excellent disease control. Local relapse (at 2 years) occurred in 15% of the patients in the no-cut group and 11% of the patients receiving surgery.

Liquid biopsy. In the frame of an exploratory analysis, circulating tumor DNA (ctDNA) was evaluated before (for 114 patients) and after (for 111 patients) neoadjuvant therapy, to obtain information regarding the value of ctDNA in predicting the probability of a complete clinical response to neoadjuvant therapy, and the correlation with recurrence. This was the first analysis in rectal cancer patients. The results

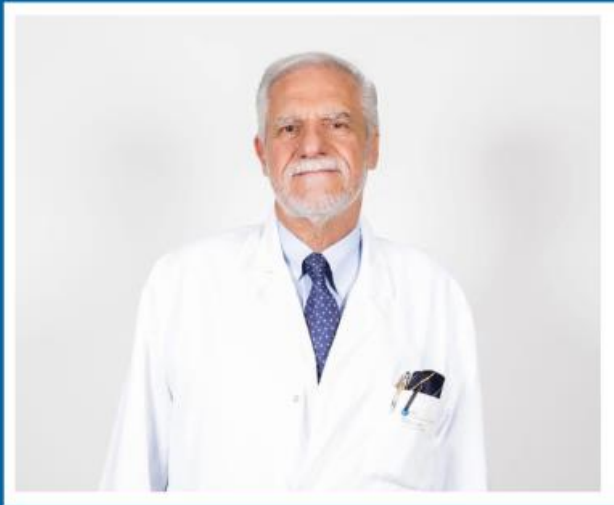
showed reduced ctDNA after neoadjuvant therapy: Before neoadjuvant treatment, ctDNA detection rate was 95% (being 95% in stage III patients, 88% in stage II, 97% in relapsing patients), which decreased to 24% after therapy, reaching 8% in those achieving complete clinical response (predictive value of the ctDNA). ctDNA persistence in the blood at the end of neoadjuvant therapy

appeared to have also a prognostic value: Among patients of the no-cut group, ctDNA detection after neoadjuvant therapy correlated with increased distant recurrence (but not local recurrence); moreover, the percentage of patients who, at the end of the surveillance period, did not need additional surgery was greater in those achieving ctDNA clearance after neoadjuvant therapy.

Reference. Total neoadjuvant therapy followed by non-operative management or surgery in stage II-III rectal cancer (NO-CUT): a multicentre, single-arm, phase 2 trial. *Alessio Amatu, Giorgio Patelli, Maria Giulia Zampino, Francesca Bergamo, Stefania Mosconi, Federica Tosi, Davide Ciardiello, Sara Lonardi, Giorgia Negrini, Daniela Sibio, Marianna Alessandra Gerardi, Sara Galuppo, Francesco Romeo Filippone, Pietro Carnevali, Simona Borin, Pierluigi Pilati, Elia Poiasina, Erica Bonazzina, Lorenzo Gervaso, Enzo Mammano, Francesco Bracco, Luca Bergamaschi, Gaya Spolverato, Matteo Origi, Uberto Fumagalli Romario, Gianluca Mauri, Nicola Fazio, Edoardo Forti, Giuseppe De Roberto, Chiara Cristofori, Cesare Burti, Luigi Asmundo, Luigi Funicelli, Gaetano Ramondo, Pietro Andrea Bonaffini, Sara Mariano, Luca Lazzari, Silvia Ghezzi, Claudio Isella, Daniela Cantarella, Maria Costanza Aquilano, Luca Bottiglieri, Emanuela Bonoldi, Massimiliano Mutignani, Valter Torri, Enzo Medico, Alberto Bardelli, Silvia Marsoni, Angelo Vanzulli, Mauro Filippo Palazzi, Giovanni Carlo Ferrari, Katia Bencardino, Andrea Sartore-Bianchi, Salvatore Siena.* Lancet Oncol 2025. doi: 10.1016/S1470-2045(25)00542-X.

News, initiatives and events from the IEO world!

Heine H. Hansen Award 2026.



Premio Heine H. Hansen (HHH) Award 2026

The European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC) announced that Filippo de Marinis is the recipient of the Heine H. Hansen (HHH) Award 2026. His contribution fully embodies the spirit of this prestigious award celebrating excellence in research, clinical innovation, and commitment to the improvement of clinical outcome of lung cancer patients.

During his direction of IEO Thoracic Oncology Division, Prof. de Marinis has always been a national and international reference for lung oncology, and particularly for innovative therapies. Over the years, he contributed to the development of an integrated program dedicated to prevention, diagnosis, treatment and research on thoracic neoplasms. His work has crucially contributed to advancing clinical research on lung cancer, making his Division a reference center for the main international clinical studies and for collaborations with high level research groups.

Over his career, de Marinis significantly contributed to the development of new therapeutic strategies for non-small cell lung cancer, for small-cell lung cancer, and other thoracic tumors, contributing to the definition of studies that have influenced the current standard of care.

As a member of the most important national and international scientific societies, de Marinis' role in promoting multidisciplinary collaboration and in advancing evidence-based clinical practice in lung cancer treatment is well known.

News, initiatives and events from the IEO world!

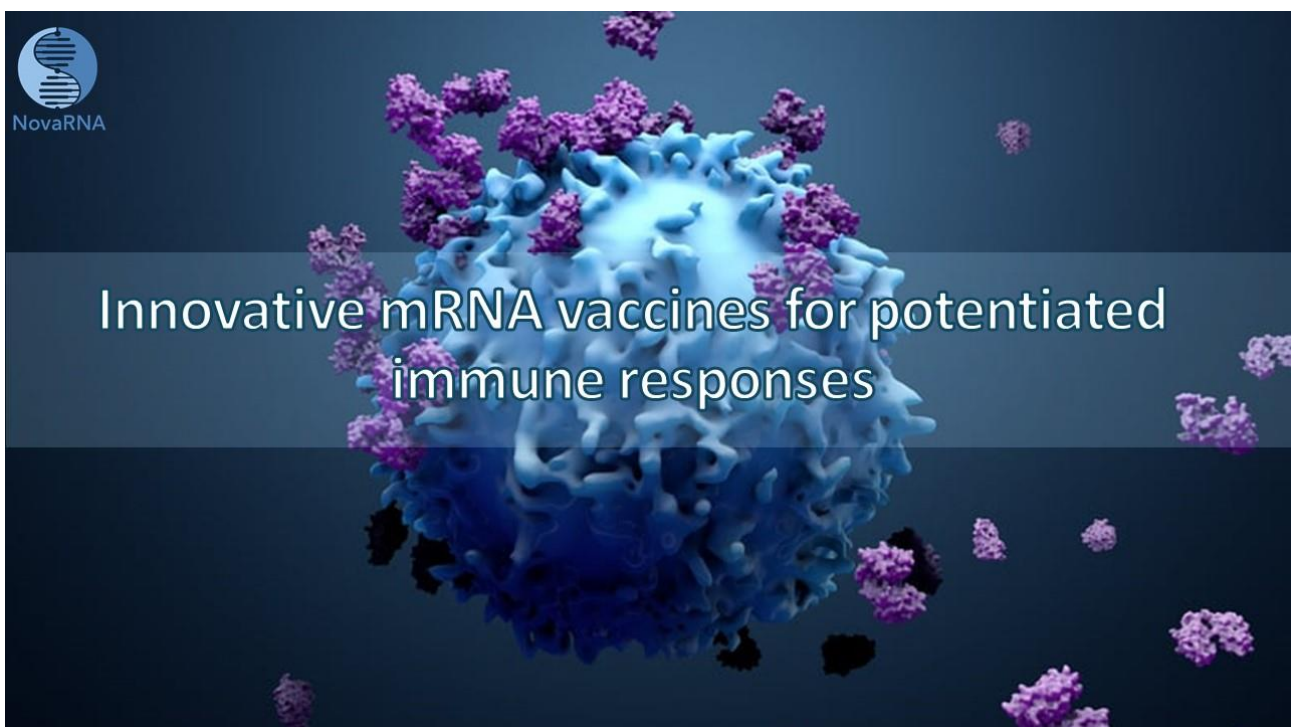
A new treatment approach for the most severe arrhythmias.



A collaboration between IEO and Monzino paves the way to new treatment approaches for malignant ventricular arrhythmias. STRA-MI-VT is the first study in Italy and one of the first in the world on the use of stereotaxic radiotherapy in one session. The results showed 80% greater control of arrhythmias; better results as compared to traditional approaches. This achievement has been made possible by the joint work of cardiologists of the Monzino Hospital, headed by Corrado Carbuicchio –Director of the Unit for the treatment of ventricular arrhythmias, who designed the study– and IEO radio-oncologists coordinated by Barbara Jereczek –Director of the IEO Radiotherapy Division–, confirming the added value of the integration between cardiological and oncological expertise.

News, initiatives and events from the IEO world!

The NovaRNA project selected for the PerfeTTO Accelerator Program.



In December 2023, funded by the Italian Ministry of Health through the PNRR, was launched the first Italian network of technology transfer offices in Italy –PerfeTTO–, aimed at promoting the culture of technology transfer, supporting technology transfer activities to ultimately enhance exploitation of research results in the industry sector.

Recently, the IEO-University of Milan project NovaRNA stood out among the candidate projects of the second edition of the TT Accelerator Program organized within the PerfeTTO network for its strong innovative

potential and translational impact, and has been selected (first in ranking) to be part of the dedicated TT Accelerator Program organized by the PerfeTTO Network, which will provide tailored mentorship, training and strategic advisory support to the most promising research projects developed within the network's institutions.

The technology developed within the NovaRNA project, led by Stefano Persano –senior researcher at IEO– under the supervision of Pier Giuseppe Pelicci and Saverio Minucci –both IEO group leaders and professors at the University of Milan–, supported by the IEO-TT (the IEO technology transfer office led by Marzia Fumagalli), and co-owned by IEO and University of Milan, is an innovative platform to enhance the antitumor immune response of mRNA-based vaccines.

The current RNA-based antitumor vaccines are commonly able to induce an antibody-based immune system response against the tumor, whereas the activation of cytotoxic T cells remains limited. This is mostly related to a key process of immune system activation, namely the expression, by specific (antigen-presenting cells) immune cells, of the tumoral (antigenic) protein coded by the vaccine RNA molecule, which is limited with conventional mRNA-based vaccines; this mechanism is needed for the robust and durable activation of cytotoxic immune (CD8+ T) cells.

The NovaRNA platform aims to resolve this issue through a dual approach: On one side, the elimination of those chemical modifications of the RNA molecules (commonly introduced during vaccine production) that, while increasing treatment tolerability (by reducing innate immunity), significantly increase manufacturing cost and technical complexity, ultimately impacting on accessibility to treatment; on the other side, by focusing on specific (untranslated regions, UTR) regions of the RNA molecule, to increase the poor expression of the tumoral antigenic protein.

By improving antigen protein expression and reducing technical complexity, NovaRNA approach results in a simpler technology, with reduced manufacturing time and production costs, which may pave the way to a novel generation of mRNA-based vaccines, in the oncology field, with the development of vaccines for other tumor types, as well as against other pathogens.

Officially starting on January 14th, the TT Accelerator Program represents a remarkable opportunity to further advance the NovaRNA project and accelerate its path toward real-world application.

“The TT Accelerator program has a 6-month duration, at the end of which there will be a business matching meeting – explain the IEO TT officers. This path will allow to further develop aspects of the project from the technology transfer perspective, with the final goal of transforming innovative results into business opportunities to be presented to investors and potential industrial partners.”

Congratulations to the entire team –scientists and technology transfer officers– on this outstanding achievement. Let's make the most out of this opportunity!

TELL ME MORE!

RNA-based vaccines work by instructing the immune system to recognize tumor-specific proteins –the antigens– and kill the (tumor) cells expressing such proteins. Specific antigen-presenting cells (APCs) play a key role, expressing RNA-coded proteins and triggering the immune system response. The expression level of this tumoral antigen protein is thus critical for an efficient antitumor immune system response.

To increase antigen protein expression, the NovaRNA approach focuses on the UTR regions of the RNA, which are known to affect transcript stability, translation efficiency, intracellular localization, and interaction with cell factors.

Specifically, through a screening approach, researchers identified UTR combinations capable of increasing antigenic protein expression by the APCs, and MHC-I-mediated antigen presentation, in turn enhancing (cytotoxic CD8+ T cell-mediated) immune system response, thus solving an issue common to many vaccine platforms, such as the poor expression of the antigenic protein. In preclinical *in vivo* melanoma models, the NovaRNA approach resulted in a significant increase of T cell immune response as compared to conventional platform-employed mRNAs, significantly reducing cancer-related mortality.

News, initiatives and events from the IEO world!

Join the SEMM Workshop "The Proteomics Revolution: Advancing Science and Society"!

On June 29th-July 1st, 2026, Milan will host the scientific workshop, organized by the European School of Molecular Medicine (SEMM), "The Proteomics Revolution: Advancing Science and Society".

The event aims at strengthening the global proteomics community, by creating a highly interactive and interdisciplinary environment.

PhD students, young and experienced researchers, from academia and pharmaceutical sector, will gather to foster scientific discussion and establish or consolidate collaborations. The interdisciplinary nature of the meeting will facilitate technical and scientific exchange as well as the transfer of technological innovations into real-world applications.

The talks, by leaders in the proteomics field from Italy, Germany, Israel, US, Austria, Canada, Netherlands, UK, Spain, Denmark, will focus on a wide range of topics including the role of proteomics in health and disease, from the identification of disease biomarkers to mechanisms and therapies; the employment of spatial proteomics to decipher the spatial information of proteomes and their dynamics in cells and tissues; the exploitation of proteomics approaches to describe the cellular signaling; and the technological innovation and computational advancement leading the "proteomics revolution". Furthermore, discussions and roundtables will be centered on the investments for the future of proteomics, on the empowerment of the next generation of proteomics scientists, and the biases in (proteomics) experimental design, both in basic science and medicine.

"This workshop is built around the idea of a true proteomics revolution, where biology, technology, and computation come together to reshape our understanding of health and disease, from

molecular mechanisms to clinical translation. By focusing on spatial and dynamic proteomics, cellular signaling, and next-generation mass spectrometry and computational tools, the programme reflects where the field is heading. Personally, I hope this meeting will also showcase the quality and energy of the proteomics community in Italy in a truly international context, giving visibility to a rapidly growing ecosystem. I see it as an inspiring step toward HUPO 2027 in Milan and a real opportunity for the next generation of proteomics scientists to help shape the future of the field!" says Tiziana Bonaldi, Associate Professor of Experimental Biology at the Università degli Studi di Milano, Group Leader at the European Institute of Oncology (IEO), and member of the organizing committee.

"While the workshop is open to scientists at all career stages, early-career researchers are truly at its core. The programme is designed to maximize visibility and interaction through extended poster sessions, ample oral presentation opportunities, and dedicated "meet-the-experts" moments with leading scientists. Young researchers will also actively shape discussions during round tables on challenges, opportunities, and career paths in proteomics. Combined with a small, welcoming conference setting and shared social moments, this creates an ideal environment for building meaningful professional connections" adds Tiziana Bonaldi."

Do not miss the opportunity to be part of a dynamic environment and benefit from the insightful discussions at the Quark Hotel in Milan. Participation is limited to 120 registered people, so hurry up! Ensure your place at "The Proteomics Revolution: Advancing Science and Society" workshop.

| Deadlines | |
|--|-------------------|
| Abstract submission deadline | February 28, 2026 |
| Chosen participant will be notified by | March 15, 2026 |
| Registration deadline | March 30, 2026 |
| REGISTRATION FEES (in euros) | |

| | |
|---|----------|
| Graduate Student/PhD Student/Post-doc | € 350,00 |
| Academic/Principal Investigator | € 450,00 |
| Industry | € 732,00 |
| For further details, check the event website here | |

See the workshop website for details: <https://www.proteomicsrevolution2026.net/>

For any inquiry about the event: Sabrina Frata (Event Management & Organizing Secretariat, Fondazione SEMM ETS) events@semm.it

News, initiatives and events from the IEO world!

Surgery rooms of IEO 3 are now up and running!

