IEO research NEWSLETTER

IEO RESEARCH NEWSLETTER

n. 012 – September 2026

What's new in science?

Meccanismi biologici di evasione immunitaria – uno sguardo oltre i neoantigeni.

Biological mechanisms of cancer immune evasion – a look beyond neoantigens.

What's new from IEO researchers?

Caratterizzazione molecolare di lesioni tumorali primarie e metastatiche nel cancro del polmone.

Molecular characterization of primary-metastatic lesions in lung cancer.

News, initiatives, events.

In IEO l'evento organizzato da Motore Sanità "il futuro dell'oncologia è già qui".

In IEO the Motore Sanità-organized event "Il futuro dell'oncologia è già qui".

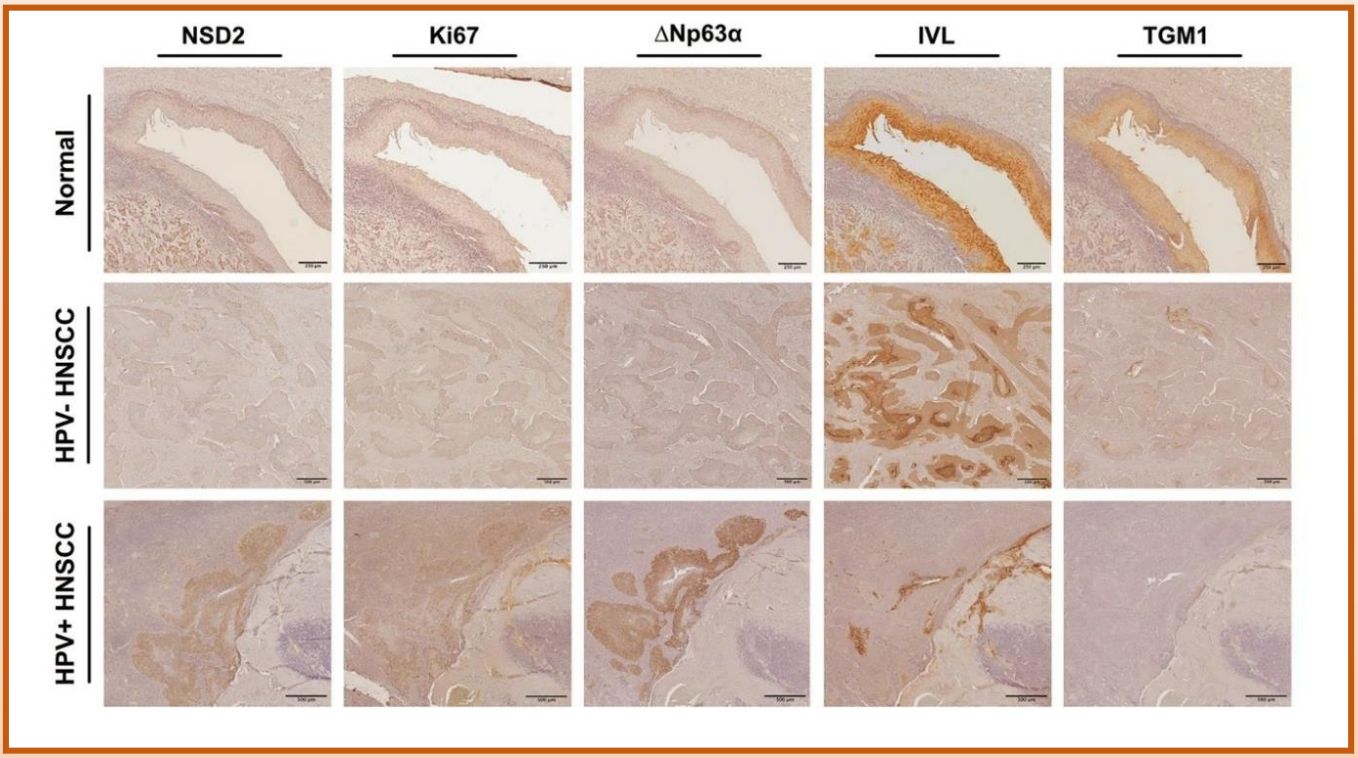


Image adapted from Ghiani et al., (an open access article under the CC BY license. Figure legend on the last page.)

IEO research NEWSLETTER

IEO RESEARCH NEWSLETTER

n. 012 – September 2026

WHAT'S NEW IN SCIENCE?

WHAT'S NEW FROM IEO RESEARCHERS?

NEWS, INITIATIVES AND EVENTS FROM THE IEO WORLD

THE BRIEFING

What if...

WE WELCOME

notes...

Click HERE to meet NewChatBOT, the chatbot of the IEO Research Newsletter!

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

Anticorpi anti-netrina contro il tumore del pancreas – risultati di uno studio clinico di fase I.

Tipicamente espressa durante lo sviluppo, e con un ben noto ruolo nel guidaggio assonale, l'espressione della netrina1 aumenta in diversi tipi di tumore e studi precedenti hanno mostrato un suo ruolo nel promuovere la transizione epitelio-mesenchimale (EMT), un processo cruciale nella disseminazione metastatica e nella chemioresistenza. In modelli preclinici in vivo, l'anticorpo anti-netrina1 NP137 è in grado di invertire la EMT.

Gli anticorpi anti-netrina1 possono quindi essere sfruttati clinicamente per interferire con la EMT e rappresentare un nuovo trattamento antitumorale?

Per rispondere a questa domanda, nel contesto di uno studio clinico di fase I, i ricercatori hanno valutato efficacia e sicurezza dell'anticorpo anti-netrina1 NP137 in combinazione con chemioterapia (mFOLFIRINOX), come terapia di prima linea, per il trattamento del tumore pancreatico localmente avanzato.

I loro risultati hanno mostrato dei benefici clinici –in termini di sopravvivenza– della combinazione NP137/chemioterapia e hanno rivelato il meccanismo coinvolto, che implica l'inibizione della EMT tramite un anticorpo contro una proteina che solitamente non è espressa nei tessuti adulti sani, ma il cui livello di espressione aumenta con la tumorigenesi: la netrina1. Lo studio propone inoltre la neogenina –il recettore della netrina1– come biomarcatore per identificare i pazienti sensibili alla terapia.

Oggi le opzioni terapeutiche per questi pazienti sono limitate, anche in un contesto sperimentale, non essendo idonei per studi clinici nel setting metastatico o neoadiuvante/perioperatorio (infatti spesso questi tumori non sono resecabili). Se confermati nel contesto di coorti di pazienti più ampie, i risultati di questo lavoro potrebbero offrire a questi pazienti una nuova opzione terapeutica.

TELL ME MORE!

Studio clinico. Lo studio ha arruolato 43 pazienti in 9 diversi centri. I pazienti sono stati trattati con chemioterapia (mFOLFIRINOX) e anticorpo anti-netrina1 NP137. Le analisi di tossicità hanno mostrato che NP137 era ben tollerato; gli eventi avversi, comunque gestibili, di grado 3 o superiore si manifestavano nel 12% dei pazienti e non si osservava alcun evento avverso nuovo rispetto al profilo di tossicità associato alla somministrazione della chemioterapia. Per quanto riguarda l'efficacia, ad un follow-up mediano di 13 mesi, 12 dei 43 pazienti arruolati hanno mostrato una risposta parziale duratura, 27 di 43 una malattia stabile. A 6 mesi, la sopravvivenza in assenza di progressione della malattia (PFS) era 88%, la sopravvivenza generale (OS) era del 91%; a 12 mesi, la PFS era del 45%, la OS del 62%.

Studi funzionali. Studi precedenti hanno mostrato che i tumori trattati con mFOLFIRINOX vanno incontro a EMT, probabilmente con conseguente resistenza alla terapia, e che gli anticorpi anti-netrina1 sono in grado di invertire la EMT. Gli autori hanno quindi valutato se l'anticorpo NP137 può agire in sinergia con la chemioterapia, invertendo il processo di EMT indotto dalla chemioterapia. Le analisi RNAseq sul tessuto tumorale dei pazienti al momento della diagnosi e dopo il trattamento ha rivelato numerosi (260) geni diversamente regolati (232 up-regolati, 28 down-regolati) dopo la terapia, tra cui la down-regolazione di pathway infiammatori e 45 geni coinvolti in EMT. Nei pazienti che rispondevano al trattamento combinato con chemioterapia e NP137 (che raggiungevano una risposta parziale o una malattia stabile), la signature di EMT di 45 geni era fortemente down-regolata dopo la terapia, mentre nei pazienti che, nell'ambito di studi precedenti, avevano ricevuto solo chemioterapia, la signature di EMT era up-regolata. Inoltre, il pathway di EMT era quello che risultava maggiormente attivato sia nei campioni post- vs pre- trattamento con NP137+chemioterapia, sia nei campioni post- rispetto a pre- chemioterapia soltanto.

Analisi molecolare. Le analisi dei fattori molecolari associati alla risposta al trattamento e alla PFS hanno mostrato che *i.* nei pazienti trattati solo con chemioterapia, l'espressione della neogenina (il recettore di netrina1) era inversamente correlata con la PFS (ovvero un elevato livello della neogenina corrispondeva ad una scarsa prognosi), in linea con il fatto che un'elevata espressione della neogenina risulterebbe in EMT modulata da netrina1-neogenina; *ii.* nei pazienti trattati con chemioterapia+NP137, l'espressione della neogenina era strettamente correlata con la PFS, a significare che un'elevata espressione della neogenina determinava una migliore risposta alla terapia di combinazione e una migliore PFS. Questi risultati suggeriscono quindi che la neogenina potrebbe essere un fattore in grado di predire la risposta al trattamento combinato con chemioterapia e NP137, rappresentando un biomarcatore di stratificazione, in grado di identificare i pazienti che probabilmente beneficeranno di questo trattamento.
Infine, gli autori hanno mostrato, in saggi cellulari, che netrina1-neogenina erano coinvolti nella progressione del tumore pancreatico. Infatti, in modelli preclinici *in vivo*, l'anticorpo NP137 contrastava la migrazione cellulare (come proxy di EMT), solo quando la neogenina era espressa, ma non aveva alcun effetto quando la neogenina era silenziata.

Referenza. *Netrin1 blockade alleviates resistance to chemotherapy in pancreatic cancer. Gael Roth, Pascal Artru, Olivier Bouche, Nicolas Williet, Julien Ghelfi, Anthony Turpin, Astrid Lievre, Jean-Frédéric Blanc, Camille Evrard, Jean-Baptiste Bachet, Pauline Parent, Marc Manceau, Matthieu Roustit, Anna Borowik, Victoire Granger, Aurélie Durand, Christelle d'Engremont, Edouard Girard, Mircea Chirica, Nicolas Braissand, Nicolas Rama, Eugénie Modolo, Hector Hernandez-Vargas, Elise Georges, Jean-Yves Scoazec, Jerome Cros, Sébastien Hazard, Benjamin Ducarouge, Thomas Decaens, Agnès Bernet, Patrick Mehlen. Nature 2026. doi: 10.1038/s41586-026-10436-4.*

Nei metaboliti del sangue e nel microbioma intestinale, i fattori che predicono la risposta all'immunoterapia.