In less than two months since the opening of IEO building 3, the new surgery rooms are officially up and running, with no disruptions in patient care. In five days only, the whole robotic platform –composed of four robotic surgery rooms– and four (of the eight planned) rooms dedicated to open



rooms are already fully operative, enabling to perform over 100 surgical procedures, more than 20% of them being robot-based. In the first two weeks of activity, the surgery platform treated 300 patients, 30% of them undergoing robotic surgery. The new surgery rooms are highly technological environments, integrating devices and tools, ensuring the highest standard of efficiency, safety, and precision, integrating technological innovation with human-centered spaces, offering comfort to both patients and healthcare workers.

The architecture and design of the recovery area as well –with natural light, serigraphed backlit panels, and carefully planned color choices– contribute to reducing anxiety and improving emotional wellbeing, promoting feelings of calmness and protection in a particularly delicate moment of the care.

“In IEO, the environment is an integral part of the therapeutic path” highlights Silvia Oldazzi, Director of Strategy and industrial plan development “the new surgery platform will also allow to increase efficiency, enabling to perform more surgical interventions and reduce waiting time”.



“Patients’ wellbeing has always driven all our choices” adds Gabriella Pravettoni, Director of the Psycho-oncology Division “IEO3 integrates patient experience with state of the art care allowed by the new technologies, incorporating ‘the future’ within the founding principles of our founder, Umberto Veronesi”.

Thanks to this combination of technology, logistic efficiency and attention to the patient, IEO 3 represents a unique reality in Italy for a cancer center, and further confirms the effort of our institute in health and innovation.

Read the press release [here](#) (Italian only)



THE BRIEFING

A glance through recent papers from IEO researchers, and from the whole scientific community.

What else is new from IEO researchers?

(text by Alex Irwin (ChatGPT) and Ai Yi (DeepSeek); revision by Stefania Averaimo)

prospective clinical trial

Thermal Ablation for Visceral (Oligoproggressive and Oligopersistent) Metastatic Breast Cancer. This single-center cohort study evaluated metastasis-directed thermal ablation (TA) combined with continuation or modulation of systemic therapy in breast cancer patients with few, progressive or persistent metastases. TA was safe, with few adverse events, and achieved meaningful post-ablation progression-free survival, particularly in persistent disease. Results support TA as a strategy to delay treatment failure within a multidisciplinary framework.

Bianco N, Valenza C, Milano M, Multinu R, Battaiotto E, Cavallone M, Malvezzi G, Trapani D, Della Vigna P, Bonomo G, Varano GM, Maiettini D, Pitoni MG, Sangalli C, Munzone E, Curigliano G, Colleoni MA, Orsi F. Metastasis-directed thermal ablation in patients with metastatic breast cancer and visceral oligoproggression or oligopersistence: a cohort study. Breast. PMID: 41317597.

retrospective clinical study

Multimodal Treatment Remains Key in Locally Advanced Breast Cancer. Using the EUSOMA database, this study analyzed outcomes of patients with locally advanced breast cancer. Multimodal treatment, including surgery, radiotherapy, and systemic therapy, was associated with improved survival. Tumor biology, age, and treatment intensity were key prognostic factors. No survival differences were found between inflammatory and non-inflammatory advanced stage (T4) tumors. The findings highlight persistent underuse of comprehensive treatment strategies and reinforce the importance of guideline-adherent multimodal care.

van Dam P, Tomatis M, Ponti A, Marotti L, Verhaegen J, Aristei C, Cardoso MJ, Cheung KL, Curigliano G, De Vries J, Santini D, Sardanelli F, Rubio IT, Eusoma Working Group. European Journal of Surgical Oncology. PMID: 41391957.

meta-analysis

Differential Breast Cancer Risk Associated With FANCM Protein-Truncating Variants. This large meta-analysis of over 144,000 breast cancer cases assessed the impact of FANCM protein-truncating variants (PTVs) on disease risk. Variants in the N-terminal region of FANCM were associated with increased risk of ER-negative and triple-negative breast cancer, while C-terminal variants showed no excess risk. Functional CRISPR-Cas9 assays supported these findings, demonstrating essential roles for the N-terminal region. The results refine genetic counseling for FANCM variant carriers.

Billaud A, Figlioli G, Mooser C, Casamassima I, Azzoni V, Srivatsa J, Colombo M, Caleca L, Ahearn TU, Andrulis IL, Antoniou AC, Beckmann MW, Behrens S, Bermisheva M, Bogdanova NV, Bolla MK, Bonanni B, Brüning T, Camp NJ, Campbell A, Castelao JE, Cessna MH, Chang-Claude J, NBCS Collaborators, Czene K, Dennis J, Devilee P, Dörk T, Dunning AM, Eriksson M, Evans DG, Fasching PA, Figueroa JD, Gabrielson M, Gago-Dominguez M, González-Neira A, Guénel P, Hadjisavvas A, Hahnen E, Hamann U, Hillemanns P,

Hollestelle A, Hooning MJ, Hoppe R, Howell A, kConFab Investigators, Jakubowska A, Kristensen VN, Lubiński J, Lush M, Manoukian S, Mavroudis D, Milne RL, Mulligan AM, Newman WG, Obi N, Panayiotidis MI, Pita G, Rashid MU, Rhenius V, Saloustros E, Sawyer EJ, Schmutzler RK, Shah M, Southey MC, Spurdle AB, Tomlinson I, Truong T, Wang Q, Wendt C, Auer PL, Boddicker NJ, Bodelon C, Burnside ES, Chen F, Couch FJ, Domchek SM, Eliassen HA, Haiman C, Hodge JM, Hu C, Huang H, Lindstrom S, Martinez ME, Nathanson KL, Neuhausen SL, O'Brien KM, Olson JE, Palmer JR, Patel AV, Ruddy KJ, Sandler DP, Teras LR, Weinberg CR, Weitzel JN, Winham SJ, Yadav S, Yao S, Zirpoli G, Janatova M, Kleibl Z, Kleiblova P, Soukupova J, CZECANCA consortium, Zhao Q, Devereux L, James PA, Campbell IG, Nguyen-Dumont T, Dowty JG, Andrieu N, Lesueur F, Stoppa-Lyonnet D, GENESIS, Hoya M, Radice P, Sørensen CS, Peterlongo P. Large-scale meta-analysis and precision functional assays identify FANCM regions in which PTVs confer different risks for ER-negative and triple-negative breast cancer. *Breast*. PMID: 41223770.

clinical/computational/research tools

Gene Fusion Landscapes in Metastatic Breast Cancer. Using AURORA multi-omics data, this study cataloged gene fusions in metastatic breast cancer and showed a higher fusion burden in metastases than primary tumors. Acquired fusions correlated with genomic instability and poor prognosis, particularly in ER-positive cancers. ESR1 fusions were linked to aggressive clinical behavior. The catalog provides a valuable resource for identifying novel therapeutic targets and understanding metastatic evolution.

Biagioni C, Fimereli D, Irrthum A, Guerrero-Zotano A, Piccart M, Cameron D, Caballero C, Raimbault A, Martins-Branco D, Romagnoli D, Agostinetti E, Venet D, Llinas-Bertran A, Seoane JA, Zoppoli G, Vivancos A, Vingiani A, Oliveira M, Curigliano G, Crestani T, Sotiriou C, Nili Gal-Yam E, Hilbers FS, Aftimos P, Benelli M. Molecular and clinical analyses of gene fusions identify therapeutic targets in paired primary and metastatic breast cancer from the AURORA program (BIG 14-01). *Clinical Cancer Research*. PMID: 41427961.

review/commentary

Lucerne Toolbox 3: A Roadmap for Digital Health and AI in Early Breast Cancer. The Lucerne Toolbox 3 initiative defines a strategic framework for integrating digital health and artificial intelligence into early breast cancer care. Using a modified Delphi process, an international multidisciplinary consortium identified 15 priority knowledge gaps and developed 13 consensus trial designs spanning screening, treatment, follow-up, and survivorship. The recommendations emphasize precision medicine, patient-centred approaches, and interdisciplinary collaboration to improve outcomes, efficiency, and equity in breast cancer management.

Pfob A, Pinker K, Vaz-Luis I, Di Meglio A, Cardoso MJ, Curigliano G, Gentilini OD, Gruber G, Hauser N, Heil J, Kaidar-Person O, Knauer M, Lee HB, Lee SB, Loi S, Mannhart M, Mastora S, Meattini I, Di Micco R, Noske A, Peccatori FA, Poulakaki F, Reinisch M, Rubio IT, Swanton C, Tausch C, Vrancken Peeters MJ, Yu JH, Weber WP, Zerbe N, Poortmans P, Denkert C, Mann R, Delaloge S, Dubsy P, Toolbox 3 Consortium. *Lancet Oncology*. PMID: 41308690.

correlative/descriptive studies

High Frequency of a Complex BARD1 Variant in Hereditary Cancer Testing. This study investigated the prevalence of the BARD1 c.1518_1519delinsCA variant in 920 individuals undergoing hereditary cancer testing. A high frequency of the combined dinucleotide substitution was observed, and confirmed by population data, highlighting that these frequencies reflect true variation rather than bias. Although individually classified as benign, the combined variant may have biological relevance, highlighting the importance of accurate variant annotation in multigene panel testing.

Marino E, Belloni E, Dal Molin M, Marabelli M, Guerrieri-Gonzaga A, Zanzottera C, Mannucci S, Calvello M, Fava F, Feroce I, Bonanni B, Bernard L, Barberis M, Pelicci PG, Bertolini F.. *Biomedicines*. PMID: 41301857.

prospective clinical trial

Long-Term Outcomes of Crizotinib in ROS1-Rearranged non-small cell lung cancer: Impact of Brain Metastases. This post hoc analysis of the phase II METROS trial assessed long-term efficacy of crizotinib in ROS1-rearranged advanced non-small-cell lung cancer. Patients with brain metastases had significantly worse outcomes, underscoring the limited intracranial activity of crizotinib. The safety profile remained consistent, supporting its use while highlighting the need for more brain-penetrant therapies.

Landi L, Chiari R, Tiseo M, Metro G, de Marinis F, Delmonte A, Novello S, Cortinovis DL, Galetta D, Bonanno L, Gridelli C, Morabito A, Grossi F, Torchia A, Giannarelli D, Borra G, Mazzone F, Pilotto S, Cappuzzo F. JTO Clinical and Research Reports. PMID: 41278398.

meta-analysis

Smoking and Survival in Non-Melanoma Skin Cancer: A Meta-Analysis. This systematic review and meta-analysis evaluated the prognostic impact of cigarette smoking in patients with non-melanoma skin cancer (NMSC). Five prospective studies were included. Current or ever smokers had more than a two-fold increased risk of death compared with never smokers. Similar results were observed for higher smoking intensity. These findings indicate that smoking is a negative prognostic factor in NMSC and support routine integration of smoking cessation counseling in patient management.

Andreou C, Gaeta A, Carretti M, Graziani A, Tosti G, Doccioli C, Saponara M, Gorini G, Suppa M, Di Maggio E, Gandini S, Caini S. Cancers (Basel). PMID: 41301036.

mechanism-oriented research

LISRR lncRNA Drives Immune Evasion and Immunotherapy Resistance via Cancer-Specific Ribosomes. This study identifies recurrent gains of chromosome 12p11.21, encoding the lncRNA LISRR, as a marker of poor prognosis across cancers. In melanoma, LISRR is upregulated in immunotherapy-resistant tumors, where it promotes drug-tolerant states by activating immune-suppressive translation programs that increase PD-L1 and glycocalyx synthesis. Mechanistically, LISRR alters ribosome core composition and recruits DAZAP1 protein to polysomes, priming the integrated stress response. Targeting LISRR restores immune sensitivity, revealing an RNA-based strategy to overcome checkpoint inhibitor resistance.

Cinque S, Verheyden Y, Adnane S, Marino A, Hanache S, Vendramin R, Cuomo A, Pozniak J, Cortes Calabuig A, Baldewijns M, Tabruyn S, Bechter O, Baietti MF, Groaz E, Bonaldi T, Leucci E. J Exp Med. PMID: 41201478.

mechanism-oriented research

Differential Cysteine Metabolism Protects Endothelial Cells From Ferroptosis. This study reveals distinct strategies deployed by proliferating versus quiescent endothelial cells to protect against ferroptosis-mediated cell death during angiogenesis. Proliferating cells rely on extracellular cystine uptake to sustain glutathione synthesis (which is needed to avoid ferroptosis), while quiescent cells activate the trans-sulfuration pathway under cystine deprivation. NRF2 signaling supports this adaptive response in quiescent cells, providing protection from ferroptosis. Hypoxia can induce similar resistance in proliferating cells. In vivo, inhibition of cystine uptake increased endothelial cell death during angiogenesis. These findings identify the cysteine/GSH/GPX4 axis as a potential therapeutic target in angiogenesis-related diseases.

Oberkersch RE, Lidonnici J, Andreuzza S, Zambon E, Imperato G, Pedretti S, Mitro N, Santoro MM. Cell Death & Disease. PMID: 41422256.

mechanism-oriented research

Human Germ Cell-Like Cells Reversibly Transition Between Pluripotent States. The authors describe an in vitro system enabling conversion of human primordial germ cell-like cells (hPGCLCs) into embryonic germ cell-like cells, using mouse-derived inductive signals. The resulting cells resemble human induced pluripotent stem cells at transcriptional and chromatin levels and can revert to germ cell-like states, demonstrating pluripotent interconvertibility. DNA demethylation observed in hPGCLCs is reversed upon

conversion. This in vitro model provides a powerful platform to study early human development, epigenetic reprogramming, and germ cell tumorigenesis.

Stucchi S, Sepulveda-Rincon LP, Dion C, Matassa G, Valenti A, Cheroni C, Vitriolo A, Prazzoli F, Young G, Rigoli MT, Nagni R, Ciprietti M, Muda B, Heckhausen Z, Hajkova P, Caporale N, Testa G, Leitch HG. Stem Cell Reports. PMID: 41418783.

prospective clinical trial

Pembrolizumab Plus Platinum-Etoposide in Chemo-Sensitive advanced Small Cell Lung Cancer (SCLC). REACTION was a randomized phase II trial evaluating pembrolizumab added to platinum-etoposide in chemo-sensitive advanced stage SCLC patients. Pembrolizumab did not significantly improve progression-free survival (PFS) compared with chemotherapy alone, although an overall survival (OS) benefit was observed. Toxicity was higher in the pembrolizumab arm. Baseline circulating tumor cell counts were independently associated with both PFS and OS, supporting their prognostic value regardless of treatment.

Menis J, Greiller L, Demontrond P, Monnet I, Novello S, Livi L, Young R, Decroisette C, Cloarec N, Robinet G, Schott R, Fayette J, Banna GL, De Marinis F, Califano R, Duchemann B, Luciani A, Colantonio I, Fournier B, Pretzenbacher Y, Caramella C, Silva M, Berghmans T, Dingemans AM, Bironzo P, Tugwood J, Zhou C, Hill S, Bradbury K, Morris K, Kilgour E, Dive C, Blackhall F, Besse B. Eur J Cancer. PMID: 41192233.

prospective clinical trial

Ten-Year Real-World Comparison of Hedgehog Inhibitors in Advanced Basal cell Carcinoma (BCC). This prospective monocentric study evaluated long-term outcomes of the two Hedgehog inhibitors sonidegib and vismodegib in advanced basal cell carcinoma. Sonidegib showed higher response rates than those reported in pivotal trials and maintained efficacy in patients switching to sonidegib after vismodegib intolerance, suggesting limited cross-resistance. These findings support sonidegib as an effective option, including after vismodegib discontinuation.

Venturi F, Zuccaro B, Perillo G, Cecchi G, Gaeta A, Gandini S, De Giorgi V. Clinical and Experimental Dermatology. PMID: 40834113.

mechanism-oriented research

Connexin-Driven Transcriptional Control of Tumor Tissue Unjamming. This study demonstrates that epithelial tissue unjamming and collective tumor cell migration require de novo transcription regulated by EGF signaling. Connexins Cx26 and Cx31 are induced via sustained ERK and AKT signaling, enhancing gap junction communication necessary for flocking behavior. Genetic or pharmacologic inhibition of connexins blocks tissue fluidization and cell motility. Constitutive connexin expression (in vocal fold carcinoma cells) correlates with sensitivity to inhibition. High Cx26 levels correlate with poor survival, identifying connexins as key drivers of collective invasion.

Abdo H, Barzaghi L, Shen Y, Bellini E, Martini E, Magni S, Barozzi S, Orsenigo F, Parazzoli D, Beznoussenko GV, Franco JD, Krautgasser F, Kaivola J, Cinquanta M, Lazzarin A, Sigismund S, Ivaska J, Cerbino R, Scita G. Advanced Science. PMID: 41431893.

retrospective clinical trial

Prognostic Value of Sarcomatoid Dedifferentiation in Grade 3 and 4 Renal Carcinoma. Using SEER database, this study evaluated the prognostic value of sarcomatoid dedifferentiation in surgically treated (undergoing cytoreductive nephrectomy) metastatic renal carcinoma (clear-cell renal cell carcinoma) patients. In grade 4 tumors, sarcomatoid features were common but did not independently predict overall mortality. In contrast, although rare in grade 3 disease, sarcomatoid dedifferentiation was strongly associated with worse survival and independently predicted higher mortality. These findings suggest sarcomatoid dedifferentiation should be routinely reported and incorporated into prognostic models for grade 3 ccmRCC.

Incesu RB, Scheipner L, Morra S, Baudo A, Siech C, Jannello LMI, de Angelis M, Assad A, Tian Z, Saad F, Shariat SF, Briganti A, de Cobelli O, Chun FKH, Carmignani L, Longo N, Ahyai S, Tilki D, Graefen M, Karakiewicz PI.

Surg Oncol. PMID: 41187454.

prospective-retrospective clinical trial

Breast Cancer Index as Predictive Biomarker in Premenopausal Breast Cancer Patients. This prospective-retrospective study evaluated the Breast Cancer Index (BCI, based on the ratio between HOXB13 and IL17BR expression) in premenopausal, Hormone Receptor-Positive women receiving either tamoxifen and ovarian function suppression therapy or exemestane and ovarian function suppression therapy. While showing that, in pre-menopausal women, BCI did not clearly predict differential benefit between the two endocrine regimens tested, results indicate, along with previous studies, that these patients may benefit from more intensive endocrine therapy.

O'Regan RM, Ren Y, Zhang Y, Siuliukina N, Schnabel CA, Kammler R, Viale G, Dell'Orto P, Munzone E, Láng I, Tondini C, Gomez HL, Chini C, Nicoletti SVL, Puglisi F, Zaman K, Goetz MP, Stearns V, Martino S, Salim M, Loibl S, Geyer CE, Bonnefoi HR, Ciruelos EM, Loi S, Colleoni M, Fleming GF, Francis PA, Walley BA, Pagani O, Treuner K, Regan MM.

JAMA Netw Open. PMID: 41182766.

prospective clinical trial

Clonal Hematopoiesis in Breast Cancer Patients Undergoing Systemic Therapy. This prospective study assessed the correlation between clonal hematopoiesis of indeterminate potential (CHIP) and patient survival or emergence of treatment-related myeloid tumors, in 380 patients with breast cancer. Using 614 serial samples, the authors found that CHIP was present in 15% of the patients at diagnosis; chemotherapy did not increase overall CHIP emergence compared with endocrine therapy. Most patients had low predicted risk of treatment-related myeloid neoplasms, although the risk of emergent TP53-mutant clones (which correlate with high risk of treatment-related myeloid tumors) increased with chemotherapy. CHIP did not correlate with survival in metastatic TNBC.

Morganti S, Gibson CJ, Jin Q, Santos K, Patel A, Wilson A, Merrill M, Vincuilla J, Stokes S, Lipsyc-Sharf M, Parker T, King TA, Mittendorf EA, Curigliano G, Hughes ME, Stover DG, Tolaney SM, Weeks LD, Tayob N, Lin NU, Garber JE, Miller PG, Parsons HA.

J Clin Oncol. PMID: 38190580

prospective (real world) clinical study

Frailty Predicts Zanubrutinib Discontinuation in Elderly Chronic Lymphocytic Leukemia (CLL). This prospective real-world study demonstrated that the Clinical Frailty Scale (CFS) predicts treatment discontinuation in elderly CLL patients treated with zanubrutinib. A CFS score above 3 identified patients at higher risk of early discontinuation, independent of traditional prognostic factors. Incorporating frailty assessment may improve therapeutic decision-making and personalization in older CLL patients.

Vigna E, Martino EA, Pitino A, Pasquale R, Ferrarini I, Moia R, Visentin A, Sanna A, Motta M, Moratti M, Sportoletti P, Chiarenza A, Maggi A, Zammit V, Merli M, Innocenti I, Giordano C, Nocilli L, Postorino M, Stelitano C, Ferrario A, Frustaci AM, Riva M, Pepe S, Ibatci A, Scardino S, Borza PA, Ballotta L, Mancuso S, Malaspina F, Mele A, Galimberti S, Catania G, Giordano A, Angeletti I, Schiattone L, Pennese E, Miccolis R, Fama A, Giordano G, Califano C, Bruzzese A, Caserta S, Farina G, Bulian P, Loseto G, Pocali B, Innao V, Galieni P, Fraticelli V, Vitale C, Romeo A, Rossi M, Scortechini I, Vozella F, Malandrucolo L, Varettoni M, Morello L, Pietrantuono G, Conte E, Cantelli M, Murru R, Caracciolo D, Derenzini E, Martina VD, Marasca R, Principe MID, Figuera A, Angotzi F, Coscia M, Renzo ND, Laurenti L, Amodio N, Musto P, Raimondo FD, Liso A, Tedeschi A, Trentin L, Gaidano G, Mauro FR, Tripepi G, Corsonello A, Morabito F, Gattei V, Gentile M.

Hematological Oncology. PMID: 41460718.

retrospective clinical trial

Aprepitant Use During Chemotherapy and Survival in Early Breast Cancer. Using nationwide Norwegian registry data, this cohort study evaluated the association between the use of the antiemetic aprepitant and survival in women with early breast cancer receiving chemotherapy. Aprepitant was associated with improved distant disease-free and survival in patients with non-luminal tumors; the effect was especially strong in triple-negative breast cancer. Longer duration of aprepitant use correlated with greater benefit, while other antiemetics showed no association. These findings suggest a potential repurposing opportunity, warranting confirmation in prospective clinical trials.

Botteri E, Hjorth S, Conforti F, Bagnardi V, Andreassen BK, Støer NC, Bhargava S, Ursin G, Gandini S, Sloan EK, Chang A.

J Natl Cancer Inst. PMID: 40658620.

review/commentary

Deep Learning in Thyroid evaluation: Challenges and Opportunities. This narrative review provides a technical overview of deep learning applications in Fine-Needle Aspiration Cytology (FNAC, the most broadly used approach for thyroid pathological evaluation), focusing on the III–IV disease categories according to the Bethesda system, which represent the toughest challenge. The authors discuss the potential of routinely adopting deep learning in diagnostic triage, classification according to the Bethesda system, and risk stratification, while highlighting key barriers to clinical adoption, including variability. The review emphasizes the need for standardized datasets, multicenter prospective validation, and explainable AI frameworks for the safe deployment of these tools in clinical practice.

Negrelli M, Frascarelli C, Maffini F, Mangione E, Di Tonno C, Lombardi M, Porta FM, Urso M, L'Imperio V, Pagni F, Bellevicine C, Nacchio M, Malapelle U, Troncone G, Marra A, Curigliano G, Venetis K, Guerini-Rocco E, Fusco N.

Cancers (Basel). PMID: 41228318.

review/commentary

Small AI Models for Breast Pathology. This perspective discusses the limitations of large foundation AI models in breast cancer pathology and advocates for smaller, task-specific systems. These models aim to predict molecular features directly from histology slides while improving interpretability and clinical integration. The authors emphasize the need for high-quality datasets, external validation, and interdisciplinary collaboration to translate AI advances into real-world breast cancer care.

Frascarelli C, Venetis K, Marra A, Concardi A, D'Ercole M, Mangione E, Negrelli M, Porta FM, Keswani S, Curigliano G, Guerini-Rocco E, Fusco N.

NPJ Breast Cancer. PMID: 41402342.

retrospective clinical trial

Bone Metastases in Neuroendocrine Neoplasms: Real-World Management and Outcomes. This nationwide multicenter retrospective study analyzed 320 neuroendocrine neoplasm patients with bone metastases across 18 Italian centers. The study describes a real world scenario of patients with neuroendocrine tumors and bone metastases, to inform prognostication and generate hypotheses for optimizing use of bone-targeted agents.

Fazio N, Maisonneuve P, Frezza AM, Ranallo N, Ibrahim T, La Salvia A, Brizzi MP, De Divitiis C, Tafuto S, Pusceddu S, Marconcini R, Cives M, Ferrari C, Campana D, De Lisi D, Santini D, Faggiano A, Modica R, Massironi S, Bianchi A, Panzuto F, Antonuzzo L, Pellegrini E, Amoroso V, Puliafito I, Merola E, Silvestris N, Grana CM, Spada F.

J Neuroendocrinol. PMID: 41255062.

prospective clinical trial

Accuracy Limits of Preoperative Biopsy in Retroperitoneal Sarcoma. This international prospective study assessed concordance between preoperative biopsy and surgical pathology in retroperitoneal sarcoma. While histologic subtype accuracy was high, tumor grade was frequently underestimated, especially in

high-grade disease. High-volume centers achieved better concordance. Diagnostic inaccuracies may affect treatment planning, highlighting the need for improved preoperative assessment strategies.

Borghì A, Fiore M, Tiné G, Strauss DC, Bonvalot S, Raut CP, Rutkowski P, Ford S, Swallow CJ, Gyorki DE, Albertsmeier M, Cananzi F, Cardona K, Nessim C, Grignol V, Pennacchioli E, Novak M, Iwata S, Salvatore D, Di Blasi E, Wilkinson M, Tzanis D, Wang J, Skoczylas J, Almond M, Gladdy RA, Mitchell C, Hayes A, Valeri S, Miceli R, Gronchi A, Transatlantic Australasian Retroperitoneal Sarcoma Working Group.

Annals of Surgery. PMID: 41423753.

clinical/computational/research tools

Mass Spectrometry-Based Profiling of Histone Post-Translational Modifications in Clinical Samples. This paper presents a robust protocol for histone extraction from diverse clinical specimens, including snap-frozen, OCT-frozen, and FFPE tumor biopsies. The workflow enables bottom-up LC-MS/MS analysis with reliable detection and quantification of key histone lysine acetylation and methylation marks. By enabling unbiased profiling of histone post-translational modifications in routine samples, this approach supports deeper epigenetic characterization of tumors and facilitates translational studies linking chromatin states to cancer biology and clinical outcomes.

Robusti G, Fulghieri P, Bonaldi T.

J Vis Exp. PMID: 41359602.

translational research - signatures/biomarkers/liquid biopsy

Immune Signatures Separate Efficacy From Toxicity in Immune Checkpoint Inhibitor (ICI) Therapy. This meta-analysis shows that baseline interferon gamma signatures can stratify melanoma patients by likelihood of benefit and toxicity from intensified ICI regimens. High-dose anti-CTLA-4 improved efficacy only in IFN- γ -low tumors, while increasing toxicity in IFN- γ -high cases. These findings support biomarker-driven personalization of immunotherapy intensity to maximize benefit and minimize harm.

Lucas MW, Burton EM, Dimitriadis P, Huang AC, Long GV, Mitchell TC, Amaria RN, Blank CU.

Immunity. PMID: 41478279.

retrospective (real world) clinical study

Zanubrutinib vs Ibrutinib in Chronic Lymphocytic Leukemia: Real-World Evidence. This multicenter real-world retrospective study compared the two Bruton Tyrosine Kinase inhibitors (BTKi) zanubrutinib and ibrutinib in 934 patients with chronic lymphocytic leukemia treated outside clinical trials. Overall, though longer follow-up is needed, zanubrutinib showed improved durability and tolerability as compared to ibrutinib, being associated with lower treatment discontinuation rates and higher time to next treatment or death. Moreover, multivariable analyses confirmed zanubrutinib as an independent predictor of longer treatment persistence. This study provides real world evidence of zanubrutinib as preferred second-generation BTKi.

Martino EA, Pitino A, Vigna E, Pasquale R, Ferrarini I, Moia R, Visentin A, Sanna A, Motta M, Moratti M, Sportoletti P, Chiarenza A, Maggi A, Zammit V, Merli M, Innocenti I, Giordano C, Nocilli L, Postorino M, Stelitano C, Ferrario A, Frustaci AM, Riva M, Pepe S, Ibatci A, Scardino S, Anticoli Borza P, Ballotta L, Mancuso S, Malaspina F, Mele A, Galimberti S, Catania G, Giordano A, Angeletti I, Schiattone L, Pennese E, Miccolis RM, Fama A, Giordano G, Califano C, Bruzzese A, Caserta S, Farina G, Bulian P, Loseto G, Pocali B, Innao V, Galieni P, Fraticelli V, Vitale C, Romeo A, Rossi M, Scortechini I, Vozella F, Malandrucolo L, Varettoni M, Morello L, Pietrantuono G, Conte E, Cantelli M, Murru R, Caracciolo D, Derenzini E, Di Martina V, Marasca R, Del Principe MI, Figuera A, Angotzi F, Coscia M, Di Renzo N, Laurenti L, Amodio N, Musto P, Di Raimondo F, Liso A, Tedeschi A, Trentin L, Gaidano G, Mauro FR, Tripepi G, Morabito F, Gattei V, Gentile M.

Blood Adv 2026. PMID: 41499776.

correlative/descriptive studies

Fecal Metabolomics as a Link Between Diet, Gut Microbiome, and Cardiometabolic Risk. Integrating fecal metabolomics, metagenomics, and dietary data from over 2,600 individuals, this study shows that fecal

metabolites accurately predict intake of multiple food groups and adherence to dietary patterns. The fecal metabolome outperformed established diet-based scores in predicting cardiovascular disease risk. Hundreds of associations between food groups, metabolites, microbial diversity, and species were identified, highlighting metabolites as key mediators between diet and microbiome. These findings support metabolite-based approaches to assess diet-related disease risk and guide interventions.

Pope R, Visconti A, Zhang X, Louca P, Baleanu AF, Lin Y, Asnicar F, Bermingham K, Wong KE, Michelotti GA, Wolf J, Segata N, Berry SE, Spector TD, Leeming ER, Gibson R, Menni C, Falchi M. Nat Commun. PMID: 41345102.

clinical/computational/research tools

A Global Reference Resource for Human Microbiome Meta-Analysis. The authors present curated Metagenomic Data 3, a harmonized collection of over 22,000 human microbiome samples from 94 studies worldwide. This resource enables robust meta-analyses linking microbial species and functions to host traits such as age, sex, BMI, and disease. The study introduces an oral enrichment score, showing that increased oral bacteria in the gut is a consistent disease-associated feature. This standardized, updatable reference provides a powerful tool for reproducible microbiome research.

Manghi P, Antonello G, Schiffer L, Golzato D, Wokaty A, Beghini F, Mirzayi C, Long K, Gravel-Pucillo K, Piccinno G, Gamboa-Tuz SD, Bonetti A, D'Amato G, Azhar R, Eckenrode K, Zohra F, Giunchiglia V, Keller M, Pedrotti A, Likhokin I, Elsafoury S, Geistlinger L, Blanco-Miguez A, Thomas AM, Zolfo M, Ramos M, Valles-Colomer M, Tamburini S, Asnicar F, Jones HE, Huttenhower C, Carey V, Davis S, Pasolli E, Oh S, Segata N, Waldron L.

Nature Communications. PMID: 41436448.

translational research - signatures/biomarkers/liquid biopsy

TERT Promoter Mutations in Oral Rinses as Head and Neck Cancer Biomarkers. This study evaluated TERT promoter (TERTp) mutations in DNA from oral rinses as non-invasive biomarkers for head and neck cancers. TERTp mutations were detected in 25% of oral rinses, with highest prevalence in oral squamous cell carcinoma and strong concordance with tumor tissue. Mutant allele frequencies correlated between samples, and mutations were more frequent in males. Analyses in cell lines confirmed increased TERT expression in mutated cells. These findings support oral rinse-based TERTp testing for early detection of oral squamous cell carcinoma.

Starita N, Tagliabue M, Gheit T, Cerasuolo A, Amiranda S, Pecchillo Cimmino T, Dassi L, Tornesello AL, De Berardinis R, Maffini F, De Palma G, Vecchio S, Paradiso A, Blandino G, Tommasino M, Ansarin M, Chiocca S, Tornesello ML.