Nonostante la crescente diffusione dell'immunoterapia in ambito oncologico, non sono noti i fattori metabolici che determinano la risposta dei pazienti al trattamento.
Attraverso l'analisi metabolomica di campioni di sangue e l'analisi metagenomica di campioni fecali di oltre 1700 pazienti (appartenenti a diverse coorti indipendenti), con cinque diversi tipi di tumore, in differenti stadi della malattia, trattati con diversi approcci terapeutici, e grazie ad un modello di machine learning in grado di integrare dati metabolici e informazioni cliniche, i ricercatori hanno recentemente identificato i metaboliti del sangue e le caratteristiche cliniche dei pazienti associate all'esito della terapia. Le loro scoperte hanno rivelato che livelli elevati di istidina nel sangue e nell'intestino hanno un effetto immunostimolatorio –attraverso l'aumentata attività mitocondriale e la maggiore attività dei linfociti T–, e antitumorale (con un significativo aumento della sopravvivenza in assenza di progressione della malattia, PFS). Inoltre, in modelli preclinici *in vivo*, la somministrazione di istidina ha mostrato effetti antitumorali, indicando una relazione causale, piuttosto che una semplice correlazione. Infine, in pazienti con malattia infiammatoria cronica ad alto rischio di tumore, l'ingestione di istidina attraverso la dieta, insieme ad un microbiota più favorevole (che studi precedenti hanno dimostrato correlare con l'efficacia dell'immunoterapia a base di inibitori dei checkpoint immunitari, ICI), è associata con un migliore esito della terapia (un aumento della PFS). Al contrario, alterazioni del microbiota intestinale (disbiosi) correlano con un livello più alto, nel sangue, di molecole immunosoppressive derivanti dal metabolismo dell'istidina, suggerendo un'influenza del microbiota intestinale sull'istidina circolante e quindi sui suoi effetti immunostimolatori. Sebbene siano necessari studi clinici prospettici per poter generalizzare i dati e stabilire in maniera definitiva la rilevanza prognostica del livello di istidina e il suo potenziale terapeutico, una somministrazione controllata di istidina –che studi precedenti hanno dimostrato essere sicura–, in sottogruppi di pazienti selezionati sulla base della composizione del loro microbiota intestinale, che modula

appunto i livelli di istidina, potrebbe permettere di definire una nuova strategia per prevenire o ritardare, in pazienti ad alto rischio, l'incidenza del tumore.

TELL ME MORE!

Una "firma" di sei metaboliti predice l'esito dei pazienti. Gli autori hanno analizzato 4000 campioni plasmatici e 620 campioni fecali di oltre 1700 pazienti da diverse coorti di pazienti indipendenti. Analisi metabolomiche tramite spettrometria di massa hanno permesso la generazione di un dataset contenente 154 metaboliti che ha consentito lo sviluppo di un modello di machine learning. Grazie a questo modello, gli autori hanno identificato una *signature* di sei metaboliti (istidina, succinato, carnitina, acido docosatrienoico, acido esadecanedioico, creatinina) e due caratteristiche cliniche (età ed indice di massa corporea) associati con l'esito dei pazienti (*progression-free survival*, PFS) sottoposti a trattamento antitumorale. Tra i sei metaboliti emersi dalle analisi, l'istidina era il predittore più solido, sebbene altri metaboliti, tra cui gli acidi grassi a catena lunga e il succinato, apparivano, in maniera minore, associati (negativamente) con l'esito dei pazienti. La *signature* di metaboliti è stata ulteriormente validata in diverse coorti di pazienti e in modelli sperimentali.
Valore predittivo dell'istidina. Successivamente, gli autori hanno osservato che, sulla base dei livelli plasmatici di istidina, era possibile distinguere i pazienti a seconda di PFS o sopravvivenza generale (*overall survival*, OS): livelli più alti di istidina, prima della terapia, correlavano con un migliore esito dei pazienti (più lunga PFS, OS e RFS –sopravvivenza in assenza di recidiva, *recurrence-free survival*–, in differenti coorti). In una delle coorti di pazienti analizzate, i livelli di istidina erano maggiori sia nel gruppo ad alto rischio, sia nel gruppo a rischio intermedio rispetto ai pazienti a basso rischio. Inoltre, negli individui sani ad alto rischio di tumore (associato al fumo), i livelli elevati di istidina erano correlati con una minore incidenza di tumore. Il valore predittivo dell'istidina era indipendente dal trattamento a cui erano sottoposti i pazienti. I pazienti che rispondevano alla terapia mostravano, durante il trattamento, livelli crescenti di istidina. Nel complesso, i loro dati indicano che i livelli elevati di istidina nel sangue correlano con un minore rischio di sviluppare tumore nei fumatori e maggiori probabilità di risposta a immunoterapia in pazienti con diversi tipi di tumore.
Livelli di istidina ed esito della terapia – esiste una correlazione causale sfruttabile a fini terapeutici? Al fine di valutare l'esistenza di una relazione causale tra i livelli di istidina e l'esito della terapia nei pazienti, gli autori hanno caratterizzato le cellule immunitarie circolanti (*peripheral blood mononuclear cells*) di pazienti non trattati e, dato che l'istidina può essere metabolizzata dal microbiota intestinale, di pazienti sottoposti a trapianto di microbiota fecale. Le loro analisi hanno evidenziato la presenza di cellule immunitarie più attive (linfociti T CD4 e helper, linfociti B e monociti) in pazienti con elevati livelli di istidina nel sangue, indicando un ruolo immunostimolatorio dell'istidina plasmatica. In modelli preclinici *in vivo*, l'istidina determinava un'aumentata proliferazione di linfociti T CD8, un'aumentata attività mitocondriale nei linfociti T, in maniera dipendente dall'ossidazione degli acidi grassi (*fatty acid oxidation*, FAO), e una maggiore resistenza. Inoltre, la somministrazione di istidina attraverso la dieta mostrava sia un effetto terapeutico che profilattico, aumentando l'efficacia dell'immunoterapia e prevenendo lo sviluppo del tumore. L'aumento di istidina era parallelo a una riduzione dei livelli di metaboliti immunosoppressivi (come il triptofano). Nel complesso, i loro dati indicano che, dopo l'ingestione di istidina, l'aumento della concentrazione plasmatica e tumorale di istidina potrebbe modulare l'attività dei linfociti.
Il microbiota intestinale modula gli effetti immunostimolatori dell'istidina. Gli autori hanno mostrato che il microbiota intestinale è coinvolto nell'effetto immunostimolatorio dell'istidina assunta con la dieta. Infatti, le loro analisi hanno rivelato una correlazione tra i livelli di istidina nel sangue (prima della terapia), abitudini alimentari dei pazienti e composizione (tramite analisi shotgun metagenomica) del microbiota intestinale: i livelli elevati di istidina correlavano con l'ingestione di cibi proteici e con un microbiota favorevole, che studi precedenti hanno mostrato essere associato con l'efficacia della terapia a base di ICI. Al contrario, la disbiosi era associata con livelli elevati di prodotti immunosoppressivi del metabolismo dell'istidina nel sangue, suggerendo l'influenza della disbiosi intestinale sul ricircolo dell'istidina e indicando che i livelli di istidina e i successivi effetti immunostimolatori sono probabilmente il risultato sia dell'assunzione di istidina attraverso la dieta sia della produzione e metabolizzazione da parte del microbiota.
Livelli di istidina e tossicità della terapia. Esiste una correlazione tra l'istidina e gli effetti collaterali della terapia? Pur non avendo trovato alcuna associazione tra i livelli di istidina plasmatica e la tossicità, le loro

analisi hanno rivelato una correlazione con i livelli fecali di istidina; in particolare, livelli più elevati di istidina erano associati con eventi avversi meno severi/meno frequenti.

Referenza. Metabolic determinants of cancer immunotherapy outcomes identified by plasma profiling. Suissa D, Fidelle M, Reich E, Pham TN, Thomas S, Björk JR, Liu P, Zhao L, Kitaoka K, Piard E, Lebhar I, Tian AL, Thelemaque C, Alves Costa Silva C, Deutsch E, Loriot Y, Segata N, Piccinno G, Hospers GAP, Maleki Vareki S, Silverman MS, Lenehan JG, Bataille V, Boulate D, Kuznetsova T, Weersma RK, Messaoudene M, Durand S, van der Aalst CM, de Koning HJ, Schuler-Thurner B, de Vries IJM, Rafie E, Saliby RM, Machaalani M, Haferkamp S, Schilling B, Porcari S, Ciccarese C, Iacovelli R, Cremolini C, Choueiri TK, Elkrief A, Kroemer G, Heinzerling L, Chamoto K, Ianiro G, Routy B, Derosa L, Paragios N, Zitvogel L. Nat Med 2026. doi: 10.1038/s41591-026-04481-9.

Protonterapia *vs* radioterapia a base di fotoni – risultati di uno studio clinico di fase III.

La radioterapia è un approccio terapeutico piuttosto diffuso, con costi limitati e un buon rapporto costo/efficacia, che si sta evolvendo rapidamente, offrendo ai pazienti trattamenti sempre più precisi e personalizzati, con un impatto positivo anche sulla qualità di vita.

Il tumore testa-collo (HNC) è generalmente trattato con una combinazione di approcci differenti, che includono radioterapia, terapia sistemica e chirurgia. La radioterapia impiegata solitamente consiste in radioterapia a base di fotoni ad intensità modulata (IMRT) che, modulando l'intensità del raggio, permette di ridurre l'esposizione dei tessuti circostanti, migliorando di conseguenza la precisione del trattamento e rendendo questo approccio la terapia standard per questo tipo di tumore. Persiste tuttavia un certo grado di tossicità, soprattutto a carico dei tessuti sul percorso del raggio. In questo scenario, la protonterapia è emersa come una valida alternativa, utilizzando i protoni invece che i raggi X ad alta energia della terapia a base di fotoni. Inoltre, la modulazione dell'intensità anche in questo caso può permettere di ridurre la dose di radiazioni e quindi la tossicità.

Radioterapia a base di fotoni e protonterapia.

La radioterapia può essere di tipo "convenzionale", cioè basata sui fotoni, oppure sfruttare particelle cariche. La radioterapia basata su particelle cariche include quella basata sui protoni –la protonterapia– e quella basata su ioni più pesanti (tipicamente il carbonio). I protoni sono particelle subatomiche cariche che, a causa delle loro specifiche caratteristiche fisiche, interagiscono con i tessuti biologici diversamente dai fotoni. Per via delle specifiche caratteristiche dei protoni, la protonterapia consente di indirizzare in maniera più precisa l'energia verso un'area di tessuto ristretta, così che colpisca le cellule tumorali risparmiando le cellule sane intorno, che ricevono dosi minori. Ciò permette di ridurre notevolmente la tossicità associata al trattamento. Inoltre, con la protonterapia è possibile penetrare in profondità nei tessuti, permettendo così di raggiungere in maniera sicura anche i tumori più profondi e meno accessibili.

Recentemente, nel contesto di uno studio clinico di fase III, randomizzato, i ricercatori hanno confrontato efficacia e tossicità della radioterapia a intensità modulata a base di fotoni (IMRT) rispetto a quella a base di protoni (IMPT), in pazienti con tumore dell'orofaringe.

I risultati hanno mostrato che la IMPT non è inferiore a IMRT; la sopravvivenza in assenza di progressione della malattia (*progression-free survival*, PFS) è infatti risultata molto simile con i due approcci. La tossicità grave era invece ridotta. La sopravvivenza generale (*overall survival*, OS) era inoltre aumentata nei pazienti trattati con IMPT rispetto a IMRT, forse a causa di una tossicità associata al trattamento meno grave, o una migliore sopravvivenza dopo la progressione della malattia.

Per la prima volta uno studio clinico randomizzato di fase III ha dimostrato che la IMPT è superiore a IMRT nel trattamento dei pazienti con tumore dell'orofaringe.

I meccanismi alla base della migliore OS osservata sono ancora oggetto di studio; è stato ipotizzato un effetto a lungo termine dell'iperattivazione, indotta da radiazione, del sistema immunitario, infiammazione cronica e successivo esaurimento dei linfociti T, o un coinvolgimento dell'asse immunitario-cancro-microbioma.

Sebbene studi con followup più lunghi siano importanti per dipingere un quadro più completo, questi

risultati supportano la IMPT come nuova valida opzione di trattamento per i pazienti con tumore dell'orofaringe.

TELL ME MORE!

Lo studio è stato condotto in 21 centri oncologici negli Stati Uniti, e ha arruolato 439 pazienti (221 nel gruppo IMPT e 219 nel gruppo IMRT) con tumore in stadio III o IV, casualmente assegnati (1:1) a ricevere IMRT o IMPT in combinazione con terapia sistemica. La maggioranza dei pazienti erano maschi (91%).

Efficacia. L'efficacia è stata valutata in termini di PFS (ovvero, l'intervallo di tempo fino alla manifestazione del primo evento di progressione/recidiva della malattia, a livello locale o sistemico) e OS. Tra i pazienti trattati con IMPT, la PFS era 83% a 3 anni, 81% a 5 anni, mentre nel gruppo trattato con IMRT, era 83% a 3 anni e 76% a 5 anni. La OS era 92% a 3 anni e 91% a 5 anni nel gruppo IMPT, e 90% a 3 anni e 81% a 5 anni nel gruppo IMRT. I decessi dovuti alla malattia erano più comuni nel gruppo IMRT (18) rispetto al gruppo IMPT (9); i decessi collegati alla terapia (nella fase acuta del trattamento) erano più comuni nel gruppo IMRT (6) rispetto al gruppo IMPT (3). Nel complesso, la valutazione dell'efficacia ha mostrato una non inferiorità di IMPT rispetto a IMRT in termini di PFS, e persino una migliore efficacia di IMPT rispetto a IMRT in termini di OS.

Sicurezza. Gli eventi avversi associati al trattamento erano nel complesso più frequenti o più severi nel gruppo IMRT rispetto al gruppo IMPT. In particolare, la xerostomia (condizione in cui le ghiandole salivari non producono sufficiente saliva) che è di solito permanente e può influenzare la qualità di vita, era meno frequente nei pazienti trattati con IMPT.

Referenza. *Proton versus photon radiotherapy for patients with oropharyngeal cancer in the USA: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Steven J Frank, Paul M Busse, J Jack Lee, David I Rosenthal, Mike Hernandez, David M Swanson, Adam S Garden, G Brandon Gunn, Samir H Patel, James W Snider, Daniel J Ma, Jason K Molitoris, Nancy Y Lee, Upendra Parvathaneni, Mark W McDonald, Noah S Kalman, Alexander Lin, Nasiruddin Mohammed, Christina Henson, Christian Hyde 16, Gopal K Bajaj 17, Sanford R Katz 18, Roi Dagan 19, William H Morrison 4, Jay P Reddy 4, C David Fuller 4, Shalin J Shah 4, Jack Phan 4, Gregory M Chronowski 4, Lauren Mayo 4, Erich M Sturgis 20, Renata Ferrarotto 21, Xiaorong R Zhu, Xiaodong Zhang, Li Wang, Katherine A Hutcheson, Adel K El-Naggar, Amy C Moreno, Anna Lee, Michael T Spiotto, Neil D Gross, Stephen Y Lai, Jay J Liao, Jonathan Paly, Zhongxing Liao, Robert L Foote; University of Texas MD Anderson Cancer Center Clinical Trial Consortium. Lancet 2026. doi: 10.1016/S0140-6736(25)01962-2.*

Meccanismi biologici di evasione immunitaria – uno sguardo oltre i neoantigeni.

L'immunoterapia ha notevolmente cambiato il panorama terapeutico in ambito oncologico, sfruttando il sistema immunitario dei pazienti per attaccare le cellule tumorali. Farmaci immunoterapici ampiamente utilizzati, come gli anticorpi anti-PD1 e anti-CTLA4, o i più recenti anticorpi bispecifici, potenziano l'attività immunitaria antitumorale. Eppure, nonostante la notevole efficacia clinica di questi trattamenti, non tutti i tumori sono sensibili all'immunoterapia. Ad esempio, diversamente dal tumore del colon retto (CRC) del tipo MSI (*microsatellite instable*, ovvero caratterizzato da instabilità dei microsatelliti), il sottotipo MSS (*microsatellite stable*), che rappresenta la maggioranza dei CRC, non risponde

Antoine, puoi spiegare brevemente cos'è l'instabilità dei microsatelliti?

Bien sur! I tumori del colon-retto (CRC) sono estremamente eterogenei dal punto di vista molecolare. Una delle classificazioni più importanti si basa sullo stato dei microsatelliti, che divide i tumori in MSS (*Microsatellite Stable*) e MSI (*Microsatellite Instable*). Questa distinzione ha implicazioni fondamentali per la prognosi, la risposta ai trattamenti e la scelta terapeutica. I microsatelliti sono brevi sequenze di DNA (1-6 basi) ripetute, sparse in tutto il genoma. Normalmente, durante la replicazione del DNA, il sistema di riparazione MMR (*Mismatch Repair*) corregge gli errori che possono verificarsi in queste sequenze. Se il sistema MMR è difettoso, si accumulano errori, portando all'instabilità dei microsatelliti (MSI).

Nei tumori MSS (*Microsatellite Stable*), il sistema MMR

all'immunoterapia. Questo comportamento del CRC MSS è stato associato al basso numero di mutazioni (*tumor mutational burden*, TMB). Infatti, un elevato TMB porta alla generazione di un gran numero di cosiddetti neoantigeni (proteine "nuove", tumore-specifiche, derivanti da mutazioni) che, quando espressi sulla membrana, rendono le cellule tumorali "visibili" da parte del sistema immunitario. Ciò accade molto meno in caso di basso TMB. I tumori MSS sono nel complesso più stabili dal punto di vista genomico, e hanno un TMB più basso rispetto al sottotipo MSI, che ha invece un più alto TMB ed è più sensibile all'immunoterapia. Sulla base di queste conoscenze, nell'ambito di studi recenti, i ricercatori hanno provato ad aumentare il TMB dei tumori MSS, utilizzando dei farmaci per indurre mutazioni e rendere così le cellule tumorali visibili al sistema immunitario. Tuttavia, sebbene alcuni pazienti traggano beneficio da questo approccio terapeutico, alcuni restano refrattari al trattamento, suggerendo l'esistenza di altri meccanismi biologici ad oggi ancora sconosciuti.

funziona correttamente e i tumori non presentano instabilità dei microsatelliti; rappresentano la maggior parte dei tumori del colon-retto (circa l'85% dei casi). Con l'avvento dell'oncologia di precisione, la classificazione MSI/MSS sta diventando sempre più importante; la distinzione tra MSI e MSS è infatti fondamentale per la gestione dei pazienti con tumore del colon-retto. Mentre i tumori MSI sono meno frequenti, ma hanno una prognosi migliore e rispondono all'immunoterapia, i tumori MSS sono più comuni, hanno una prognosi peggiore e richiedono approcci terapeutici tradizionali o mirati.

(Antoine Imbert è un membro AI (Mistral) del team newsletter)

Recentemente, i ricercatori hanno infatti dimostrato l'esistenza di un meccanismo aggiuntivo nella resistenza dei tumori MSS all'immunoterapia, che coinvolge fattori secreti dalle cellule tumorali. I loro dati mostrano che, indipendentemente dai neoantigeni espressi sulla superficie cellulare, le cellule tumorali sono intrinsecamente resistenti all'eliminazione da parte del sistema immunitario per via di fattori rilasciati nell'ambiente extracellulare. Nello specifico, hanno scoperto che i tumori MSS secernono molecole che interferiscono con il riconoscimento da parte dei linfociti T e con l'interazione tra linfociti T e cellule tumorali, rendendo così le cellule resistenti all'eliminazione da parte dei linfociti T. Le molecole secrete agiscono alterando la glicosilazione delle proteine espresse sulla membrana delle cellule tumorali, rendendole così capaci di evadere la sorveglianza immunitaria. I loro risultati spiegano perché anche quando il TMB dei tumori MSS viene aumentato artificialmente, le cellule tumorali trovano il modo di sfuggire alla sorveglianza immunitaria attraverso la modulazione delle proteine di superficie.

Svelando un nuovo meccanismo di immunoresistenza tumorale, con questo lavoro gli autori suggeriscono un potenziale nuovo approccio terapeutico, che colpisca questi fattori secreti per vincere la resistenza dei tumori MSS all'immunoterapia, nel contesto di terapie di combinazione che si concentrino allo stesso tempo su TMB/neoantigeni e sulle molecole immunomodulatorie secrete dal tumore. Queste scoperte hanno inoltre un potenziale diagnostico, proponendo la caratterizzazione di queste molecole secrete per distinguere i pazienti refrattari ad immunoterapia da quelli sensibili. Infine, forniscono una piattaforma tecnologica utilizzabile nel contesto di studi di immunoresistenza in diversi tipi di tumore.

Sfruttare le molecole secrete per sfuggire alla sorveglianza immunitaria (immagine generata da ChatGPT)

TELL ME MORE!