Frontiers in Oncology. PMID: 41487579.

retrospective clinical study

BRAF Variant Allele Frequency Predicts Response in Metastatic Melanoma. This retrospective study assessed BRAF variant allele frequency (VAF) as a predictor of response to BRAF/MEK inhibitors in metastatic melanoma. Higher BRAF-VAF was associated with shorter progression-free and overall survival. Normalization of VAF by tumor cellularity improved predictive performance and emerged as an independent prognostic factor. These findings support integrating quantitative molecular metrics into clinical decision-making to refine response prediction in targeted melanoma therapy.

Guida M, Apollonio B, Romano L, Spagnolo F, Quaglino P, Depenni R, Pinto R, Squicciarini T, Fucci L, Di Tullio P, Scaini MC, Maccallini MT, Indini A, Troiani T, Natalicchio I, Brugnara S, Lombardo M, Pellegrini C, Queirolo P, Perrone F, Minisini A, Tucci M, Conca R, Costabile S, Macrì M, Tanda E, Croce E, Senetta R, Fava P, Pugliese G, Pellegrini S, Melucci E, Vecchio MD, Caraglia F, Girlando S, De Summa S, Strippoli S, Italian Melanoma Intergroup (IMI).

Journal of Translational Medicine. PMID: 41408295.

prospective clinical trial

Neoadjuvant Dual Checkpoint Blockade Enables Organ Preservation in CSCC. The MATISSE trial assessed neoadjuvant nivolumab alone or combined with ipilimumab in resectable cutaneous squamous cell carcinoma. High pathological response rates were achieved, particularly with combination therapy, without delaying surgery. Some patients achieved durable complete remission without surgery, preserving organ function. Early metabolic imaging predicted response. These results support response-guided de-escalation strategies and establish neoadjuvant immunotherapy as a transformative approach in CSCC.

Breukers SE, Traets JJH, van Dijk SW, Ostos MM, Fraterman I, Crommelin RD, van der Hulst H, Qiao X, Boere T, van de Poll-Franse LV, Retèl V, van der Noort V, Vos JL, Toppenberg AGL, van der Heijden M, Missale F, Balm F, van den Brekel M, Dirven R, Karakullukcu MB, Karssemakers L, Klop WMC, Lohuis PJFM, Schreuder WH, Smeele LE, van der Velden LA, Plasmeijer E, Smit LA, de Boer JP, Navran A, Westerink B, de Koekkoek-Doll PK, Castelijns J, Wondergem M, Vogel WV, Kuijpers A, van Houdt WJ, Onderwater S, Maas-Bannink E, Cornelissen S, Broeks A, Tijink BM, Devriese LA, de Bree R, Blank CU, Schumacher TN, Thommen DS, Haanen JBAG, Zuur CL.
Nature Medicine. PMID: 41062829.

review/commentary

Telomere Length Alterations and Cancer Risk. This comprehensive review examines telomere length dynamics in cancer and hematologic disorders. Both telomere shortening and excessive elongation are linked to genomic instability, cancer initiation, and progression. The authors discuss current methodologies for telomere length assessment and critically review evidence connecting telomere abnormalities with solid and hematologic malignancies, as well as non-malignant dysfunctions. The review underscores telomere length as a complex biomarker with context-dependent implications for carcinogenesis.

Tarella C, Ferrero D, Herrera Sanchez MB, Canestrone AR, Kholia S, Silengo L, Derenzini E, Ricca I.
Biomedicines. PMID: 41463021.

sex/gender

Sex-Specific Metabolic Signatures of Stress Vulnerability in Depression. This study investigated sex-specific metabolic mechanisms underlying stress vulnerability in major depressive disorder using female rats. Targeted metabolomics in the ventral hippocampus showed that stress-vulnerable females developed anhedonia (as behavioral trait) alongside enhanced fatty acid β -oxidation (as a metabolic trait), mirroring findings previously observed in males. In contrast, resilient females did not activate specific metabolic pathways but showed modulation of antioxidant and neuroprotective processes. These findings highlight shared vulnerability mechanisms across sexes but distinct resilience pathways, reinforcing the need to study sex-specific biology in depression.

Brivio P, Pedretti S, Gallo MT, Palumbo A, Boccazzi M, Gruca P, Lason M, Litwa E, Biala D, Fumagalli F, Papp M, Mitro N, Calabrese F.
Biomedicine & Pharmacotherapy. PMID: 41223762.

meta-analysis

Low Infectious Potential of Airborne SARS-CoV-2 RNA. This systematic review and meta-analysis assessed infectious SARS-CoV-2 in air samples using viral culture and molecular methods. Across 26 studies, only 14% of RNA-positive air samples yielded culturable virus, indicating a low likelihood of airborne infectiousness despite detectable RNA. Data were insufficient to define infectivity thresholds or distance effects. The authors highlight inconsistent reporting and call for standardized protocols, including Ct (cycle threshold) value reporting, to better assess airborne transmission risks.

Onakpoya IJ, Plüddemann A, Rosca EC, Gandini S, Maltoni S, Brassey J, Jefferson T, Heneghan CJ, Evans DH, Conly JM.
BMC Infectious Diseases. PMID: 41449370.

prospective clinical trial

Video-Assisted Informed Consent Improves Patient Understanding. This randomized prospective study compared traditional informed consent with a multimedia video-assisted approach in breast cancer patients undergoing implant-based reconstruction. Patients exposed to a short educational video demonstrated significantly improved comprehension of surgical risks and outcomes. Anxiety and decisional conflict were lower, though not significantly. The findings support the use of multimedia tools to enhance patient education and informed decision-making in oncologic reconstructive surgery.

De Lorenzi F, Carbonaro R, Marzorati C, Pagan E, Miranda S, Bagnardi V, Sangalli C, Negri M, Pravettoni G, Veronesi P.

Aesthetic Plastic Surgery. PMID: 41392053.

review/commentary

Molecular testing in early-stage non-small cell lung cancer: A review. This review discusses the growing importance of comprehensive molecular testing in early-stage (I-III) non-small cell lung cancer (NSCLC). The advent of next-generation sequencing (NGS) and evidence of actionable mutations now make comprehensive profiling increasingly relevant. Identifying driver mutations can directly influence adjuvant treatment planning, refine the role of immunotherapy, and provide prognostic insight. Certain driver subtypes are associated with higher recurrence risk, suggesting a need for intensified surveillance. NGS enables personalized postoperative strategies, including tailored follow-up and potential circulating tumor DNA monitoring, ultimately aiming to improve patient outcomes through precision oncology.

Attili I, Pisapia P, Spitaleri G, Aliaga PT, Del Signore E, Napoli VM, Passaro A, Malapelle U, Troncone G, de Marinis F.

Therapeutic advances in medical oncology. PMID: 41555859.

review/commentary

Safety management of lorlatinib in ALK-positive NSCLC. This article analyzes the safety profile of lorlatinib, a third-generation ALK inhibitor approved for ALK-positive advanced non-small cell lung cancer, and outlines a comprehensive safety management framework. The most frequent adverse events (AEs) are hypercholesterolemia and hypertriglyceridemia, emerging early after treatment initiation. The 5-year analysis of the CROWN study showed minimal changes in AE rates over time. The proposed framework emphasizes patient preparation and regular monitoring, indicating AE-specific interventions and mitigation strategies. Lorlatinib's toxicity appears generally predictable and manageable, and the framework offers pragmatic guidance for clinicians.

Ardizzoni A, Cortinovis D, Gori B, Nuzzo A, Pasello G, de Marinis F.

Future oncology. PMID: 41532596.

review/commentary

Proton therapy and systemic treatments in breast cancer: A review. This review evaluates current preclinical and clinical data on the integration of proton therapy (PT) with systemic treatments in breast cancer. PT is an alternative to conventional radiotherapy, reducing dose exposure to healthy tissues. The findings highlight PT's potential to minimize side effects, particularly cardiotoxicity, and potentially to enhance the efficacy of systemic treatments such as immunotherapy, thereby improving therapeutic outcomes.

Alterio D, Dicuonzo S, Zaffaroni M, Vincini MG, Zagami P, Criscitiello C, Braga F, Milovanova E, Leonardi MC, Veronesi P, Kirby AM, Orecchia R, Curigliano G, Jerezek-Fossa BA.

Cancer treatment reviews. PMID: 41687350.

clinical/computational/research tools

curatedMetagenomicData 3: A large-scale resource for human microbiome meta-analyses. curatedMetagenomicData (cMD) 3 is a resource containing uniformly processed data of over 22,000 human microbiome samples, from 94 studies and 42 countries. It enables meta-analyses to identify links between microbiome microorganisms and human health. Through such analysis, hundreds of microbial species and thousands of functions were found to be significantly associated with sex, age, BMI, and

disease status. Moreover, an "oral enrichment score" (OES) was developed, based on the abundance of oral bacteria in the gut. A higher OES in the gut was consistently observed in individuals with disease, proposing it as a quantifiable signal of altered microbiome health.

Manghi P, Antonello G, Schiffer L, Golzato D, Wokaty A, Beghini F, Mirzayi C, Long K, Gravel-Pucillo K, Piccinno G, Gamboa-Tuz SD, Bonetti A, D'Amato G, Azhar R, Eckenrode K, Zohra F, Giunchiglia V, Keller M, Pedrotti A, Likhokin I, Elsafoury S, Geistlinger L, Blanco-Miguez A, Thomas AM, Zolfo M, Ramos M, Valles-Colomer M, Tamburini S, Asnicar F, Jones HE, Huttenhower C, Carey V, Davis S, Pasolli E, Oh S, Segata N, Waldron L.

Nature communications. PMID: 41436448.

translational research - signatures/biomarkers/liquid biopsy

TERT promoter mutations in oral rinses as non-invasive biomarkers for head and neck cancer. This study evaluated TERT promoter (TERTp) mutations in tumor DNA from oral rinses as biomarkers for head and neck squamous cell carcinoma (HNSCC). Using droplet digital PCR, TERTp mutations (C228T, C250T) were detected in 25% of oral rinses from 132 HNSCC patients and 27% of tumor tissues from 63 patients. Mutation rates were highest in oral squamous cell carcinoma (OSCC), present in 50% of oral rinses and 46% of matched tissues, with 96% concordance. Mutations were more frequent in males and uncommon in non-OSCC cases. TERTp mutations show high concordance between oral rinses and tumors, supporting their potential as non-invasive biomarkers for OSCC detection.

Starita N, Tagliabue M, Gheit T, Cerasuolo A, Amiranda S, Pecchillo Cimmino T, Dassi L, Tornesello A, De Berardinis R, Maffini F, De Palma G, Vecchio S, Paradiso A, Blandino G, Tommasino M, Ansarin M, Chiocca S, Tornesello M.

Frontiers in oncology. PMID: 41487579.

clinical/computational/research tools

Small, task-oriented AI models for diagnosis and prognosis in breast cancer pathology. This article examines the opportunities of small, task-oriented artificial intelligence (AI) models designed to predict clinical relevance of molecular features –such as hormone receptors (HRs), HER2, and somatic mutations– in breast cancer directly from digitized whole slide images (WSIs). To overcome the limitations of large "big data" foundation models, approaches like model distillation (in which a new model learn from the output of the original model rather than from raw data) and weak supervision are critically examined. Progress in this field depends on high-quality datasets, rigorous multi-institutional validation, and collaboration, to deliver clinically actionable innovations.

Frascarelli C, Venetis K, Marra A, Concardi A, D'Ercole M, Mangione E, Negrelli M, Porta FM, Keswani S, Curigliano G, Guerini-Rocco E, Fusco N.

NPJ breast cancer. PMID: 41402342.

correlative/descriptive studies

Gene fusion landscape in metastatic breast cancer from the AURORA program. This study utilized multi-omics data from the AURORA program to characterize gene fusions in metastatic breast cancer. Analyzing RNA sequencing from 325 primary tumors and 350 metastatic lesions across 476 patients, a higher burden of gene fusions was observed in metastatic as compared to matched primary tumors. Fusions involving genes within the same topologically associating domain (TAD) were common in HER2-positive tumors, and frequently acquired in metastatic triple-negative breast cancer. The presence of acquired gene fusions, including ESR1 fusions, was associated with poor prognosis in ER-positive/HER2-negative tumors. This work provides a valuable resource for identifying targetable gene alterations.

Biagioni C, Fimereli D, Irrthum A, Guerrero-Zotano A, Piccart M, Cameron D, Caballero C, Raimbault A, Martins-Branco D, Romagnoli D, Agostinetto E, Venet D, Llinas-Bertran A, Seoane JA, Zoppoli G, Vivancos A, Vingiani A, Oliveira M, Curigliano G, Crestani T, Sotiriou C, Nili Gal-Yam E, Hilbers FS, Aftimos P, Benelli M.

Clinical cancer research: an official journal of the American Association for Cancer Research. PMID: 41427961.

translational research - signatures/biomarkers/liquid biopsy

sMAdCAM-1 as a prognostic biomarker in metastatic renal cell carcinoma. This study evaluated soluble MAdCAM-1 (sMAdCAM-1) as a prognostic biomarker in 1,051 patients with metastatic renal cell carcinoma from three different cohorts. Baseline higher sMAdCAM-1 levels were associated with progression-free and overall survival. Low sMAdCAM-1 levels were associated with an immunosuppressive gut microbiota profile dominated by Enterocloster species. The findings suggest sMAdCAM-1 deserves further investigation as a biomarker-guided tool for microbiota-targeted interventions.

Alves Costa Silva C, Machaalani M, Saliby RM, Zhong C, Xie W, Pasolli E, Piccinno G, Dalban C, Fidelle M, Meurisse A, Vernerey D, Lee GM, Birebent R, Saad E, Steiner C, Flippot R, Barros-Monteiro J, Segata N, Thiery-Vuillemin A, Formenti S, Kuznetsova T, Escudier B, Derosa L, Zitvogel L, Choueiri TK, Albiges L. Nature medicine. PMID: 41501493.

translational research - signatures/biomarkers/liquid biopsy

Molecular alterations and myelodysplastic syndrome risk. Through the genomic and gene expression profiling of CD34+ bone marrow progenitors, the authors identified, in low risk myelodysplastic syndrome, early molecular alterations associated with high risk MDS and secondary acute myeloid leukemia. Such alterations involved the binding of PU.1 to genomic regions associated with immunity, increased T-cell and NK activation, and a higher frequency of SRSF2 mutations, as well as greater susceptibility to infections and cardiovascular events, and an elevated risk of disease progression. Notably, PU.1 inhibition suppressed MDS cell proliferation, identifying key epigenetic factors predisposing to progression.

Vallelonga V, Gandolfi F, Zampini M, Riva E, Maggioni G, Ventura D, Saba E, Termanini A, Polletti S, Prosperini E, Crisafulli L, Campagna A, Ferrari I, Pinocchio N Jr, Todisco G, Pedretti S, Calvi M, Di Vito C, Mavilio D, Mitro N, Ficara F, Della Porta MG, Ghisletti SML. Blood. PMID: 41538708.

correlative/descriptive studies

Extensive baby-to-baby microbiome transmission in nursery settings. This metagenomic study modeled microbiome transmission among 134 individuals, including babies, their educators, and families, over the first year of nursery. Longitudinal sampling of 1,013 fecal samples revealed extensive baby-to-baby microbiome transmission within nursery groups after only one month. By the end of the first term, nursery-acquired strains accounted for a proportion of the infant gut microbiome comparable to that from family. Transmission networks became increasingly intricate over time. Having siblings was associated with higher microbiome diversity and reduced strain acquisition from peers, while antibiotic treatment was the strongest factor associated with increased strain influx.

Ricci L, Heidrich V, Punčochář M, Armanini F, Ciciani M, Nabinejad A, Fazaeli F, Piperni E, Servais C, Pinto F, Valles-Colomer M, Asnicar F, Segata N. Nature. PMID: 41565819.

review/commentary

Axillary management in early-stage HR+/HER2- breast cancer: A narrative review. This narrative review summarizes current strategies in axillary management for patients undergoing upfront surgery for hormone receptor-positive, HER2-negative early breast cancer. It explores the role of sentinel lymph node biopsy (SLNB), indications for axillary lymph node dissection (ALND), and the integration of adjuvant systemic therapy. While some trials (Z0011, AMAROS, SENOMAC) have demonstrated that omission of ALND is safe in some patients (with limited nodal involvement) when combined with radiotherapy, other trials (MonarchE and OlympiA) have introduced systemic therapies (according to the nodal status), suggesting that a reconsideration of disease staging may be needed. Modern management involves assessing feasibility of de-escalated surgery and risk-adapted systemic therapy through individualized care.