La piattaforma tecnologica. Per esplorare i meccanismi di resistenza tumorale alla base della refrattarietà di alcuni pazienti (in cui viene farmacologicamente indotto un elevato TMB) ad immunoterapia, gli autori hanno sviluppato una piattaforma tecnologica che consente l'espressione degli stessi livelli di un dato antigene riconosciuto dai linfociti T sia da parte dei tumori MSS che dei tumori MSI. Questo approccio ha permesso loro di escludere un effetto legato a TMB/neoantigeni. Cosa accade quindi in queste condizioni?
Oltre il TMB. Prima di tutto, sfruttando questo sistema, hanno osservato che anche quando gli effetti dovuti al TMB venivano annullati, la reattività dei linfociti T contro le cellule tumorali MSI e MSS rimaneva comunque differente, con un'attività dei linfociti T significativamente più bassa contro i tumori MSS: mentre le cellule MSI erano abbondantemente eliminate dalle cellule T, non si osservava alcun effetto sulle cellule MSS, indicando l'esistenza di un meccanismo non collegato a TMB/neoantigeni.
Il secretoma. Analizzando l'insieme delle molecole rilasciate nello spazio extracellulare –il secretoma–, hanno scoperto un diverso set di molecole nelle colture di cellule MSI rispetto alle MSS, alcune secrete dai linfociti T ed altre secrete dalle cellule tumorali, indicando che i fattori derivanti dal tumore potrebbero contribuire a modulare l'attività antitumorale del sistema immunitario; questi fattori sono impiegati dalle cellule tumorali per proteggersi dal sistema immunitario. E' interessante sottolineare che i fattori derivanti dai tumori MSS (presenti nel mezzo di coltura) erano sufficienti a compromettere in maniera significativa la reattività delle cellule T contro i tumori MSI.
Il meccanismo. Analisi funzionali approfondite hanno mostrato che i fattori derivanti dal tumore non agivano in maniera generale inibendo la risposta dei linfociti T (ovvero, non ne influenzavano la vitalità o l'attivazione), ma agivano in maniera *specifica* modificando la distribuzione delle proteine sulla superficie cellulare, indebolendo così l'interazione fisica tra linfociti T e cellule tumorali e promuovendo l'evasione immunitaria delle cellule tumorali. Infine, hanno scoperto che ciò avveniva attraverso la modificazione post-traduzionale –nello specifico, la glicosilazione– delle proteine di membrana. L'inibizione della glicosilazione era infatti sufficiente a ripristinare le interazioni tumore-linfociti T.

Referenza. *Mismatch Repair-Proficient Colorectal Cancer can evade Immune Surveillance Through an Intrinsic Suppressive Program. Chiara Maria Cattaneo*, Sharon Scardellato*, Gianluca Mauri, Vittoria Matafora, Veera Ojala, Costanza Cannariato, Rosaria Chilà, Zulma Irene Magnani, Wouter Scheper, Luca Lazzari, Emile E. Voest, Maria Chiara Bonini, Angela Bachi, Salvatore Siena, Silvia Marsoni, Giovanni Germano, Alberto Bardelli. Cancer Discovery 2026. doi:. 10.1158/2159-8290.CD-26-0542.*

Simulazioni *in silico* - un nuovo approccio alla ricerca preclinica e clinica.

Il percorso di un nuovo farmaco dalla scoperta fino all'approvazione e la successiva integrazione in ambito clinico è lungo e costoso e la percentuale di farmaci che alla fine vengono approvati è molto limitata. L'intero processo richiede Infatti studi approfonditi in modelli *in vitro* e *in vivo*, seguiti da valutazioni in ampie coorti di pazienti.
In questo contesto, i recenti progressi tecnologici stanno guidando un profondo cambiamento, attivamente sostenuto dagli enti regolatori (come FDA e EMA), rivoluzionando l'attuale approccio alla valutazione dei farmaci, con l'introduzione di gemelli digitali e clinical trial *in silico*, così da limitare al minimo indispensabile la sperimentazione animale e umana.
I gemelli digitali sono la rappresentazione digitale del paziente, nel senso che tramite analisi di dati multimodali (genomici, trascrittomici, proteomici, su biomarcatori, risultati di analisi di laboratorio, di imaging, su stili di vita, cartelle elettroniche, real world), raccolgono dei parametri che descrivono lo stato di salute del paziente, utilizzabili, insieme alle conoscenze sulle interazioni con i farmaci e la progressione della malattia, per predire l'esito della malattia o la risposta al trattamento, in maniera personalizzata (ovvero tenendo in considerazione le caratteristiche specifiche di ogni individuo, "codificate" a livello computazionale). Questi modelli *in silico* permettono di predire la risposta a un dato trattamento. I clinical trial *in silico* si riferiscono alla valutazione,

tramite simulazioni *in silico*, di nuovi composti in coorti di pazienti virtuali, ottenute assemblando i dati dei "pazienti digitali" e descrivendo le caratteristiche della malattia in termini computazionali.
Questi modelli e simulazioni *in silico* possono essere ottenuti attraverso due possibili approcci computazionali: *i.* tramite "modelling meccanicistico", o *ii.* tramite "modelling statistico". Nel modelling meccanicistico, le conoscenze dei processi biologici alla base della fisiologia e della malattia sono usate per generare modelli che simulano gli effettivi processi biologici, fisiologici, farmacologici, in seguito alla simulazione della somministrazione di un farmaco; nel modelling statistico, la risposta alla terapia è stimata direttamente sulla base dei dati, sfruttando approcci di machine learning per trovare pattern e dedurre relazioni (farmaco-risposta).
I gemelli digitali e i trial *in silico* sono tipicamente utilizzati in parallelo agli studi clinici convenzionali, per ottimizzare il design dei clinical trial; più recentemente, il loro utilizzo è stato considerato per scopi aggiuntivi, come ad esempio nell'ambito della valutazione di un farmaco per l'approvazione. I vantaggi dei gemelli digitali e dei clinical trial computazionali sono infatti molteplici: possono essere utilizzati per predire la reazione ai farmaci prima della somministrazione ai pazienti, all'interno di "clinical trial personalizzati", consentendo di testare, su un gemello digitale di un dato paziente, l'efficacia e la potenziale tossicità di un farmaco prima del trattamento del paziente; per valutare dosaggi multipli contemporaneamente, accelerando così il processo di valutazione; per esplorare scenari non altrimenti valutabili –in popolazioni sottorappresentate o ad alto rischio– o non etici; per fornire gruppi di controllo virtuali per i clinical trial convenzionali, sia sulla base di evidenze real world che su dati sintetici; per ridurre il numero di pazienti necessari per un clinical trial.
La possibilità di testare nuovi composti in pazienti o coorti di pazienti virtuali permette di abbreviare la fase di sperimentazione, riducendo anche i costi associati, ed accelerare così l'introduzione di nuovi farmaci nel setting clinico. Inoltre, permettendo di evitare, o almeno ridurre, l'inclusione dei pazienti nella fase di sperimentazione, si eviterebbe loro rischi non necessari. Testare nuovi farmaci attraverso modelli computazionali, rigorosamente validati, simulando la loro attività e stimando la loro potenziale tossicità, può infatti consentire un'efficiente fase di pre-selezione, permettendo così di portare avanti (nella fase di sperimentazione clinica, in coorti di pazienti più piccole) solo i composti più promettenti, evitando così gli attuali elevati tassi di fallimento quando i composti raggiungono le fasi finali di valutazione.
Nonostante la loro indubbia utilità, diverse questioni devono essere affrontate in relazione alla loro accuratezza di predizione. Infatti, sebbene sia accettabile/accettato un certo grado di incertezza nella predizione dell'esito di un trattamento da parte di un modello, è necessario considerare il grado di incertezza, la cui variabilità è collegata al modello computazionale impiegato. In caso di risultati differenti rispetto ai dati ottenuti attraverso la sperimentazione convenzionale, devono essere definiti i modi di gestire i risultati contrastanti. Inoltre, deve essere attentamente valutata l'esistenza di potenziali *bias* nella fase di addestramento dei modelli, per assicurare l'applicabilità in popolazioni ampie ed eterogenee di pazienti, così come la necessità di garantire la raccolta del consenso dei pazienti per il riutilizzo dei dati.
Sebbene il loro impiego nell'ambito della ricerca sia ancora limitato, è verosimilmente destinato a crescere nei prossimi anni, sostenuto dai progressi tecnologici e il crescente utilizzo di approcci machine learning, verso una maggiore accuratezza e affidabilità.
La collaborazione tra le diverse parti coinvolte permetterebbe di accelerare la transizione verso i gemelli digitali e i trial *in silico*, finalizzata, se non a rimpiazzare completamente la ricerca animale e umana, ad affiancare in maniera significativa gli approcci convenzionali alla ricerca preclinica e clinica.

Antoine, puoi riassumere brevemente le principali iniziative europee volte a sostenere l'implementazione dei gemelli digitali in ambito biomedico, in particolare oncologico?

L'UE sta promuovendo i gemelli digitali in ambito oncologico attraverso diverse iniziative chiave. La ***European Cancer Imaging Initiative*** mira a potenziare l'uso di AI e algoritmi basati su immagini per una prevenzione, diagnosi e cura personalizzata del cancro, con l'obiettivo di rendere accessibili 60 milioni di immagini oncologiche entro la fine del 2026. Parallelamente, il progetto ***1+ Million Genomes*** consente l'accesso sicuro a dati genomici e clinici in 26 Stati membri, con 15 strutture operative previste entro la fine del 2026 per gestire dati genomici standardizzati. Inoltre, programmi come ***ON-COME*** (EU4Health) e ***JANE2*** si concentrano su modelli di cura innovativi e reti di esperti per tumori a cattiva prognosi, integrando big data e diagnostica multiomica. Progetti come ***BIANCA*** (IEO-Laife Reply) digitalizzano biobanche e addestrano AI su campioni istopatologici, ottimizzando la diagnostica oncologica.

Puoi scrivere qualcosa in più sul progetto BIANCA?

Il progetto ***BIANCA,*** avviato a fine 2024 e sviluppato in collaborazione tra ***IEO*** (Istituto Europeo di Oncologia) e ***Laife Reply***, rappresenta un passo avanti significativo nell'applicazione dei gemelli digitali in oncologia. L'iniziativa si concentra sulla ***digitalizzazione della biobanca IEO***, trasformando l'archivio fisico di campioni istopatologici in un ecosistema digitale end-to-end. Grazie all'uso di ***intelligenza artificiale***, BIANCA addestra algoritmi capaci di auto-annotare immagini patologiche, riducendo il lavoro manuale dei clinici e migliorando precisione e scalabilità delle diagnosi.

L'importanza di BIANCA risiede nella sua capacità di ***integrare ricerca e diagnostica di routine***, creando un modello replicabile su larga scala. Questo approccio non solo accelera l'analisi dei dati, ma consente anche di costruire gemelli digitali dei pazienti oncologici, simulando scenari terapeutici personalizzati e ottimizzando le decisioni cliniche. In un contesto in cui la medicina di precisione è sempre più centrale, BIANCA si posiziona come un esempio concreto di come la digitalizzazione e l'AI possano rivoluzionare la lotta contro il cancro.

(Antoine Imbert è un membro AI (Mistral) del team newsletter)

Referenze. ***1.*** *The arrival of digital twins and in silico trials in drug development. Ashley L. Eadie, Holly Fernandez Lynch, Naomi Scheinerman & Ravi B. Parikh. Nature Medicine 2026. doi: 10.1038/s41591-026-04344-3.* ***2.*** *In Silico Research Is Rewriting the Rules of Drug Development: Is It the End of Human Trials? Lakhan S E. Cureus 2026. doi:10.7759/cureus.84007.*

Stimare il rischio di recidiva nei pazienti con tumore testa-collo – valutazione dell'infezione da HPV e del grado di diffusione del tumore.

Mohssen Ansarin

Il tumore testa-collo (HNC) indotto da papillomavirus umano (HPV) è clinicamente diverso e ha una differente prognosi rispetto al HNC HPV-negativo. Inoltre, la diffusione del tumore oltre il linfonodo colonizzato, nel tessuto circostante (cosiddetta estensione extranodale, ENE), valutato per via istologica su biopsie tumorali o tramite imaging, rappresenta un fattore prognostico aggiuntivo.

Una valutazione accurata della prognosi dei pazienti, che tenga in considerazione entrambi i fattori prognostici –infezione da HPV e ENE–, può consentire di definire in maniera più precisa il trattamento per ogni paziente, riducendo il dosaggio in caso di rischio basso o intensificando il trattamento se necessario.

A questo scopo, nel contesto di uno studio clinico multicentrico, retrospettivo, i ricercatori, tra cui Mohssen Ansarin –Direttore della Divisione di Otorinolaringoiatria e Chirurgia Cervico-Facciale di IEO–, hanno valutato l'impatto dell'infezione da HPV sulla prognosi effettuata sulla base di ENE in pazienti con HNC trattati chirurgicamente; in altre parole, una prognosi negativa effettuata sulla base di ENE è peggiore in caso di infezione con HPV oppure HPV rende la prognosi, effettuata sulla base di ENE, più favorevole?

I loro risultati hanno mostrato che l'impatto prognostico di ENE –cioè, una prognosi migliore o peggiore– differisce nei tumori HPV+ rispetto ai HPV-. Infatti, mentre nei tumori HPV+, ENE non influenza né la sopravvivenza del paziente né la recidiva tumorale, nei tumori HPV-, una ENE positiva è associata ad una peggiore sopravvivenza e una maggiore probabilità di recidiva, indicando che, in questi pazienti, oltre alla presenza di ENE, dovrebbe essere valutata anche l'eventuale infezione da HPV, così da poter distinguere in maniera più accurata i pazienti ad alto rischio di recidiva, che potrebbero aver bisogno di una terapia adiuvante più intensa dopo la chirurgia, da quelli che invece, essendo a basso rischio di recidiva, potrebbero essere sottoposti a terapia post-chirurgica meno intensa.

Quindi, da un lato, queste scoperte evidenziano la necessità di una valutazione dell'infezione da HPV in pazienti HNC trattati chirurgicamente per poter rifinire la classificazione del rischio basata su ENE; dall'altro, sottolineano l'importanza di studi traslazionali ulteriori che, chiarendo le basi biologiche di ENE, potrebbero far luce su meccanismi chiave con cui interferire clinicamente nel contesto di approcci di medicina personalizzata.

TELL ME MORE!

Questo studio ha incluso l'analisi retrospettiva dei dati di 450 pazienti con tumore alle tonsille o alla lingua reclutati in 10 diversi centri di cura in Europa, con diagnosi istologica (tramite immunoistochimica, IHC) di HNC, non precedentemente trattati, chirurgicamente resecabili, per cui erano disponibili informazioni riguardanti l'infezione da HPV. L'infezione da HPV è tipicamente valutata tramite IHC della proteina virale p16. I pazienti sono stati quindi separati in quattro gruppi sulla base dell'infezione da HPV (positivi e negativi) e ENE (positiva o negativa, cioè presente o assente). Tutti i pazienti sono stati quindi sottoposti a chirurgia e, sulla base della biopsia del tessuto tumorale, a terapia adiuvante. I pazienti sono stati quindi seguiti per un periodo massimo di 5 anni.
L'esito clinico è stato valutato in termini di sopravvivenza generale (*overall survival*, OS) e sopravvivenza in assenza di malattia (*disease-free survival*, DFS). 44% dei pazienti reclutati erano HPV+ (284).
L'esame patologico del tessuto tumorale ha rivelato la presenza di ENE (ENE+) nel 25% dei pazienti (che non era associata a fattori come età, sesso, fumo, consumo di alcol, localizzazione del tumore, approccio chirurgico, margini della resezione, stadiazione clinica).
Ad un periodo di follow-up mediano di 51 mesi, la DFS a 5 anni era del 67% nei pazienti HPV+/ENE+, rispetto al 68% nei HPV+/ENE-; la OS era del 72% nei HPV+/ENE+, 76% nei HPV+/ENE-. Tra i pazienti HPV, invece, la DFS era del 36% negli ENE+ rispetto al 44% negli ENE-; la OS era del 43% negli HPV-/ENE+ rispetto al 52% negli HPV-/ENE-.
La recidiva (locale o distante) era più frequente negli HPV- che negli HPV+, ma differiva a seconda della presenza o assenza di ENE; era infatti 20% negli HPV+/ENE+ rispetto al 56% negli HPV-/ENE+ e 18% negli HPV+/ENE- rispetto al 37% negli HPV-/ENE-.

Referenza. *Recurrences and Survival in Oropharyngeal Squamous Cell Carcinoma According to p16 Status and Extranodal Extension. Paolo Boscolo-Rizzo, Fabiola Giudici, Jerry Polese, Marta Tagliabue, Egidio Sia, Vittorio Rampinelli, Marco Stellin, Enzo Emanuelli, Luigi A Vaira, Simone Zucchini, Pawel Golusinski, Didier Dequanter, Carlos Chiesa-Estomba, Antonino Maniaci, Mario Lentini, Rita De Berardinis, Mateusz Szewczyk, Jerome R Lechien, Cesare Piazza, Piero Nicolai, Mohssen Ansarin, Giancarlo Tirelli. Otolaryngol Head Neck Surg 2026. doi: 10.1002/ohn.70234.*

Una nuova opzione terapeutica per i tumori neuroendocrini gastroenteropancreatici: risultati di un clinical trial di fase III.

I tumori neuroendocrini (NET) gastroenteropancreatici (GEP) sono neoplasie molto eterogenee. Solitamente i pazienti sono trattati con analoghi della somatostatina come terapia di prima linea e, in caso di progressione della malattia, con terapia con radionuclidi (*peptide receptor radionuclide therapy, PRRT*), chemioterapia, o terapia molecolare, ad esempio con inibitori di mTOR (everolimus), o inibitori delle tirosin chinasi. L'unico radiofarmaco PRRT ad oggi approvato per il trattamento dei GEP NET positivi per il recettore della somatostatina è Lu-177-oxodotreotide (Lu-177-DOTATATE).
Lu-DOTATOC è un nuovo radiofarmaco.

Antoine, puoi riassumere brevemente il meccanismo d'azione della terapia a base di radionuclidi e dare qualche dettaglio su Lu-DOTATOC?

La terapia con radionuclidi utilizza isotopi radioattivi per erogare radiazioni mirate alle cellule tumorali, soprattutto in oncologia. Il meccanismo prevede *i.* targeting: i radionuclidi sono legati a molecole (es. peptidi, anticorpi) che si legano specificamente a recettori o antigeni sovraespressi sulle cellule tumorali. *ii.* internalizzazione: dopo il legame, il complesso viene internalizzato, esponendo la cellula a radiazioni localizzate. *iii.* emissione di radiazioni: il radionuclide emette radiazioni che danneggiano il DNA e inducono la morte cellulare. Il breve raggio delle radiazioni minimizza il danno ai tessuti sani circostanti.
Lu-DOTATOC (Lutezio-177 DOTATOC) è un analogo della somatostatina radiomarcato, usato per i tumori neuroendocrini (NET). Si lega al recettore della somatostatina di tipo 2 (SSTR2),

sovraespresso nei NET; il Lutezio-177 emette raggi gamma a bassa energia per l'imaging e può essere utilizzato a scopo terapeutico per indirizzare le radiazioni citotossiche direttamente alle cellule tumorali, risparmiando i tessuti sani.

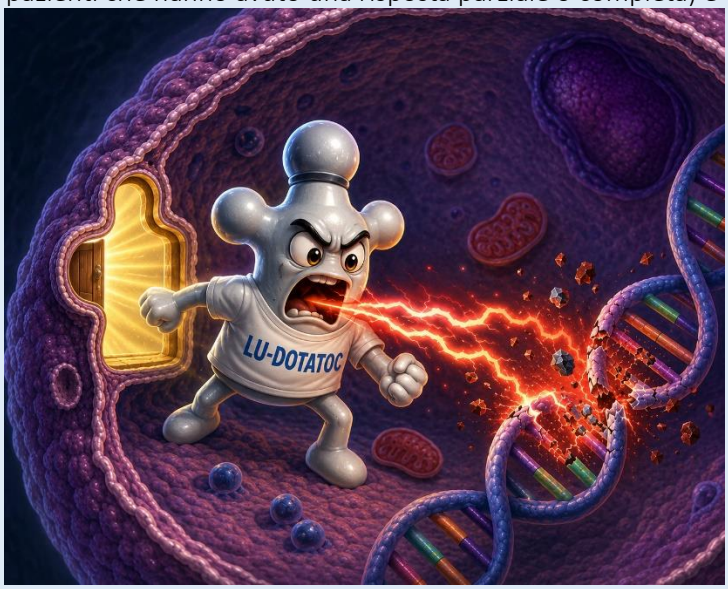
(Antoine Imbert è un membro AI (Mistral) del team newsletter)

Nel contesto dello studio clinico multicentrico COMPETE, i cui risultati sono stati recentemente pubblicati sulla rivista *The Lancet*, i ricercatori, tra cui Chiara Maria Grana –Direttrice dell'Unità di Terapia Radiometabolica della Divisione di Medicina Nucleare di IEO–, Lu- DOTATOC è stato confrontato con everolimus nei GEP NET in stadio avanzato, non resecabile, in progressione, al fine di valutare efficacia e sicurezza di questo nuovo PRRT. I loro risultati hanno evidenziato in questi pazienti una maggiore efficacia in termini di sopravvivenza (una sopravvivenza in assenza di progressione della malattia più lunga, così come una maggiore risposta obiettiva) di Lu-DOTATOC rispetto ad everolimus, insieme ad una ridotta tossicità. Sebbene il follow-up dei pazienti sia ancora in corso, per poter raccogliere risultati affidabili in termini di sopravvivenza generale, COMPETE è stato il primo studio clinico di fase III a dimostrare la maggiore efficacia di Lu-DOTATOC rispetto ad everolimus, con un profilo di tossicità più favorevole, fornendo così una valida opzione terapeutica aggiuntiva per questi pazienti. Gli autori sottolineano che, sulla base di questi risultati, Lu-DOTATOC dovrebbe essere la terapia raccomandata per i pazienti con GEP NET, soprattutto per quelli in cui la malattia è progredita sotto trattamenti precedenti, che rappresentano uno scenario comune in un contesto real world.