Abahssain H, Pasquier D, Laabid K, Barani M, Borges S, Poitureau S, Bettache G, Nguyen TL, Bytha M, Rodriguez J, Lemaire A, Curigliano G, Souadka A.
Cancers. PMID: 41514640.

retrospective clinical study

Post-progression outcomes in HR+/HER2- advanced breast cancer after CDK4/6 inhibitor therapy. This retrospective study described clinical outcomes of 452 patients with HR+/HER2- advanced breast cancer who progressed under treatment with endocrine therapy and a CDK4/6 inhibitor. Among 300 patients who progressed, 250 received subsequent treatment. Patients with visceral progression and CDK4/6i duration <12 months were more likely to receive anthracyclines or taxanes. PFS and OS of these patients were better with endocrine therapy plus everolimus or capecitabine over chemotherapy. After first post-CDK4/6i treatment failure, capecitabine showed better survival. Findings suggest many patients retain endocrine sensitivity after CDK4/6i failure and may benefit from subsequent endocrine-based therapy, delaying chemotherapy.

Torrise R, Giugliano F, Giordano L, Saltalamacchia G, Jacobs F, Schianca AC, Milano M, Bianco N, Sangalli CA, De Sanctis R, Masci G, Curigliano G, Santoro A, Munzone E.
The oncologist. PMID: 41520162.

retrospective/prospective clinical study

Managing malignant pericardial effusion: A single-center experience. This study investigated the efficacy of a surgical approach, consisting in the creation of a pericardio-peritoneal window (PPW), for malignant pericardial effusion (MPE, a severe complication in some cancer types) in 44 patients. The procedure showed a 95.5% success rate (in terms of pericardial relapse requiring further procedures). While 30-day mortality was 9%, the recurrence rate was low. The study concludes that PPW is a safe and effective surgical approach for resolving MPE in patients with a favorable short-term prognosis, whereas pericardial drainage is recommended for those with a less favorable prognosis.

Mazzella A, Caffarena G, Bardoni C, Nicolosi G, Maisonneuve P, Cerretani G, Sedda G, Bertolaccini L, Lo Iacono G, Casiraghi M, Spaggiari L.
Journal of clinical medicine. PMID: 41517333.

sex/gender

Sex and gender differences in adverse events from immunotherapy and targeted therapy in melanoma. This systematic review and meta-analysis investigated the effect of sex and gender on adverse events (AEs) during immunotherapy and/or targeted therapy in melanoma. Through the analysis of 69 studies, women appeared to have a significantly higher risk of thyroid-related AEs compared to men. No significant differences were found for grade III-IV, dermatological, gastrointestinal, or other toxicities.

Gaeta A, Nuvoli L, Doccioli C, Caini S, Saponara M, Cimminiello C, Cosma C, Palmieri G, Cossu A, Vicini F, Mazzarella L, Tosti G, Queirolo P, Gandini S.
British journal of cancer. PMID: 41275011.

correlative/descriptive studies

Integrative multi-specimen analysis of dicarbonyl stress in colon cancer. This targeted mass spectrometry-based, integrated analysis of matched tumor tissue, adjacent mucosa, plasma, and stool, from 26 colon cancer patients, measuring Advanced Glycation Endproducts (AGEs) derived from the reaction of proteins with dicarbonyls compounds (such as MGO, GO, 3-DG, implicated in inflammation and tumorigenesis), showing their marked accumulation in tumors. Tumor MGO levels correlated with upregulation of GLO1, DDOST, and TPI proteins, and downregulation of CD36. The tumor MGO/GO ratio was positively associated with abundances of *Fusobacterium nucleatum* and *Parvimonas micra*, and with metagenomic signatures of oral taxa. The study highlights coherent associations among tissue, circulating, and microbial levels of MGO-derived AGEs.

Ferrero G, Mastrocola R, Tarallo S, Pardini B, Scheijen J, van de Waarenburg M, Gallo G, Chatziioannou AC, Robinot N, Keski-Rahkonen P, Piccinno G, Segata N, Aglago EK, Hughes DJ, Jenab M, Schalkwijk CG, Naccarati A.

Free radical biology & medicine. PMID: 41579975.

prospective clinical trial

Effects of a lifestyle intervention on dietary patterns in breast cancer survivors. This secondary analysis of the InForma trial evaluated the effects of a lifestyle intervention on dietary patterns in 260 overweight or obese breast cancer survivors. Participants were randomized to dietary, physical activity, combined, or minimal intervention, and followed for 24 months. Dietary intervention and age (≥ 60 years) significantly predicted weight loss $>5\%$. Significant reductions in energy and nutrient intake were observed, particularly at 6 months. Adherence to the mediterranean diet improved across the whole study population. The study provides insights into the effectiveness of personalized lifestyle interventions in promoting long-term dietary changes.

Gnagnarella P, Carioni G, Dragà D, Raja S, Baggi F, Simoncini MC, Mazzocco K, Masiero M, Bassi FD, Peradze N, Zorzino L, Pravettoni G, Sieri S, Maisonneuve P.

Nutrition, metabolism and cardiovascular disease: NMCD. PMID: 41145327.

mechanism-oriented research

SH3BP5L as a driver of metastatic progression in aggressive breast cancer. This study identified SH3BP5L as the most highly expressed guanine nucleotide exchange factor (GEF) for RAB11A in breast cancer. High SH3BP5L expression was associated with advanced tumor stage, distant metastasis, and poor prognosis, particularly in HER2+ and triple-negative breast cancer (TNBC). Using FRET sensors and AI-assisted microscopy, researchers showed that SH3BP5L-dependent activation of RAB11A and assembly of a complex with KIF5B was required for cargo delivery to the plasma membrane, governing key metastatic features like integrin recycling. Inhibition of SH3BP5L reduced metastases in zebrafish and murine models, revealing a potential therapeutic vulnerability.

Li H, De Santis MC, Tucci FA, Tosoni D, Zhang P, Jenkins ML, Villari G, Filippone MG, Guerrera E, Tealdi S, Gozzelino L, Gulluni F, Prever L, Zanini C, Forni M, Franco I, Martini M, Burke JE, Serini G, Campa CC, Pece S, Margaria JP, Hirsch E.

The journal of clinical investigation. PMID: 41623179.

clinical/computational/research tools

Mass spectrometry-based analysis of histone H1 variants in clinical samples. The authors describe a mass spectrometry (MS)-based label-free approach to simultaneously analyze all somatic histone H1 variants in patient-derived samples. Histone H1 variants are essential chromatin components that play a role as drivers in cancer and may serve as biomarkers. To overcome the limitations of antibody- and RNA-based methods, this MS-based approach enables the analysis of low-amount clinical samples, such as those obtained through laser capture microdissection of tissue sections, allowing for the study of histone H1 variant expression in specific cell populations.

Bonaldi T, Nuberini R.

Methods in molecular biology. PMID: 41629714.

mechanism-oriented research

L-PGDS in Schwann cells controls peripheral nerve myelin. This study demonstrates that Prostaglandin D2 synthase (L-PGDS) expressed in Schwann cells is part of a coordinated program controlling myelin homeostasis. In vivo and in vitro analyses confirmed that in the absence of L-PGDS, myelin lipid composition, Schwann cell metabolism, and key enzymes are altered. Schwann cells undergo metabolic rewiring, turning to acetate as an energy source and producing ketone bodies. These changes correlate with morphological myelin alterations, suggesting that myelin lipids serve as a reservoir for ketone bodies, providing adaptive substrates to sustain the axo-glial unit.

Trimarco A, Audano M, La Marca R, Pellegatta M, Canevazzi P, Cariello M, Falco M, Pedretti S, Imperato G, Cestaro A, Podini P, Dina G, Quattrini A, Massimino L, Caruso D, Mitro N, Taveggia C.
Glia. PMID: 41631456.

translational research - signatures/biomarkers/liquid biopsy

Circulating tumor DNA dynamics predict outcomes in HR+/HER2- advanced breast cancer. This phase 3b study evaluated the prognostic and predictive value of circulating tumor DNA (ctDNA) in 287 postmenopausal patients with HR+/HER2- advanced breast cancer treated with first-line ribociclib/letrozole. Baseline ctDNA alterations in TP53, MYC, and HER- and CDK4/6-pathway genes were linked to early progression. Absence of a detectable mutation at baseline was associated with better prognosis. Among patients with a detectable mutation, early clearance was observed in 47.1% and was associated with improved progression-free survival. Patients without new emerging mutations also had lower risk of progression, highlighting ctDNA dynamics as a promising biomarker.

Bianchini G, Malorni L, Caputo R, Zambelli A, Puglisi F, Bianchi GV, Del Mastro L, Paris I, Montemurro F, Colleoni M, Allegrini G, Tamperi S, Zamagni C, Cazzaniga ME, Orditura M, Guarneri V, Adamo V, Romagnoli E, Valerio MR, Cinieri S, Benelli M, Callari M, Valsecchi D, Castelletti D, Grasso D, Fenderico N, Arpino G, De Laurentiis M.

Clin Cancer Res 2026. PMID: 41587113.

prospective clinical trial

Single-port robotic surgery in gynecologic oncology: A prospective cohort study. This prospective cohort study evaluated the feasibility and safety of single-port (that is, through a single incision) robotic surgery (an emerging technology in Europe) for suspected or confirmed gynecologic cancer in 63 patients at a high-volume referral center. Endometrial cancer was the most common indication. All procedures were completed without conversion to multi-port or open surgery. No intra-operative complications occurred. Post-operative pain was minimal, and median hospital stay was 2 days. Three major post-operative complications (4.8%) occurred, all managed surgically. Single-port robotic surgery appears feasible and safe for selected patients, though larger studies are needed.

Ribero L, Schivardi G, Achilarré MT, Aloisi A, Betella I, Xhindoli L, Garbi A, Aletti GD, Colombo N, Maggioni A, Multinu F, Zanagnolo V.

Int J Gynecol Cancer. 2026. PMID: 41620340.

prospective clinical trial

Impact of lobular histology on CDK4/6 inhibitor (CDK4/6i) effectiveness in advanced breast cancer. The authors present the results of a subgroup analysis of the PALMARES-2 trial, investigating the predictive and prognostic value of histology in HR+/HER2- advanced breast cancer patients treated with endocrine therapy (ET) and CDK4/6i. The results showed, in a real world scenario, that tumor histology is indeed a predictor of efficacy of ET+CDK4/6i. Moreover, their results highlight a comparable efficacy of all the three CDK4/6i tested, suggesting that the choice of the specific inhibitor should be guided by tolerability, manageability and patient preferences.

Mazzoli G, Provenzano L, Dieci MV, Curigliano G, Giuliano M, Botticelli A, Lambertini M, Rizzo G, Pedersini R, Sirico M, La Verde N, Gennari A, Zambelli A, Toss A, Piras M, Giordano M, Tagliaferri B, Generali D, Sartori D, Fotia G, De Monte M, Ligorio F, Jacobs F, Armani G, Zurlo C, Menichetti A, Griguolo G, Faso V, Schianca AC, Munzone E, Marra A, Chiappe E, Scagnoli S, Pisegna S, Capasso C, De Angelis C, Arpino G, Criscitiello C, Guarneri V, Pruneri G, Mariani L; PALMARES-2 study group; Vernieri C.

Breast. PMID: 41619649.

clinical/computational/research tools

Nomogram for predicting tumor recurrence after intraoperative electron radiotherapy (IOERT). This study developed and validated a nomogram to predict in-breast tumor recurrence (IBTR) in 3,397 breast cancer patients treated with intraoperative radiotherapy using electrons (IOERT). With a median follow-up of 6.1 years, the 5- and 10-year cumulative incidence of IBTR was 4.4% and 13.5%, respectively. Key risk

factors for IBTR included age under 60, certain histologic subtypes, positive axillary nodes, and intermediate/high tumor grade. The nomogram may be a useful tool for treatment decision-making in patients eligible for IOERT.

Rojas DP, Frassoni S, Maisonneuve P, Intra M, Kouloura A, Zerella MA, Fodor CI, Cornacchia L, Bergamaschi L, Sangalli C, Comi S, Morra A, Dicuonzo S, Galimberti V, Veronesi P, Zaffaroni M, Vincini MG, Bagnardi V, Orecchia R, Jereczek-Fossa BA, Leonardi MC.

Breast cancer research and treatment. PMID: 41615490.

psychoncology studies

Improving quality of life of breast cancer survivors. This pilot study examined the effectiveness of a combined 1-week intervention of daily sailing lessons and group psychological sessions for 60 female breast cancer survivors. Quality of life significantly improved after the intervention, with gains in physical well-being, emotional well-being, and breast cancer-specific concerns. No changes were observed in social or functional well-being, and anxiety levels remained stable. The study suggests that a short-term group intervention in a natural environment may enhance quality of life, particularly in physical and emotional domains, warranting further investigation.

Sebri V, Ongaro G, Giudice AV, Mazzocco K, Pravettoni G.

Eur J Cancer Prev. PMID: 41612634.

retrospective clinical study

Factors influencing outcomes in trastuzumab deruxtecan-treated HER2+ metastatic breast cancer. This retrospective analysis of the Italian DE-REAL study evaluated the impact of clinical characteristics and drug-drug interactions (DDIs) on clinical outcomes in 143 patients with HER2+ metastatic breast cancer receiving trastuzumab deruxtecan (T-DXd). Age did not significantly affect progression-free survival (PFS), but patients >65 years had reduced overall survival. Patients with BMI >25 demonstrated significantly longer PFS but experienced higher toxicity rates. DDI risk classification did not impact survival. The study reinforces T-DXd's efficacy in a broad real-world population but suggests personalized monitoring for elderly and higher BMI patients.

Pisegna S, Scagnoli S, Gentile G, Chiavassa A, Caputo R, De Laurentiis M, Curigliano G, Lambertini M, Pantano F, Orlandi A, Palazzo A, Paris I, Vernieri C, Tedesco B, Giampaglia M, Palleschi M, Ballatore Z, Alesini D, D'Auria G, Fabbri MA, Rossi L, Fiscon G, Marchetti P, Fabi A, Botticelli A.

The oncologist. PMID: 41587947.

prospective clinical trial

Tailoring surgical and systemic treatment in melanoma patients: 5-year outcomes from the PRADO trial. This report presents updated (5-year) survival data of 99 patients with stage III macroscopic melanoma receiving neoadjuvant ipilimumab plus nivolumab (the phase II PRADO trial; first clinical trial in melanoma evaluating a surgical de-escalation approach). Event-free survival was 71%, relapse-free survival 74%, distant metastasis-free survival 79%, and overall survival 86%. Ongoing grade 1-2 immune-related adverse events occurred in 69% of surviving patients. Major pathologic response (MPR), high tumor mutational burden (TMB), high interferon-gamma (IFN γ) signature, and PD-L1 expression \geq 1% were associated with favorable outcomes. Combined high TMB, IFN γ , and PD-L1 yielded 100% MPR and event-free survival (conversely, low TMB, IFN γ and PD-L1 expression correlated with poor outcomes).

Hoeijmakers LL, Dimitriadis P, Wijnen SCMA, Reijers ILM, Lopez-Yurda M, Menzies AM, Broeks A, Cornelissen S, Torres Acosta A, van der Wal A, Saw RPM, Versluis JM, van Houdt WJ, Wouters MW, Romano J, Rozeman EA, Grijpink-Ongering LG, Kapiteijn E, van der Veldt AAM, Suijkerbuijk KPM, Eriksson H, Hospers GAP, van der Hage JA, Grünhagen DJ, Witkamp AJ, Lijnsvelt JM, Klop WMC, Zuur CL, Bruining A, Al-Mamgani A, Pennington TE, Shannon KF, Ch'ng S, Colebatch AJ, Gonzalez M, Spillane AJ, Haanen JBAG, Rawson RV, Scolyer RA, van de Wiel BA, van Akkooi ACJ, Long GV, Blank CU.

Nature medicine. PMID: 41606118.

review/commentary

Rare non-squamous cell carcinoma malignant laryngeal tumors: A retrospective study and systematic review. This study combined a bicentric retrospective cohort of 74 patients with a systematic literature review to assess rare non-squamous cell carcinoma malignant laryngeal tumors, including sarcomas, neuroendocrine carcinomas, malignant salivary gland tumors, and mucosal melanomas. Surgery was the primary treatment in 98.6% of cases. Sarcomas and salivary gland tumors demonstrated favorable survival, whereas neuroendocrine carcinomas showed poor outcomes with high recurrence rates. Radical tumor excision achieved effective loco-regional control across histologies. The literature review revealed marked heterogeneity. The study highlights the need for multicenter collaboration to optimize treatment strategies for these rare entities.