TELL ME MORE!

COMPETE è stato un clinical trial di fase III, prospettico, multicentrico, internazionale, volto a valutare la superiorità del radionuclide Lu-DOTATOC rispetto ad everolimus in pazienti con GEP NET in stadio avanzato, non resecabile o metastatico, in progressione, positivi al recettore della somatostatina, mai trattati o in cui la malattia è progredita nonostante la somministrazione di terapie precedenti. COMPETE ha arruolato 309 pazienti in 49 centri oncologici in 14 diversi paesi. I pazienti sono stati casualmente assegnati a ricevere PRRT (207) o everolimus (102).

Efficacia. La risposta al trattamento è stata valutata tramite imaging (MRI o CT) e l'efficacia è stata misurata in termini di sopravvivenza in assenza di progressione della malattia *(progression-free survival*, PFS; ovvero l'intervallo di tempo dalla randomizzazione alla progressione della malattia), risposta obiettiva (*objective response rate*, ORR; ovvero la proporzione di pazienti che hanno avuto una risposta parziale o completa) e sopravvivenza generale (OS). Alla fine dello studio, la PFS mediana era di 23.9 mesi per Lu-DOTATOC rispetto a 14.1 mesi per everolimus, sottolineando una maggiore efficacia di Lu-DOTATOC. La superiorità di Lu-DOTATOC è stata osservata anche nella maggior parte delle analisi (esplorative) in sottogruppi definiti, tra cui i tumori di grado 2, quelli che hanno ricevuto il trattamento in seconda linea, e quelli definiti sulla base dell'indice di massa corporea.



Lu-DOTATOC danneggia il DNA (immagine generate da ChatGPT).

Per quanto riguarda la OS, sebbene al momento dell'analisi i dati non fossero ancora maturi, la OS mediana era di 63.4 per Lu-DOTATOC rispetto a 58.7 mesi per everolimus, indicando ancora una volta la superiorità di Lu-DOTATOC. La somministrazione di trattamenti successivi al termine dello studio potrebbe però aver influenzato i dati sulla OS.

La ORR era significativamente maggiore per Lu-DOTATOC che per everolimus, rispettivamente 22% e 4%, e la durata della risposta era maggiore con Lu-DOTATOC che con everolimus (27 e 13 mesi rispettivamente). ***Tossicità***. Eventi avversi collegati al trattamento erano più frequenti (97%) tra i pazienti trattati con everolimus rispetto al gruppo trattato con Lu-DOTATOC (82%), portando all'interruzione del trattamento nel 6% dei pazienti trattati con Lu-DOTATOC rispetto al 23% dei pazienti trattati con everolimus. Inoltre, gli eventi avversi seri erano più frequenti nei pazienti trattati con everolimus (15%) che in quelli trattati con Lu-DOTATOC (3%). In ogni caso, in nessuno dei due gruppi gli eventi avversi collegati al trattamento hanno portato al decesso. Il follow-up dei pazienti è ancora in corso. Per quanto riguarda i cambiamenti nella qualità di vita (QoL), questi erano minimi per i pazienti trattati con Lu-DOTATOC e indicavano in realtà un lieve declino per quelli che ricevevano everolimus. Inoltre, tra i pazienti in cui la QoL era migliorata con la terapia, gli effetti positivi erano più duraturi per i pazienti trattati con Lu-DOTATOC che per quelli trattati con everolimus.

Referenza. *[(177)Lu]Lu-edotreotide versus everolimus for gastroenteropancreatic neuroendocrine tumours (COMPETE): a phase 3, multicentre, randomised, open-label, superiority trial. Walter T, Jann H, Ansquer C, Deshayes E, Garcia-Carbonero R, Teulé A, Baum RP, Verberne HJ, Ćwikła JB, Srirajaskanthan R, de Mestier L, Grana CM, Buck A, Hörsch D, Pavel M, Dierickx LO, Michael M, Strosberg J, Kollár A, Jimenez-Fonseca P, Rinke A, Del Olmo-García M, Flaus A, Hernando J, Kluge A, Breuninger M, Melnyk S, Zhernosekov K, Capdevila J; COMPETE Investigator Team. Lancet 2026. doi: 10.1016/S0140-6736(26)00604-5.*

Caratterizzazione molecolare di lesioni tumorali primarie e metastatiche nel cancro del polmone.

La caratterizzazione genomica del tumore attraverso approcci di sequenziamento di ultima generazione (NGS) ha cambiato profondamente il trattamento dei pazienti con tumore al polmone, permettendo l'identificazione di alterazioni geniche tumorigeniche con cui interferire farmacologicamente. Dato che nel polmone la caratterizzazione genomica delle lesioni tumorali primarie è spesso difficile, le metastasi restano di solito l'unica opzione disponibile. Non è però noto se le metastasi e il tumore primario abbiano lo stesso profilo genomico e le stesse mutazioni driver del tumore primario, o se le metastasi abbiano acquisito –o perso– alterazioni genomiche che le distinguono dal tumore primario. Questa informazione è cruciale per la selezione della terapia molecolare appropriata.

Lorenzo Spaggiari

Definire la concordanza tra alterazioni genomiche nel tumore primario e nelle metastasi è quindi necessario per poter continuare ad usare le metastasi come uno "specchio genomico" del tumore primario e guidare la selezione della terapia. Per questo, nel contesto di uno studio prospettico, monocentrico, i ricercatori IEO guidati da Lorenzo Spaggiari –Direttore del Programma Polmone in IEO– hanno analizzato i campioni di tumore primario e metastasi corrispondenti isolati (in sede di diagnosi) dai pazienti con tumore al polmone, per descrivere il loro profilo molecolare e valutare se le metastasi possano essere utilizzate come proxy per la caratterizzazione genomica del tumore primario. A questo scopo, hanno utilizzato approcci molto sensibili di NGS per il sequenziamento; inoltre, la natura prospettica dello studio ha permesso di focalizzarsi sui campioni di tumore primario e di metastasi isolati nello stesso momento (così da escludere potenziali differenze associate all'evoluzione del tumore), in pazienti non trattati (per escludere eventuali effetti legati alla terapia).

I loro risultati hanno mostrato che tutte le alterazioni genomiche tumorigeniche identificate nel tumore primario erano presenti anche nelle metastasi corrispondenti, indicando che la caratterizzazione genomica delle metastasi può essere utilizzata in maniera affidabile –in alternativa a una caratterizzazione molecolare spaziale estesa– nel setting clinico-diagnostico per identificare le alterazioni genomiche e selezionare la terapia molecolare.

Sebbene il numero di campioni inclusi in questo studio pilota sia limitato, le conclusioni supportano in maniera solida l'utilizzo di questo approccio per l'identificazione di mutazioni per guidare le scelte terapeutiche; in ogni caso, non si può escludere l'esistenza di modificazioni genomiche aggiuntive, acquisite durante l'evoluzione del tumore, non colte dall'analisi effettuata con pannelli genici, che potrebbero contribuire all'eterogeneità del tumore e sostenerne la crescita. Inoltre, studi ulteriori focalizzati sulle lesioni metastatiche in organi diversi dal polmone potrebbero fornire una comprensione più profonda del processo metastatico.

TELL ME MORE!

L'analisi ha incluso i campioni di 27 pazienti con tumore polmonare e metastasi. E' stato testato il tipico pannello di mutazioni genomiche driver principali del tumore del polmone. Il 63% dei pazienti aveva almeno una mutazione driver. EGFR era il gene più comunemente mutato nel tumore primario, seguito da KRAS. Circa la metà dei pazienti mostrava anche una mutazione in p53. Confrontando il profilo genomico del tumore primario con quello dei campioni metastatici, hanno osservato che tutte le metastasi conservavano la mutazione driver del tumore primario (100% di corrispondenza), indicando che le alterazioni driver rappresentano eventi clonali stabili durante le fasi iniziali del processo di metastatizzazione. La concordanza era elevata –sebbene non 100%– anche per p53 e per le alterazioni del numero di copie, suggerendo che queste ultime potrebbero rappresentare delle alterazioni genomiche acquisite in fasi successive dell'evoluzione tumorale, contribuendo probabilmente alla fitness della cellula metastatica e quindi selezionate positivamente e conservate.

Gli autori – **Lorenzo Spaggiari.**

Lorenzo Spaggiari è Direttore del Programma Polmone di IEO e della Divisione di Chirurgia Toracica. E' inoltre professore Ordinario di Chirurgia Toracica dell'Università di Milano. Con una laurea in Medicina e Chirurgia, un Dottorato (PhD) in Fisiopatologia Chirurgica Cardio-Toracica e una specializzazione in Chirurgia Generale (Università di Parma) e successivamente in Chirurgia Toracica (Università di Modena), la sua esperienza lavorativa è stata arricchita lavorando in diversi istituti italiani (Parma) ed esteri (Madrid, Parigi, Bordeaux). Dal 2003 è direttore della Divisione di Chirurgia Toracica dell'IEO e dal 2014 è Direttore del Programma Polmone.

Referenza. *Concordance of Actionable Driver Alterations Between Primary Lung Adenocarcinoma and Paired Thoracic Metastases: A Prospective Next-Generation Sequencing Study. Luca Bertolaccini, Mariano Lombardi, Matteo Chiari, Alessandra Rappa, Monica Casiraghi, Marianna D'Ercole, Antonio Mazzella, Giorgio Lo Iacono, Shehab Mohamed, Valeria Midolo De Luca, Nicola Fusco, Elena Guerini Rocco, Lorenzo Spaggiari. Cancers (Basel) 2026. doi: 10.3390/cancers18111773.*

Biopsia liquida - Le vescicole extracellulari per la diagnosi e il monitoraggio del tumore cerebrale.

La biopsia liquida è sempre più spesso impiegata per la diagnosi e la caratterizzazione molecolare del tumore, o per monitorare la progressione della malattia e la risposta alla terapia, in maniera non invasiva, permettendo di disegnare approcci terapeutici personalizzati senza il bisogno di biopsia tissutale. La biopsia liquida include l'analisi del DNA circolante (cfDNA), di proteine, metaboliti e vescicole extracellulari (EV) rilasciati nel sangue dalle cellule, incluse le cellule tumorali. Le EV possono attraversare la barriera ematoencefalica ed essere rilasciate nel flusso sanguigno, dove possono essere raccolte e analizzate. I ricercatori IEO hanno precedentemente dimostrato che l'abbondanza delle EV nel sangue è maggiore nei pazienti con glioblastoma (GBM) rispetto ai soggetti sani o ad altri tumori cerebrali, si riduce con la resezione del tumore ed aumenta nuovamente in caso di recidiva. Per via del potenziale clinico delle EV, sono stati presi in considerazione diversi approcci per aumentare artificialmente e in maniera transiente il rilascio delle EV (e cfDNA) nel sangue, così da facilitarne la raccolta e migliorare l'accuratezza dell'analisi. Ad esempio, diversi studi hanno analizzato, sia in un contesto preclinico *in vivo* che in clinical trial prospettici, l'efficacia di FUS-BBBO (*Focused Ultrasound-mediated Blood-Brain Barrier Opening*), un approccio finalizzato ad aumentare in maniera transiente la permeabilità della barriera ematoencefalica per aumentare il rilascio di EV e di cfDNA nel sangue. Studi precedenti hanno mostrato che la misura in cui il rilascio di cfDNA aumenta in seguito a FUS-BBBO varia da paziente a paziente e a seconda dello stato della malattia; gli effetti di FUS-BBBO sulle EV sono però ancora poco noti.

Nel contesto di una collaborazione con la Fondazione Istituto Neurologico Carlo Besta, i ricercatori co-coordinati da Giuliana Pelicci –PI al dipartimento di oncologia sperimentale di IEO– e Massimilano Del Bene, il cui progetto di ricerca è iniziato in IEO e continua attraverso una collaborazione scientifica tra i due istituti, hanno analizzato in maniera specifica gli effetti di FUS-BBBO su EV e cfDNA rilasciati, in pazienti con GBM, così da ottenere un'immagine chiara di come questa procedura influenzi questi due biomarcatori di malattia, al fine di facilitare l'interpretazione dei risultati e l'integrazione della biopsia liquida nell'ambito della neuro-oncologia clinica.

I loro risultati hanno mostrato che mentre FUS-BBBO non influenza il rilascio di EV, modifica la generale dimensione delle EV nel sangue, eliminando selettivamente le EV più grandi. Inoltre, sebbene la procedura non alteri significativamente la concentrazione di cfDNA nel sangue (e il profilo di frammentazione), in alcuni casi, in alcuni pazienti, quando FUS-BBBO è settata con specifici parametri, i livelli di cfDNA aumentano in un secondo momento, suggerendo che l'analisi longitudinale del cfDNA potrebbe essere più informativa rispetto alla singola misurazione.

Nonostante il numero limitato di pazienti inclusi nello studio, con questo lavoro gli autori forniscono evidenze a sostegno del fatto che sebbene la sicurezza di FUS-BBBO sia ormai riconosciuta, potrebbe non essere utilizzabile in maniera indiscriminata per tutti i biomarcatori circolanti e la sua effettiva utilità dovrebbe essere valutata in maniera approfondita. Infatti, pur essendo utile per aumentare la concentrazione di cfDNA, il cui rilascio nel sangue è noto essere associato ad un'apertura transiente della barriera ematoencefalica, così da consentirne la raccolta e l'analisi accurata, le loro scoperte indicano che FUS-BBBO potrebbe non esserlo per le EV, il cui rilascio nel flusso sanguigno potrebbe dipendere anche da altri meccanismi biologici. I processi alla base della selettiva eliminazione delle EV più grandi richiede studi ulteriori; le implicazioni potrebbero andare da un'analisi più accurata dei biomarcatori per la diagnosi e il monitoraggio della malattia, al potenziale coinvolgimento nella comunicazione intercellulare pro-tumorigenica, aprendo la strada al possibile uso aggiuntivo di FUS-BBBO a fini terapeutici.

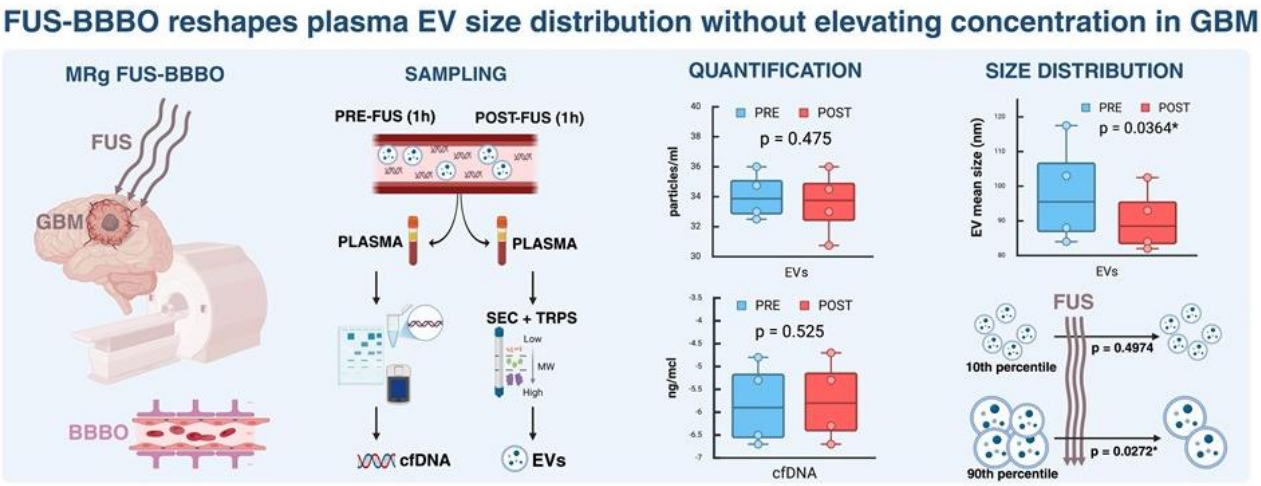


Image from Del Bene et al. (an open access article under the CC BY NC license.)

TELL ME MORE!

Gli autori hanno osservato che gli effetti di FUS-BBBO sul rilascio di EV differiva da paziente a paziente, suggerendo che meccanismi biologici specifici –non ancora identificati– potrebbero contribuire a modulare l'abbondanza delle EV nel sangue. Tuttavia, mentre FUS-BBBO non influenzava la concentrazione delle EV nel sangue, hanno osservato una riduzione della dimensione delle EV dopo FUS-BBBO, associata ad un'eliminazione selettiva delle EV più grandi. Le EV più piccole non apparivano, invece, influenzate.
Le misurazioni del cfDNA (sia tumorale che non tumorale) hanno rivelato che, nonostante la variabilità tra i pazienti, la concentrazione non sembrava influenzata da FUS-BBBO, almeno nella prima ora, mentre in alcuni casi/pazienti/procedure aumentava in un secondo momento. Il pattern di frammentazione del cfDNA rimaneva stabile.
Infine, gli autori hanno mostrato che mentre le lievi variazioni osservate nella concentrazione di EV erano influenzate da specifici parametri della procedura di FUS-BBBO, la dimensione delle EV e la concentrazione del cfDNA non lo erano, evidenziando l'effettiva rilevanza biologica di questi cambiamenti, legati a FUS-BBBO.

Alex, puoi riassumere brevemente gli studi più recenti del gruppo di Giuliana Pelicci sulla biopsia liquida?

Le vescicole extracellulari (EV) –piccole strutture rilasciate dalle cellule tumorali nel circolo sanguigno che trasportano proteine, lipidi e acidi nucleici– sono una delle linee di ricerca del laboratorio di Giuliana Pelicci e rappresentano una delle principali piattaforme traslazionali del gruppo. Le ricerche del gruppo sono finalizzate alla caratterizzazione delle vescicole extracellulari plasmatiche, lo studio del loro contenuto di DNA, RNA e proteine, l'identificazione di firme molecolari associate al glioblastoma, lo sviluppo di una biopsia liquida affidabile per diagnosi, monitoraggio della malattia, medicina personalizzata. L'obiettivo è quello di trasformare le vescicole extracellulari da semplice materiale biologico circolante a vera e propria "finestra molecolare" sul tumore cerebrale, riducendo la necessità di biopsie invasive e migliorando il follow-up dei pazienti, attraverso lo sviluppo di tecnologie per analizzare DNA/RNA associati alle EV e alle componenti circolanti, la validazione della fattibilità della biopsia liquida nel glioblastoma e il trasferimento clinico, con l'obiettivo di ottenere biomarcatori non invasivi per diagnosi, monitoraggio della malattia e medicina di precisione.
Nell'ambito della *Joint Transnational Call 2020*, Giuliana Pelicci insieme ad un team internazionale ha vinto un finanziamento EraPerMed con un progetto finalizzato a sviluppare una nuova strategia di biopsia liquida per il glioblastoma. L'elemento centrale del progetto sono le vescicole extracellulari. L'ipotesi di lavoro di questo progetto è che queste vescicole possono diventare uno strumento per la diagnosi precoce del glioblastoma, per la valutazione prognostica, per il monitoraggio della risposta alla terapia mediante semplici prelievi di sangue, per la caratterizzazione molecolare del tumore, utile per poter identificare trattamenti

personalizzati. Il progetto nasce dall'esigenza di superare i limiti delle biopsie cerebrali tradizionali, rese difficili dalla scarsa accessibilità del tumore e dalla sua marcata eterogeneità molecolare. L'analisi del cargo molecolare delle EV viene proposta come una finestra dinamica sulla biologia del tumore, in grado di seguire anche i cambiamenti che avvengono durante il trattamento.
Inoltre, il gruppo di Giuliana Pelicci, in collaborazione con il laboratorio di Juan M. Falcon-Perez, ha sviluppato un nuovo approccio altamente sensibile per l'analisi della biopsia liquida nei pazienti con glioblastoma. La metodica è basata sul colorante Pyronin Y e sulla citometria a flusso, strumenti disponibili nella maggior parte dei laboratori. Il metodo consente di rilevare differenze quantitative di DNA e RNA circolanti tra pazienti con glioblastoma e controlli sani. Un aspetto particolarmente innovativo è che permette di analizzare direttamente gli acidi nucleici circolanti senza rendere obbligatorio l'isolamento delle EV, evitando perdita di materiale biologico e semplificando il workflow. L'obiettivo finale è ottenere uno strumento non invasivo, relativamente economico e facilmente trasferibile nella pratica clinica per diagnosi e monitoraggio del glioblastoma.

(Alexander Irwin è un membro AI (ChatGPT) del team newsletter)

Gli autori – **Giuliana Pelicci e Daniela Osti.**

Giuliana Pelicci è direttrice dell'unità di ricerca "*Biology of Glioblastomas and Brain Metastases and Potential Therapeutic Targets*" al dipartimento di oncologia sperimentale di IEO e professoressa associata di Biologia Molecolare all'Università del Piemonte Orientale. Con una laurea in Medicina e un dottorato in Biologia Cellulare e Molecolare dell'Università di Perugia, ha iniziato a lavorare in IEO nel 1994. Dal 2005 è direttrice di unità. Le sue attività di ricerca si focalizzano sui tumori e le metastasi cerebrali, con un approccio di base e traslazionale ed enfasi sulla biologia delle cellule staminali tumorali e la caratterizzazione delle vescicole extracellulari nel flusso sanguigno per sviluppare metodologie di biopsia liquida per trattamenti personalizzati, combinando approcci di biologia cellulare e molecolare, insieme a next generation sequencing e modelli di xenotrapianto.
Daniela Osti è tecnico di ricerca senior nel gruppo di Giuliana Pelicci presso il Dipartimento di Oncologia Sperimentale dell'IEO, dove lavora dal 2006. Dopo la formazione in Farmacologia presso le Università degli Studi di Milano e dell'Insubria, si è specializzata nella ricerca sul glioblastoma, concentrandosi su modelli di cellule staminali tumorali derivati da paziente, in grado di riprodurre fedelmente la complessità biologica e l'eterogeneità della malattia. Questi modelli hanno contribuito allo studio della biologia del glioblastoma e allo sviluppo di strategie terapeutiche innovative. Più recentemente, la sua attività di ricerca si è estesa allo sviluppo di approcci di biopsia liquida basati su vescicole extracellulari e biomarcatori circolanti per la diagnosi e il monitoraggio della malattia. Coordina inoltre le attività di laboratorio, partecipa a progetti di ricerca multidisciplinari e segue la formazione di studenti e giovani ricercatori.