Chu F, Benzi P, Tagliabue M, Mossinelli C, Zorzi SF, Gandini s, Romelli M, Filauro M, landelli A, Marchi F, Peretti G, Ansarin M.

Oral oncology. PMID: 41643539.

review/commentary

Four approaches to move beyond correlation to causation in chemical mixture research. This article introduces four approaches designed to advance understanding of harmful chemical mixtures, to examine health benefits of reducing exposure, and move beyond correlation, to causation and intervention. These approaches are: 1) 'hMIX', to identify potentially harmful mixtures using human reference data and experimental evidence (and go from correlation in data to actual causality); 2) the Similar Mixture Approach (SMACH), linking the hMIX data with actual human exposure to such chemical mixtures, across populations (for risk assessment); 3) hybrid epidemiology, bridging population-based (descriptive) and experimental-based (mechanistic) understanding; and 4) counterfactual modelling, estimating the potential impact of interventions (to go from observation to actual intervention). The authors propose an integrative framework combining these approaches to predict and prevent chemical mixture-related health effects.

Elagali A, Rüegg J, Caporale N, Testa G, Sapounidou M, Fini JB, Andersson PL, Dunlop S, Bornehag CG, Gennings C.

Neurotoxicology. PMID: 41654310.

review/commentary

Ribosome biogenesis rate as a determinant of cancer cell sensitivity to chemotherapy. This review discusses how the rate of ribosome biogenesis (RiBi) and genomic alterations of ribosomal proteins (RPs) influence cancer cell sensitivity to RiBi-inhibiting chemotherapies. These drugs work by freeing RPs that bind to and inhibit MDM2, stabilizing p53 and inducing cell death. A high RiBi rate leads to strong MDM2 inhibition, while a low RiBi rate or RP mutations/deletions may cause resistance. The review suggests evaluating RiBi rate and RP status in tumors to predict drug sensitivity and choose appropriate therapeutic protocols, including combining RiBi inhibitors with p53-stabilizing drugs or MDM2 inhibitors in resistant cases.

Tréré D, Montanaro L, Derenzini M, Agostinelli C, Derenzini E.

Oncology reviews. PMID: 41660279.

meta-analysis

Anti-EGFR rechallenge in metastatic colorectal cancer: A meta-analysis. This systematic review and meta-analysis of three phase II randomized trials with 320 patients investigated anti-EGFR rechallenge versus standard of care (SoC) in chemorefractory metastatic colorectal cancer (mCRC) with wild-type RAS/BRAF circulating tumor DNA (ctDNA). Anti-EGFR rechallenge significantly improved disease control rate, objective response rate, and progression-free survival compared to SoC. No overall survival benefit was detected. The findings support the use of anti-EGFR rechallenge as later-line treatment, particularly when tumor shrinkage is a clinical priority.

Kuznetsova O, Battaiotto E, Malvezzi G, Gervaso L, Zampino MG, Cella CA, Benini L, Spada F, Fedyanin M, Tryakin A, Carbone F, Maiorano BA, Ciardiello D, Fazio N.

Critical reviews in oncology/hematology. PMID: 41651313.

clinical/computational/research tools

An adjusted BCI model to identify premenopausal women with very low risk of distant recurrence. This study validated, in 2,025 premenopausal patients with hormone-receptor-positive node-negative breast cancer from the SOFT and TEXT trials, an adjusted Breast Cancer Index (BCI) model to identify premenopausal women at very low risk of distant recurrence. The adjusted model re-classified about 18-20% of patients into a minimal-risk group, with estimated 2.0-2.3% of 10-year distant recurrence (DR) rates. According to this adjusted model, the low-risk group had instead an estimated 10-year DR rates of 4.1-4.6%. The study confirmed the prognostic ability of the adjusted model including an additional risk group (the minimal-risk group) comprising premenopausal patients at very low risk of DR, thus providing relevant information for personalizing adjuvant endocrine therapy.

O'Regan RM, Ren Y, Zhang Y, Fleming GF, Francis PA, Pagani O, Walley BA, Kammler R, Dell'Orto P, Viale G, Loi S, Colleoni M, Treuner K, Regan MM.

Breast. PMID: 41637791.

retrospective clinical study

Adjuvant therapy in older, low-risk, luminal A-like breast cancer patients. This study assessed oncological outcomes in 9,660 early-stage, luminal A-like, low-risk breast cancer patients aged ≥ 65 after conserving surgery, using data from EUSOMA-certified units. Patients received endocrine therapy (ET) alone, whole breast irradiation (WBI) alone, both, or no adjuvant therapy. Compared with no therapy, ET+WBI significantly improved in-breast tumor recurrence-free survival (IBTRFS) and breast cancer-specific survival (BCSS). ET alone, WBI alone, and both combined significantly lowered mortality. Despite short follow-up, this large series showed that adjuvant treatments positively impacted outcomes in these low-risk patients.

Aristei C, Tomatis M, Ponti A, Marotti L, Battisti NML, Leung Cheung K, Hartmann OJ, Rubio IT, Santini D, Sardanelli F, Senkus E, van Dam P, Curigliano G; Eusoma Working Group .

European journal of cancer. PMID: 41690148.

What else is new in science?

(text by Ai Yi (DeepSeek); revision by Stefania Averaimo)

Superiority of ctDNA Methylation for Early Detection of Liver Cancer. This study compared the power of biomarkers based on ctDNA mutation and methylation for detecting hepatocellular carcinoma (HCC). In a large multi-center cohort, a methylation-based model significantly outperformed mutation analysis. Researchers developed a cost-effective, multiplex PCR-based assay (MBA-seq) and further refined it to a two-marker panel (HCCtect). HCCtect showed high accuracy, surpassing alpha-fetoprotein, and could be considered as a promising non-invasive tool for early detection and monitoring of high-risk individuals.

Journal of Hematology & Oncology. PMID: 41163059

Sucralose Impairs Immunotherapy Efficacy via Gut Microbiome. This study reveals that consumption of the artificial sweetener sucralose alters gut microbiota, reducing the levels of arginine available for the microbiota. This leads to impaired T-cell metabolism and function, ultimately blunting the response to anti-PD-1 immunotherapy in mouse models and cancer patients. Restoring arginine or transplanting healthy microbiota can rescue T-cell function and therapy response.

Cancer Discovery. PMID: 40742298

An Immunogen-Free CRISPR Platform for In Vivo Screens. Conventional CRISPR-Cas9 tools trigger immune responses in immunocompetent hosts, skewing screen results. This work introduces StealTHY, an immunogen-free CRISPR platform exploitable both in syngeneic and humanized models. Using this system, researchers identified the AMH-AMHR2 axis as a previously concealed regulator of metastasis, revealing new therapeutic targets.

Cell. PMID: 41205600

Ultrasensitive ctDNA Monitoring Predicts Lung Cancer Relapse. Using a whole-genome ctDNA assay, this study analyzed nearly 3,000 plasma samples from non-small cell lung cancer patients. Ultrasensitive detection before and after surgery was highly prognostic. Monitoring ctDNA kinetics during adjuvant therapy identified patients who cleared ctDNA and had better outcomes, providing a refined schema for risk stratification and treatment guidance.

Cell. PMID: 41205598

Oxygen Sensing Orchestrates Innate Immune Cell Function. This review summarizes how acute and chronic hypoxia shape innate immune responses. Oxygen-sensing hydroxylases and epigenetic modifiers regulate HIF (hypoxia-inducible factor) pathways and reprogramming, tailoring immune cell metabolism and function within tissue microenvironments. The dual role of hypoxia in different contexts is highlighted, along with therapeutic strategies targeting these pathways to restore immune competence.

Nature Immunology. PMID: 41203908

DNA Breaks Cause Heritable “Chromatin Fatigue”. A single DNA double-strand break (DSB) within a topologically associated domain (TAD) causes lasting alterations in 3D chromatin structure that persist after repair is complete. These changes, featuring topological rearrangements and loss of local RNA, are transmitted to daughter cells and heritably impair gene expression, revealing a new dimension of DNA damage called post-repair chromatin fatigue.

Science. PMID: 41196998

CRISPR Screen Identifies PTGES3 as a Critical Androgen Receptor (AR) Stabilizer. Using a novel endogenous AR fluorescent reporter and genome-scale CRISPRi screens, researchers identified genes regulating AR protein levels in prostate cancer. PTGES3 emerged as a key, previously poorly characterized hit. PTGES3 binds directly to AR, stabilizing it and enabling its nuclear function. Its expression correlates with therapy resistance, marking it as a potential therapeutic target to overcome resistance to AR-targeted therapies.

Nature Genetics. PMID: 41193657

Immune Evasion in Colorectal Cancer Follows a “Big Bang” Pattern. Multi-omic analysis of colorectal cancers reveals that immune escape and exclusion occur early, near the point of malignant transformation, and define subsequent cancer-immune evolution. Somatic alterations in chromatin accessibility contribute to silencing neoantigens. Later intratumoral differences in immune editing are minimal, supporting a “Big Bang” evolutionary model for immune evasion.

Nature Genetics. PMID: 41193656

A Call for Accelerated Tumor-Agnostic Drug Development. This perspective advocates for a paradigm shift from anatomic to molecular-driven cancer treatment, accelerating the development of tumor-agnostic therapies, aiming for 50-100 approved agents within 25 years to ensure every patient receives therapy based on their tumor's molecular identity, eliminating therapeutic inequities.

Cancer Discovery. PMID: 41104556

Germline Mutations as Expanding Cancer Drug Targets. This review discusses the growing therapeutic actionability of germline mutations in cancer, beyond classic hereditary syndromes. Advances in synthetic lethality, immunotherapy, and vaccines support the feasibility of universal germline testing. It compares diagnostic approaches and envisions a future where germline profiling guides access to an effective and expanding therapeutic portfolio.

Cancer Discovery. PMID: 41178351

TROP2 CAR-T Cells Eliminate Drug-Tolerant Cells in EGFR-Mutant non-small cell lung cancer. EGFR-mutant lung cancers treated with tyrosine kinase inhibitors relapse due to drug-tolerant persister (DTP) cells. These DTPs highly express TROP2. While a TROP2-targeted antibody-drug conjugate only modestly

delayed recurrence, a single infusion of TROP2-directed CAR-T cells significantly prolonged relapse-free survival and achieved cure in mouse models, highlighting a promising strategy to prevent relapse.
Cancer Discovery. PMID: 40762432

Targeting Dormant Cancer Cells to Prevent Metastasis. Metastases often arise from dormant cancer cells (DCCs), which evade therapy and immune detection in a non-proliferative state. This review provides a comprehensive overview of DCC biology, the challenges in detecting these rare cells, and the experimental strategies and therapeutic approaches under clinical investigation aimed at eradicating them to improve patient outcomes.
Molecular Cancer. PMID: 41225537

Intracellular Bacteria Detected in Brain Tumor Microenvironment. A multi-institutional study detected intracellular bacterial signals within glioma and brain metastasis samples. Spatial analyses linked these microbial elements to local immune-metabolic signatures. The bacteria showed sequence overlap with oral/gut microbiota, introducing intratumoral microbes as a novel component of the brain tumor microenvironment.
Nature Medicine. PMID: 41238915

Targeting a Novel Phosphorylation Site in PTEN-Deficient Cancers. Loss of tumor suppressor PTEN leads to phosphorylation of PI3K β at tyrosine 962 (p-PI3K β Y962), driving tumorigenesis via interactions with EPHA2 and SRC. This study developed an antibody detecting this phospho-form in tumors. The FDA-approved SRC/EPHA2 inhibitor dasatinib reduced p-PI3K β Y962 and suppressed tumor growth specifically in PTEN-null models, revealing a new druggable target.
Cancer Discovery. PMID: 41237375

CRISPR Screens in NK Cells Reveal New Engineering Targets. Genome-wide CRISPR screens in primary human NK cells identified MED12, ARIH2, and CCNC as key negative regulators. Knocking out these genes enhanced NK cell antitumor function, metabolic fitness, and cytokine production against refractory cancers in vitro and in vivo, providing a resource for engineering next-generation NK cell therapies.
Cancer Cell. PMID: 40845844

In Vivo CAR Cell Therapy: Towards Ready-to-Use Therapeutics. This review discusses in vivo CAR-T therapy, where CAR genes are delivered directly to a patient's T cells, bypassing complex ex vivo manufacturing. This approach offers a more efficient, economical, and accessible "ready-to-use" approach compared to conventional autologous CAR-T.
Journal of Hematology & Oncology. PMID: 41261423

Synergizing Nanotechnology with Bispecific Antibodies for Cancer Immunotherapy. This review explores the synergistic potential of combining bispecific antibodies (bsAbs) with nanotechnology. Strategies include encapsulating therapeutic bsAbs within nanocarriers to improve delivery, and using mRNA-loaded nanocarriers to generate bsAbs in vivo, aiming to enhance efficacy and reduce toxicity.
Molecular Cancer. PMID: 41250091

DNMT3A Mutations Are Dispensable for AML Maintenance. In acute myeloid leukemia, DNMT3A R882 mutations are known initiators that alter DNA methylation. However, using CRISPR to correct these mutations in patient-derived leukemic cells showed that, while being needed for tumor initiation, they are largely dispensable for disease maintenance, challenging the assumption that initiating oncogenes are always required for cancer persistence.
Cancer Discovery. PMID: 41263425

G2E3-Catalyzed H3K14 Ubiquitination Guides Heterochromatin Formation. This study identifies G2E3 as an E3 ligase that catalyzes H3K14 mono-ubiquitination (H3K14ub) at pericentromeric heterochromatin during the G2/M phase. H3K14ub is essential for the recruitment of SUV39H and HP1, ensuring proper

chromatin compartmentalization. Loss of G2E3 disrupts this organization, causing widespread transcriptional repression.

Nature. PMID: 41094145

26 Years of Immune Checkpoint Inhibitor Therapy – A Review. This review comprehensively covers the landscape of immune checkpoint inhibitor (ICI) therapy from 2000 to 2025. It details the success of CTLA-4, PD-1, and PD-L1 inhibitors, the emergence of LAG-3 and bispecific antibodies, and discusses predictive biomarkers, immune-related adverse events, mechanisms of resistance, strategies to overcome them, and future directions in the field.

Journal of Hematology & Oncology. PMID: 41310835

Cryo-IEF: A Foundation Model for Automated Cryo-EM Processing. To democratize cryo-EM, researchers introduce Cryo-IEF, a model pre-trained on 65 million particle images. It enables tasks like particle classification and quality assessment. Building on this, the fully automated CryoWizard pipeline resolves high-resolution structures and mitigates preferred orientation, overall broadening Cryo-EM application.

Nature Methods PMID: 41310054

Epithelial Plasticity in Colorectal Cancer. In colorectal cancer, oncogenic MAPK signaling induces a regenerative stem-like state. Inhibiting this pathway triggers rapid transcriptional remodeling toward a Wnt-associated canonical stem phenotype, driving acute resistance in KRAS-mutant and delayed resistance in BRAF-mutant tumors. Restraining this plasticity, such as in early metastatic disease, or through the targeting of Rnf43 mutations, enhances therapeutic response.

Nature PMID: 41286180

The Tumor Microenvironment in Colorectal Cancer for Immunotherapy. This review describes the immunosuppressive tumor microenvironment (TME) in microsatellite-stable colorectal cancer (CRC) and why it resists immune checkpoint blockade. It covers immune components at various disease stages, the impact of current therapies on immunity, and novel strategies to modulate the TME to enhance CRC sensitivity to immunotherapy.

Nature Reviews Cancer PMID: 40983666

Multi-omic Atlas Reveals Heterogeneity in Glioma Microenvironment. Multi-omic spatial analyses of 670 lesions from 310 glioma patients aimed at describing the tumor microenvironment and identifying hallmarks of cancer cell escape to therapy shows that targetable antigens are expressed in less than 50% of tumor cells in most gliomas. The immune microenvironment of recurrent IDH-mutant gliomas shifts from T-cell-rich to microglia and macrophage-dominated microenvironment. N-glycosylation best classifies tumor grade, while immune signatures predict survival.

Cancer Cell PMID: 41386224

Fasting Enhances Endocrine Therapy via Glucocorticoid Receptor Activation. Periodic fasting combined with endocrine therapy delays resistance in ER α -positive breast cancer. Fasting induces epigenetic reprogramming, activating glucocorticoid receptor (GR) and progesterone signaling. GR activation is pivotal; its knockout hinders the benefit, and corticosteroid administration recapitulates the enhanced anti-tumor effect.

Nature PMID: 41372410

Microtubules Sequester Signaling Proteins via C1 Domains to Regulate RhoA. Microtubules directly bind the C1 domain of the signaling protein GEFH1, sequestering and inactivating it. Mutations disrupting this binding release GEFH1, activating RhoA-dependent immune responses. This microtubule-C1 domain interaction is a conserved structural mechanism. These findings highlight how microtubules can work in spatiotemporal signal regulation, integrating different pathways and cell processes.

Cell. PMID: 41365297

Novae: A Graph-Based Foundation Model for Spatial Transcriptomics. Novae is a novel foundation model, trained on nearly 30 million cells from 18 tissues, representing a useful tool for spatial transcriptomic analysis and biomedical research.

Nature Methods. PMID: 41372623

Axillary surgery in breast cancer with residual micrometastases after neoadjuvant chemotherapy. This retrospective study of 1585 patients found that, when nodal radiotherapy was given, omitting axillary lymph node dissection (ALND) did not significantly increase the overall 3-year axillary recurrence rate. However, patients with triple-negative breast cancer had higher recurrence without ALND. The findings suggest ALND omission is feasible for many, but tumor biology must be considered.

The Lancet. Oncology. PMID: 41449148.

Proton therapy reduces toxicity in oropharyngeal cancer versus photon therapy. This phase 3 trial showed that intensity-modulated proton therapy (IMPT) was non-inferior to photon therapy (IMRT) in terms of progression-free survival, while it improved overall survival. IMPT resulted in significantly lower rates of severe toxicity (including dysphagia, xerostomia, and gastrostomy tube dependence), establishing it as a new standard option.

Lancet (London, England). PMID: 41391462.

Assessing the value of genomic sequencing in healthcare. Integrating genomics into clinical care requires robust evaluation methods that capture personal utility, data reuse potential, and system-wide impacts. Traditional frameworks fall short. The review discusses emerging best practices and the need for standardized outcomes and real-world data to guide sustainable, equitable implementation.

Nature medicine. PMID: 41310283.

Immune cell senescence linked to melanoma immunotherapy resistance. Non-responders to checkpoint inhibitors exhibited increased cellular senescence in CD8+ T, CD4+ T, B, and NK cells compared to responders. This senescence was independent of clinical features and conferred immunosuppressive properties, driving treatment failure. Targeting immune cell senescence may improve immunotherapy outcomes.

Molecular cancer. PMID: 41372921.

Gut microbiota influences pancreatic cancer immunity and therapy. The gut microbiome regulates antitumor immunity in pancreatic cancer by modulating immune cell functions. Microbial metabolites and communities can impact the efficacy of immunotherapies. Interventions like dietary changes, probiotics, and fecal transplantation show promise in improving treatment responses and may serve as predictive biomarkers.

Molecular cancer. PMID: 41469665.

Chronic pancreatitis mutations cooperate with Kras in early pancreatic cancer. In a mouse model, a human chronic pancreatitis-associated CPA1 mutation combined with oncogenic Kras dramatically increased pancreatic remodeling, fibrosis, and metaplastic lesions. The mutation induced acinar and ductal cell plasticity and specific inflammatory cell-cell communication networks, cooperating with Kras to drive early carcinogenesis.

Gut. PMID: 41419303.

NPM1 supports WNT-driven tumorigenesis by alleviating cellular stress. NPM1 is upregulated in WNT-driven intestinal and liver tumors. Its loss induces ribosome pausing, triggering a protein synthesis stress response and p53 activation, which inhibit tumorigenesis. NPM1 is dispensable in adult epithelial normal tissue, making it a promising therapeutic target in p53-proficient, WNT-driven cancers like colorectal cancer.

Nature genetics. PMID: 41413654.

Secondary bile acids from gut bacteria causally promote colorectal cancer. A Western diet increased secondary bile acids and tumorigenesis in a pig CRC model. Human CRC patients had more gut bacteria with bile acid 7 α -dehydroxylating activity. Introducing these bacteria into mice increased tumor burden, while a genetically modified strain lacking this activity reduced tumors, proving a causal role.
Gut. PMID: 41412727.

In macrophages, WDR4 promotes liver cancer progression and immunotherapy resistance. In hepatocellular carcinoma, WDR4 is upregulated in tumor-associated macrophages (TAMs) where it promotes pro-tumoral TAM polarization by enhancing ABCA1 translation and cholesterol efflux, independently from its RNA modification role. WDR4 silencing in TAMs suppressed tumor growth and enhanced anti-PD-1 therapy efficacy.
Nature cell biology. PMID: 41315768.

Core molecular features of extracellular vesicles in the human plasma. A high-resolution proteomic and lipidomic analysis of over 140 human plasma samples defined a conserved core set of 182 proteins and 52 lipids characteristic of circulating extracellular vesicles (EVs). The study identifies ADAM10 and PS(36:1) as specific EV markers and provides a public resource for understanding EV biology.
Nature cell biology. PMID: 41315767.

Efficacy of neoadjuvant immunotherapy in early-stage colon cancer. Results of a phase II trial showed that, in early stage mismatch-repair-proficient colon cancer patients, nivolumab plus ipilimumab before surgery led to a 26% response rate. Responders showed circulating tumor DNA clearance and had tumors with higher genomic instability and proliferation signatures, identifying potential biomarkers for patient selection.
Nature. PMID: 41115454.

Machine learning improves precision oncology workflows. The growing complexity of molecular data challenges clinical interpretation. Integrating machine learning with large clinico-genomic datasets can enhance variant interpretation, streamline case review, and generate therapeutic hypotheses. Responsible implementation and rigorous evaluation are crucial for clinical adoption.
Nature reviews. Cancer. PMID: 41478861.

Spatial omics reveals organization of tumor ecosystems. Spatial technologies map tissue organization and cell interactions within tumors, uncovering functional niches that shape evolution and therapy response. Analytical advances integrate multimodal data and foundation models. The field aims to translate spatial discoveries into clinically deployable assays for predictive oncology.
Cancer cell. PMID: 41478277.

p53 inactivation drives breast cancer brain metastasis through fatty acid synthesis. Analysis of breast cancer brain metastases revealed pervasive p53 pathway disruption. p53 loss upregulated SCD1 and fatty acid synthesis, essential for brain metastasis growth. Astrocytes enhanced this metabolic reprogramming. Targeting fatty acid synthesis inhibited p53-deficient metastasis in models.
Nature genetics. PMID: 41461910.

Inhibiting NSD2 reverses prostate cancer lineage plasticity and restores drug sensitivity. In castration-resistant neuroendocrine prostate cancer, the histone methyltransferase NSD2 maintains an epigenetic state driving lineage plasticity. NSD2 inhibition reverts neuroendocrine tumors back to an androgen receptor-positive adenocarcinoma state, restoring sensitivity to androgen receptor-targeted therapy like enzalutamide.
Nature. PMID: 41299174.

Catalytic NSD2 inhibition is a therapeutic vulnerability in KRAS-driven cancers. A first-in-class NSD2 inhibitor reverses oncogenic H3K36me2-driven chromatin plasticity in KRAS-driven pancreatic and lung

cancers, silencing pathological gene programs. NSD2 inhibition alone prolonged survival in mouse models and synergized with a KRAS(G12C) inhibitor to induce profound tumor regression.
Nature. PMID: 40770093.

Hallmarks of Cancer: New Dimensions and Therapeutic Opportunities. This review synthesizes the conceptualization of cancer hallmarks from the past 25 years, covering aspects such as aberrantly acquired capabilities, enabling characteristics, hallmark-conveying cells in microenvironments, and systemic interactions, which define the mechanistic dimension of tumorigenesis, and proposes that co-targeting of these hallmarks, guided by the mechanistic understanding of cancer processes, could offer impactful new therapeutic strategies.
Cell. PMID: 41616779.

The LINUX Trial. The LINUX phase II trial (NCT05594095) investigated AI-guided precision therapy for HR+/HER2- metastatic breast cancer following CDK4/6 inhibitor resistance. Using artificial intelligence, 105 patients were classified into four distinct subtypes (SNF1-4) and randomly assigned to receive subtype-matched therapy or treatment of physician's choice. The precision approach significantly improved objective response rates, particularly in the SNF2 (65% vs. 30%) and SNF4 (70% vs. 20%) groups, with comparable safety profiles (37% grade 3-4 adverse events in both arms). These results demonstrate that AI-driven subtyping can effectively identify targeted treatments, offering a promising new strategy for patients who have progressed on standard therapies and warranting confirmation in larger phase III trials.
Cancer Cell. 2026. PMID: 41349543.

The PreA LLM Chatbot. Researchers developed PreA, a large language model (LLM) chatbot co-designed with stakeholders to automate pre-specialist consultations. In a trial across 24 disciplines with 2,069 patients, those using PreA independently were compared to those with staff-assisted use or no PreA use. The PreA-only group achieved a 28.7% reduction in specialist consultation time and significant improvements in both physician-rated care coordination and patient-reported communication ease. The chatbot operated autonomously, matching the performance of the staff-assisted group. This study highlights that co-designing AI with local stakeholders is a powerful strategy for improving healthcare efficiency and patient-centered care, particularly in resource-constrained settings.
Nat Med 2026. PMID: 41555035.

DeepMet: A Chemical Language Model for Discovering Novel Mammalian Metabolites. Large parts of the mammalian metabolome remain unexplored due to challenges in structure elucidation. DeepMet is a chemical language model that learns from known metabolites to anticipate the existence of uncharacterized ones. Integrated with mass spectrometry data, it facilitated the discovery of dozens of structurally diverse mammalian metabolites, demonstrating the power of language models in mapping metabolism.
Nature. PMID: 41535467.

The Interplay Between CHIP and Inflammageing in Age-Related Disease. Clonal haematopoiesis of indeterminate potential (CHIP) arises from mutant hematopoietic stem cells (HSCs) which, being resistant to the functional decline induced by the inflammation linked to aging (inflammageing), gain a selective advantage, while normal HSCs are impaired by inflammageing. This review discusses the molecular and cellular mechanisms of CHIP, its interplay with inflammageing, and the pathophysiological consequences for age-related diseases, highlighting translational implications for older individuals.
Nature Reviews. Molecular Cell Biology. PMID: 41491423.

AI Agents in Cancer Research: Capabilities and Applications. Since 2022, large language models (LLMs) have evolved to function as agents, capable of planning and executing complex workflows with minimal human input. In cancer research, AI agents can autonomously optimize drug design and propose

therapeutic strategies. This review clarifies their capabilities, distinguishes them from traditional AI, and discusses emerging applications and real-world challenges for cancer researchers.

Nature Reviews. Cancer. PMID: 41526721.

MUSK: A Multimodal AI Foundation Model for Pathology and Clinical Decision-Making. MUSK is a vision-language foundation model pretrained on unlabeled pathology images and clinical reports text. It demonstrates superior performance in image retrieval, classification, and molecular biomarker prediction. Importantly, MUSK effectively combines pathology images with clinical reports to improve outcome prediction, such as melanoma relapse and immunotherapy response, showing promise for advancing precision cancer therapy.

Nature. PMID: 39779851.

Optimizing Radiation Therapy for Synergy with Immunotherapy. Radiation therapy can modulate immune responses, but combining it with immune checkpoint blockade (ICB) has shown mixed clinical results. The dose and fractionation of radiation profoundly impact whether the immune response is stimulated or suppressed. This review examines how these parameters shape immunity, advocating for a shift from empirical combinations to immunologically-informed radiation protocols to maximize the potential of radioimmunotherapy.

Nature Reviews. Cancer. PMID: 41577962.

Urine tumor DNA Analysis Predicts Response to Treatment in Bladder Cancer. Somatic mutations in tumor-adjacent normal urothelium (the field effect) limit the specificity of urine tumor DNA (utDNA) analysis. A new approach removes these field-effect mutations to improve minimal residual disease (MRD) detection. Applied to non-muscle invasive bladder cancer patients, it identified responders to surgery and to adjuvant BCG treatment, revealing that molecular features such as pre-existing immune activation and higher mutation burden predict BCG but not surgery response.

Cell. PMID: 41605210.

ER-Phagy Drives Adaptive ER Remodeling During Aging. Ageing is characterized by a conserved reduction in ER volume and a shift from rough sheets to tubular ER across species. This morphological transition, driven by Atg8/ULK1-dependent ER-phagy and regulators like TMEM-131, correlates with a proteome shift from protein synthesis to lipid metabolism. ER-phagy is required for mTOR-dependent lifespan extension, indicating that ER remodeling is a proactive, protective response during ageing.

Nature Cell Biology. PMID: 41629400.

Tumor Stem Cells Sculpt Neutrophil Heterogeneity to Evade Immunotherapy. Single-cell RNA sequencing shows that anti-PDL1+CD40 agonist immunotherapy can induce interferon responses in tumor-associated neutrophils (TANs), restoring anti-tumor activity in squamous cell carcinoma (SCCs). However, TANs at the tumor-stroma interface remain suppressive. SOX2-high tumor-initiating stem cells at this interface enhance PGE2 signaling in TANs (by upregulating *Fads1* to produce arachidonic acid), in turn disrupting the interferon response, ultimately preventing anti-tumor activity and driving cancer relapse.

Cancer Cell. PMID: 41349542.

A Preclinical Platform Reveals Vulnerabilities in Triple-Negative Breast Cancer (TNBC). Multi-parametric analyses in an immunocompetent TNBC mouse model identified four distinct TNBC clusters defined by intrinsic and immune features, paralleling human subtypes and clinical outcomes. Such hallmarks were conserved even after engraftment in recipient animals. Treatment testing revealed that chemo-immunotherapy benefited neutrophil-enriched tumors, while immunotherapy alone was more effective in macrophage-enriched tumors, highlighting the interplay between tumor-intrinsic and immune features.

Molecular Cancer. PMID: 41520125.

Extracellular Vesicles in Colorectal Cancer (CRC): Roles and Therapeutic Potential. Extracellular vesicles (EVs) are pivotal messengers in the CRC tumor microenvironment, creating an immunosuppressive environment and modulating other cells. They hold potential as biomarkers for early diagnosis and metastasis prediction. Therapeutic strategies leveraging EVs include adjuvant immunotherapy, stem cell-derived EVs, and engineered EVs. The review emphasizes current limitations and future prospects for realizing EV-based precision diagnosis and treatment.

Molecular Cancer. PMID: 41351158.

Targeted Protein Degradation: A New Frontier in Cancer Immunotherapy. Targeted protein degradation (TPD) technology harnesses cellular machinery to eliminate disease-associated proteins. Strategies based on UPS and lysosomal pathways (PROTAC, LYTAC, AbTAC) can directly degrade immune checkpoints or clear immunomodulatory factors in the TME to reverse immunosuppression. This review discusses the design, preclinical validation, and clinical translation of TPD-based immunotherapeutic agents, alongside challenges like off-target effects.

Journal of Hematology & Oncology. PMID: 41345706.

USP7 Inhibition Enhances Radioimmunotherapy by Preventing Cytosolic DNA Degradation. Cytosolic DNA exonuclease TREX1 is degraded by the E3 ligase SPOP but stabilized by deubiquitinase USP7. Cancer-associated SPOP mutations or USP7 overexpression elevate TREX1, degrading cytosolic DNA and impairing cGAS-STING-mediated immune activation after DNA damage. In this scenario, high USP7 correlates with poor response to chemoradiotherapy and USP7 inhibitors reduce TREX1 levels and restore immune responses following radiation, representing a potential combination strategy.

Cancer Cell. PMID: 41512867.

Glial Progenitor Cells Identified as the Cell of Origin for IDH-Mutant Gliomas. Deep sequencing of tissues from IDH-mutant glioma patients revealed low-level IDH mutations in the peritumoral cortex in 37.9% of cases. Integrating cell-type-specific mutation analysis, clonal evolution, spatial transcriptomics, and a mouse model, the study determined that glial progenitor cells harboring an initial IDH mutation are responsible for the development of these gliomas.

Science (New York, N.Y.). PMID: 41505555.

Metastatic Organotropism is Dictated by a Complex Interplay of Environmental Nutrients and Intrinsic Cell Features. The quantification of 124 metabolites in several mouse tissues revealed that no single nutrient dictates where breast cancer cells can metastasize. Purine synthesis emerged to be required for tumor growth across many tissues. The findings highlight a complex interplay between multiple environmental nutrients and intrinsic cellular properties in defining metastatic sites.

Nature. PMID: 41501456.

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Nat Med 2026. PMID: 41555035.

LY6D Marks a Gastric-like Cell State Driving Pancreatic Cancer (PDAC) Initiation. scRNA-seq identified LY6D as a marker of a gastric-like cell state in PDAC heterogeneity. This LY6D+ population exhibits stemness and a dependency on oxidative phosphorylation (OXPHOS). Mechanistically, LY6D act as scaffold for a network of kinases at the level of lipid rafts, driving FOSL1-dependent reprogramming. In human PDAC, LY6D+ cells display EMT (epithelial-to-mesenchymal) signatures, and high LY6D expression is an independent prognostic marker of poor survival.
Gut. PMID: 41545197.

Prognostic Value of cancer-associated fibroblasts (CAF) subtypes in Pancreatic Cancer. Multiomics analyses revealed that complement-secreting CAFs (csCAF) and inflammatory CAFs (iCAF) share transcriptional profiles. During carcinogenesis, csCAF composition declines, potentially due to csCAF differentiating into iCAF. Tumors enriched with csCAF had lower TGF- β , fewer M2 macrophages, and patients displayed longer survival. Reprogramming iCAF into csCAF could be a promising therapeutic strategy.
Gut. PMID: 41534892.

DLL3 Expression on Circulating Tumor Cells (CTCs) Predicts Tarlatamab Benefit in small-cell lung cancer (SCLC). In SCLC, single-cell sequencing reveals heterogeneity in DLL3 expression. In a prospective cohort,

high DLL3 expression in CTCs before treatment predicted, with high sensitivity and specificity, clinical benefit of tarlatamab. Acquired resistance was linked to either DLL3 loss (while other neuroendocrine epitopes persisted) or DLL3 retention with concurrent T cell dysfunction, highlighting CTCs as a dynamic biomarker.

Cancer Discovery. PMID: 41532856.

Pathogenic Mechanisms and Targeted Therapies in Leukemia. Next-generation sequencing has enabled the identification of recurrent genetic events in leukemia, impacting prognosis and therapy. A broad therapeutic arsenal is now available, including small molecule inhibitors, bispecific T cell engagers, antibody-drug conjugates, and CAR-T cells. This review provides an overview of pathogenic mechanisms and the main research progress in leukemia therapies, including targeted and RNA-based approaches.

Journal of Hematology & Oncology. PMID: 41521321.

Infiltrative Tumor Growth and Organ Failure in Brain Metastases. Neurological failure is a major cause of mortality in brain metastasis patients. Using two experimental models, this study shows that the pattern of tumor growth dictates the cause of organ failure: In the infiltrative E0771-LG model, cancer progression led to widespread secondary dissemination (and recolonization of the brain by secondary metastasis-initiating cells), a process largely overlooked in clinical practice, highlighting that the pattern of tumor growth may represent a potential predictor of the cause of organ failure in patients with brain metastases.

Molecular Cancer. PMID: 41580751.

Mitochondrial Dysfunction in Cancer: From Mechanisms to Therapies. Mitochondrial dysfunction, including metabolic reprogramming and impaired quality control, contributes to cancer initiation and progression. This review summarizes the relationships between mitochondrial dysfunction and cancer, covering metabolism, mtDNA stability, and ion homeostasis. It also discusses mitochondria-targeted therapies, translational gaps, and future directions for targeting mitochondrial homeostasis.

Molecular Cancer. PMID: 41593460.

AlphaGenome: A Unified Model for Predicting the Functional Genome from DNA Sequence. AlphaGenome is a unified DNA sequence model that, by taking up to 1 Mb of sequence as input, can predict thousands of functional genomic tracks (gene expression, chromatin accessibility, etc.), at single-base resolution. Trained on human and mouse genomes, it excels at predicting the effect of genomic variants and can accurately recapitulate mechanisms of clinically relevant variants.

Nature. PMID: 41606153.

Metabolic Reprogramming Drives Multi-Kinase Inhibitor Resistance in liver cancer. Metabolic reprogramming, including altered glycolysis, lipid metabolism, and amino acid metabolism, is a critical mechanism driving resistance to multi-kinase inhibitors (MKIs) like sorafenib in hepatocellular carcinoma (HCC). This review examines these pathways and their key molecular regulators as potential targets. It also discusses combining metabolic modulators with MKIs and the role of metabolism in the tumor immune microenvironment to overcome resistance.

Molecular Cancer. PMID: 41593671.

Single-Cell Insights into the Lymph Node Metastasis Microenvironment. Lymph node metastasis (LNM) profoundly impacts prognosis, with tumor-draining lymph nodes playing a key role in anti-tumor immunity. This review summarizes new insights, novel LNM targets, and the current status of LNM-related immunotherapy research.

Molecular Cancer. PMID: 41629958.

Tissue-Specific Regulation of NK and Innate Lymphoid Cells in Cancer. Natural killer (NK) cells and innate lymphoid cells (ILCs) are regulated by tissue-specific cues and local checkpoints that shape their cellular

states and effector functions in cancer. This review discusses how these regulatory circuits operate within tissues and how targeting these innate checkpoints could inform new strategies for treating solid malignancies, moving beyond conventional immunotherapy targets.

Cancer Discovery. PMID: 41636041.

Metabolic Coordination in Hematopoietic Stem Cell Health and Leukemia. Hematopoietic stem cells (HSCs) rely on precise metabolic programs for quiescence, self-renewal, and differentiation, which are supported by dynamic interactions with the bone marrow microenvironment. Alterations in this metabolic homeostasis are linked to leukemogenesis. This review analyzes how HSC metabolism is regulated and how leukemic cells co-opt and dysregulate these pathways to support their growth and survival.

Nature Cell Biology. PMID: 41673169.

LLMs Fail to Improve Public Health Advice Accuracy in a User Study. While large language models (LLMs) score highly on medical exams, a controlled study with 1,298 participants found they did not improve a user's ability to identify conditions or choose a course of action in medical scenarios. Participants using LLMs performed no better than a control group, highlighting user interaction as a major deployment challenge and the need for systematic human testing before public use.

Nature Medicine. PMID: 41663592.

Expanding Synthetic Lethality Beyond DNA Repair. By inhibiting remaining DNA repair mechanisms in (homologous recombination) repair deficient cancers, PARP inhibitors (PARPi) target the so-called synthetic lethality (SL, a therapeutic approach in which the inhibition of a cellular mechanism in a cell context characterized by specific molecular alterations results in cancer cell death) killing cancer cells. However, resistance to PARPi is common. Epithelial ovarian cancer provides a model for exploring novel SL approaches, beyond classic DNA repair (targeting the interplay among DDR components, cell cycle, metabolism, and epigenetics). This review discusses multidimensional SL strategies that combine different targets to elicit or restore drug sensitivity, offering personalized options for this heterogeneous disease.

Molecular Cancer. PMID: 41668072.

Exploring cell migration. Cell migration is essential for processes like development, yet it remains challenging to study due to the complexity of available assays and the need for advanced microscopy. Two complementary reviews provide a comprehensive guide to cell migration research, covering the entire workflow from selecting an assay to analyzing the resulting data: The first review focuses on the computational analysis of cell migration data. It explains how to calculate key quantitative parameters from raw data —such as speed, persistence, and diffusivity— to understand the biophysical nature of movement. It also highlights modern imaging and AI-based technologies that enable robust cell tracking and heterogeneity analysis. The second one serves as a practical guide for choosing the right experimental setup. It details various commercial and custom assays for both in vitro and in vivo contexts, offering a decision tree to help researchers select the most appropriate method for their specific biological question. This guidance aims to improve our understanding of migration by ensuring assays are used correctly, encouraging future method development. Together, these reviews offer a complete resource for cell migration studies from conception to quantitative analysis.

Nat Methods. 2026. PMID: 41413346 and 41413344.

notes...

How to adapt PhD training in the AI era? (from nature)

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6th SUNRiSE Meeting
("Tumor heterogeneity and plasticity in cancer")
May 26-28/[registration](#) open

I've earned my PhD — what now?

[Six steps](#) to protect researchers' digital security

Protect yourself —and your data— with these cybersecurity [tips](#)

ELISIR 2026- EPFL Life Sciences Independent Research Scholar [program](#) Lausanne Switzerland

AIRC Short-term [Fellowships](#)

[VALT symposium](#) (Valencia Long-read Transcriptomics) (june29 → july 1, 2026) – registration open

[PRISM](#) - Write, edit, and collaborate on scientific documents in LaTeX with Prism—a free workspace integrating GPT-5.2 into research and writing

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Keystone [Conference](#) on Epigenetics and Gene Regulation

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FEBS [Workshop](#) "Protein Termini 2026: From Mechanisms to Biological Impact" (Palermo, June 3-6, 2026).

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ncRNA2026: From Molecular Mechanisms to Clinical Impact [Conference](#)

[Physicians](#) as context engineers in the era of generative AI.

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[Using](#) AI responsibly in scientific publishing.

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AI [Co-Scientists](#) Move to the Front Lines of Cancer Research.

FRRB Early Career Award – [III Edition](#)

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Hematology pills – a podcast ([spotify](#) – [apple podcast](#))

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Sex and gender policies mark a [step change](#) for medical research.



DIAMO IL BENVENUTO A

WE WELCOME

Bonacina Francesco, Fellow, Chiocca Group; **Bortolotto Elettra**, Fellow, Gandini Group; **Budnik Nicolas**, Post doc, Scaffidi Group; **Candido Roberta**, Undergraduate Student, Di Fiore; **Cocconcelli Gaia**, Undergraduate Student, Mapelli Group; **De Rosa Giacomo Maurizio**, Undergraduate Student, Pece Group; **Denaro Sofia**, Temporary, BioComputational Unit; **Franceschini Alessia**, Undergraduate Student, Mitro Group; **Golob Greta**, Undergraduate Student, Mazzarella Group; **Gorgoglione Nicolò**, Undergraduate Student, Mazzarella Group; **Komeili Mahdi**, Fellow, Di Fiore Group; **Kotwal Akshata**, PhD Student, Mazzarella Group; **Limosani Roberta Valeria**, Post doc, Lanfrancone Group; **Lupoli Gianpiero**, Fellow, Pece Group; **Maltoni Anna**, Fellow, Mitro Group; **Manioudaki Georgia**, Undergraduate Student, Schaefer Group; **Moreno Silvestre Carlos**, Undergraduate Student, Schaefer Group; **Norton Thomas Ernest**, Undergraduate Student, Natoli Group; **Oberti Gabriele**, Undergraduate Student, Schaefer Group; **Olivari Lorenzo**, Undergraduate Student, Mitro Group; **Panno Giulia**, Temporary, Pelicci PG Group; **Parihar Dolly**, PhD Student, Scaffidi Group; **Pasionek Iwona Malgorzata**, Temporary, Scaffidi Group; **Picco Giulia**, Post doc, Natoli Group; **Pirra Piscazzi Maria**, Post doc, Cavallaro Group; **Rangaswamy Uday**, Post doc, Amati Group; **Rebegea Codrina Alexandra**, Undergraduate Student, Lanfrancone Group.

What if...

researchers of the past could use today's advanced technologies?

S

Yi, can you briefly summarize the experiments leading to the identification of the role of p53 in cancer?

Early experiments in the 1970s found a 53 kDa protein binding SV40 T-antigen. The oncogene view prevailed until 1989, when Bert Vogelstein's team discovered that wild-type p53 (TP53) was frequently deleted or mutated in colorectal cancers, suggesting it was a tumor suppressor, not an oncogene. Crucially, Li-Fraumeni syndrome families inherited mutant TP53, confirming its germline role. Knockout mice (1992) developed multiple tumors, solidifying p53 as a "guardian of the genome" that induces cell-cycle arrest, DNA repair, or apoptosis in response to damage. Its inactivation is now known as a cornerstone event in most human cancers.

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Leveraging the existing technologies, what kind of experiments would you design to demonstrate it?

To demonstrate p53's tumor suppressor role today, I would design a multi-angled experimental strategy:

1. **Genomic/Transcriptomic Analysis:** Use whole-exome or targeted NGS on matched tumor-normal samples to identify TP53 mutations. Integrate with single-cell RNA-seq to link mutations to dysfunctional transcriptional programs (e.g., loss of CDKN1A/p21 induction).
2. **Functional Validation in Models:**
 - a. **CRISPR-Cas9:** Knockout TP53 in normal human organoids or isogenic cell lines. Phenotype: loss of cell-cycle arrest after DNA damage (e.g., irradiation), genomic instability, and potential immortalization.
 - b. **Xenografts:** Compare growth of p53-wildtype vs. p53-null engineered cells in mouse models; null cells should show aggressive, metastatic potential.
3. **Mechanistic Studies:** Use CUT&Tag or ChIP-seq on your models to show mutant p53 loses binding to target gene enhancers/promoters. Live-cell imaging with fluorescent DNA damage reporters (e.g., 53BP1) can visualize failed repair.
4. **Therapeutic Link:** Treat p53-mutant tumor models with p53-reactivating compounds (e.g., APR-246) or synthetic lethal drugs (e.g., PARP inhibitors) to show phenotype reversal or selective cell death, confirming its pivotal role.

This integrated approach from genotype to phenotype to mechanism provides conclusive, contemporary evidence.

Y

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Alex, what about you? Leveraging the existing technologies, what kind of experiments would you design to demonstrate it?

To demonstrate the role of p53 as a tumor suppressor, I'd design a set of complementary experiments that converge on the same conclusion from different angles. By using existing, well-established technologies —focused on logic and outcomes, rather than lab recipes—, I would do the following:

1. Loss-of-Function: What happens when p53 is removed? To show that loss of p53 promotes cancer-like behavior, I would compare cells with functional p53 to cells where p53 is inactivated (e.g., deletion or mutation), both exposed to DNA damage (radiation or genotoxic stress). I would expect to see cell cycle arrest, DNA repair, or apoptosis in normal cells, and continued proliferation despite damage and genomic instability in p53-deficient cells. This would make me conclude that p53 is required to prevent propagation of damaged cells.

2. Gain-of-Function/Rescue Experiment. To show that restoring p53 suppresses tumor behavior, I would start with a cancer cell line lacking functional p53, reintroduce wild-type p53, compare to cells receiving mutant p53 or no p53. I would expect to see that wild-type p53 restores growth arrest or apoptosis, while mutant p53 fails to suppress growth. This would make me conclude that functional p53 is sufficient to suppress malignant traits.

3. Animal Models: p53 and tumor formation *in vivo*. To demonstrate p53's role at the organism level, I would use animals with *i.* two functional p53 alleles, *ii.* one deleted allele, *iii.* both alleles deleted. Then, I would monitor spontaneous and induced tumor development over time. I would expect to see p53-null animals develop tumors earlier, more frequently, and with greater diversity. That would make me conclude that p53 loss directly increases cancer susceptibility in living organisms.

4. Genomic Analysis of Human Tumors. To establish the clinical relevance, I would analyze cancer genomic databases for: *i.* p53 mutation frequency, *ii.* correlation with tumor grade, therapy resistance, or survival. I would expect to see p53 among the most frequently mutated genes in human cancers, and p53 mutations correlate with poor prognosis. That would make me conclude that p53 dysfunction is a central driver of human cancer.

5. Cell Competition Experiment. To show selective advantage of p53-deficient cells, I would co-culture p53-normal and p53-deficient cells under stress and track population dynamics. I would expect to see p53-deficient cells outcompete normal cells when damage accumulates. That would make me conclude that loss of p53 confers a survival and growth advantage under oncogenic stress.

6. Mutation-Specific Effects. To distinguish tumor-suppressing vs tumor-promoting p53 mutants, I would compare wild-type p53 to common cancer-associated p53 mutants, and measure invasion, proliferation, and survival. I would expect to see some mutants not only lose suppression but actively promote malignancy. That would make me conclude that p53 mutations can have dominant-negative or gain-of-function effects.

A

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What about you? How would you that?

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