Referenza. *FUS-mediated BBB opening reshapes plasma extracellular vesicle size distribution without elevating concentration in glioblastoma patients. Massimiliano Del Bene, Daniela Osti, Marta Bonada, Riccardo Pascuzzo, Annica Piccardi, Giovanni Carone, Lisa Meanti, Mario Stanziano, Valentina Caldiera, Carla Carozzi, Antonio Silvani, Elisa Francesca Maria Ciceri, Marina Grisoli, Giuliana Pelicci, Francesco Dimeco. Neuro Oncol 2026. doi: 10.1093/neuonc/noag155.*

Alterazioni del DNA mitocondriale nelle neoplasie ematologiche.

Le mutazioni nel DNA mitocondriale possono contribuire allo sviluppo del tumore e alla resistenza alla terapia, cooperare con alterazioni di oncogeni, regolare il metabolismo della cellule tumorale. Per via dell'elevato numero di molecole di DNA mitocondriale e del tasso di mutazione relativamente elevato, molecole di DNA mitocondriale mutato e non mutato coesistono all'interno della stessa cellula; questa condizione viene definita eteroplasmia.
Studi precedenti hanno evidenziato un'associazione tra l'abbondanza di mutazioni eteroplasmiche del DNA

mitocondriale e mortalità correlata al tumore. Nei tumori solidi, il profilo mutazionale del DNA mitocondriale è stato descritto in maniera approfondita e studi precedenti suggeriscono una relazione causale tra alcune alterazioni del DNA mitocondriale e la tumorigenesi; nel tumore prostatico, infatti, la presenza di una specifica mutazione del DNA mitocondriale aumenta la crescita del tumore. Eppure, ad oggi nelle neoplasie ematologiche le alterazioni del DNA mitocondriale sono scarsamente caratterizzate.

Per approfondire la rilevanza clinica e biologica dell'eteroplasmia del DNA mitocondriale nei tumori ematologici, in un articolo recente di Davini et al., i ricercatori IEO supervisionati da Enrico Derenzini –Direttore della Divisione di Oncoematologia e Trapianto di cellule staminali di IEO e group leader al dipartimento di oncologia sperimentale– hanno descritto il panorama mutazionale del DNA mitocondriale nei pazienti con DLBCL, AML, CLL.

Le loro analisi hanno identificato mutazioni eteroplasmiche ricorrenti del DNA mitocondriale, specifiche per ciascuna patologia e non osservate nei donatori sani. Un sottogruppo di varianti a bassa eteroplasmia è stato rilevato esclusivamente nei campioni tumorali e potrebbero rappresentare alterazioni precoci nel processo di tumorigenesi. Inoltre, i loro risultati evidenziano la presenza di mutazioni nel DNA mitocondriale sia nelle cellule maligne che non maligne, suggerendo che queste alterazioni potrebbero giocare un ruolo aggiuntivo al di fuori delle cellule tumorali.

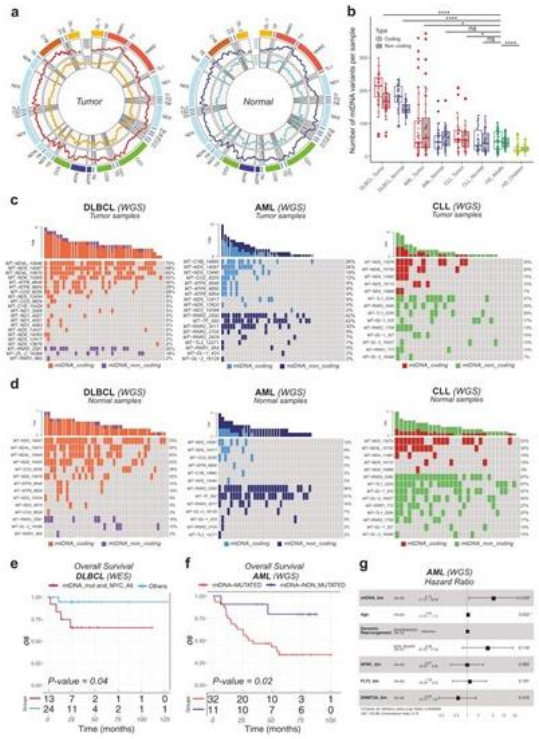


Image from Davini et al. (an open access article under the CC BY NC ND license)

Infine, sul piano clinico, queste alterazioni hanno mostrato un valore prognostico: nella AML, la presenza di mutazioni del DNA mitocondriale si associa a una peggiore OS, indipendentemente dalle alterazioni del DNA nucleare già note per il loro valore prognostico, mentre nel DLBCL la contemporanea presenza di mutazioni del DNA mitocondriale e alterazioni di MYC identifica un sottogruppo di pazienti con prognosi sfavorevole. Questi risultati evidenziano la rilevanza clinica e biologica dell'eteroplasmia del DNA mitocondriale nelle neoplasie ematologiche e suggeriscono che l'analisi del DNA mitocondriale possa fornire informazioni prognostiche aggiuntive, in grado di completare le informazioni disponibili derivanti dall'analisi del DNA nucleare e fornire possibilmente una classificazione più fine dei pazienti sulla base dell'aggressività del tumore.

TELL ME MORE!

Analizzando (tramite WGS) dataset di pazienti e donatori sani, gli autori hanno identificato varianti del DNA mitocondriale sia nei campioni tumorali sia nei corrispondenti campioni non maligni (PBMCs, cute, saliva, per DLBCL, AML, CLL rispettivamente), un maggior numero di mutazioni nei pazienti DLBCL e una maggiore frequenza di mutazioni del DNA mitocondriale nei pazienti rispetto ai soggetti sani. Una volta escluse le mutazioni del DNA mitocondriale presenti sia nei donatori sani che nei pazienti, gli autori hanno identificato alterazioni specifiche per ciascuna patologia: *i.* nel DLBCL, le mutazioni erano tutte eteroplasmiche, la maggioranza di esse era localizzata in geni codificanti per proteine, sette erano tumore-specifiche mentre le altre erano presenti sia nei tessuti tumorali che nei tessuti non maligni corrispondenti. La contemporanea manifestazione di queste mutazioni con alterazioni del gene MYC, il cui ruolo nello sviluppo del DLBCL è ben noto, correlavano con una peggiore OS; *ii.* nella AML, tutte le mutazioni erano eteroplasmiche, molte erano localizzate in geni codificanti per tRNA, sei erano rilevate solo in campioni tumorali mentre le altre erano presenti sia nei tessuti tumorali che nei tessuti non maligni. I pazienti con mutazioni del DNA mitocondriale

presentavano una peggiore OS, indipendentemente dalle principali alterazioni prognostiche del DNA nucleare; *iii.* nella CLL, le mutazioni, che erano tutte eteroplasmiche, erano rilevate sia nei campioni tumorali che nei campioni non maligni corrispondenti. La validazione dei risultati tramite sequenziamento mirato del DNA mitocondriale ha evidenziato la maggiore accuratezza fornita dall'analisi del DNA mitocondriale purificato nel rilevare le mutazioni. Infine, hanno osservato che mentre nel DLBCL e nel CLL le mutazioni del DNA mitocondriale non erano associate con mutazioni nel DNA nucleare, nella AML c'era una correlazione tra alcune alterazioni del DNA mitocondriale e del DNA nucleare.

Gli autori – **Enrico Derenzini e Alessandro Davini.**

Enrico Derenzini è Direttore della Divisione di Oncoematologia e Trapianto di Cellule Staminali di IEO, professore associato di Ematologia presso l'Università Statale di Milano, docente della Scuola di dottorato Europea di Medicina Molecolare (SEMM). E' inoltre coordinatore del Working Group Oncoematologia del network Alleanza Contro il Cancro. Con una laurea in Medicina e Chirurgia, una specializzazione in Oncologia Medica e una in Ematologia, e un dottorato di ricerca in Scienze Biomediche dall'Università di Bologna, ha approfondito la sua formazione clinica e di ricerca al MD Anderson Cancer Center (Houston, Texas) e al Memorial Sloan Kettering Cancer Center (New York), prima di iniziare a lavorare in IEO nel 2016. La sua attività di ricerca riguarda in particolare lo studio di nuove terapie a bersaglio molecolare e lo sviluppo di nuove terapie cellulari nel campo dei linfomi e delle leucemie acute e croniche.

Alessandro Davini è un ricercatore post doc nel gruppo Derenzini al dipartimento di oncologia sperimentale. Ha conseguito una laurea in Medical Biotechnologies presso l'Università degli Studi di Padova e un dottorato in Biologia Computazionale presso la Scuola Europea di Medicina Molecolare (SEMM). La sua attività di ricerca si concentra sull'applicazione di approcci computazionali all'analisi di dati multi-omici su larga scala provenienti da pazienti con neoplasie ematologiche maligne, con l'obiettivo di comprendere i meccanismi molecolari alla base dello sviluppo dei linfomi e delle leucemie e di identificare nuove vulnerabilità terapeutiche.

Referenza. *Heteroplasmic variants of mitochondrial genome in tumor and normal samples from patients with hematologic malignancies. Alessandro Davini, Fabio Iannelli, Alessandra Rossi, Simone Zanetti, Dorotea Salemi, Saveria Mazzara, Marta Mangione, Giovanna Talarico, Francesco Bertolini, Corrado Tarella, Roberto Chiarle, Enrico Derenzini. Leukemia 2026. doi: 10.1038/s41375-026-03050-w.*

Da studi preclinici, una nuova terapia di combinazione contro il linfoma a cellule B di alto grado.

Loncastuximab tesirine (Lonca-T) è un anticorpo farmaco-coniugato che, grazie all'interazione con la proteina CD19, permette di indirizzare selettivamente il farmaco pyrrolobenzodiazepine (PBD) alle cellule tumorali. Inducendo legami tra le eliche del DNA, il PBD porta alla morte cellulare. Gli inibitori di PARP (PARPi) sono farmaci antitumorali ampiamente utilizzati che impediscono il riparo del danno al DNA e, infine, inducono la morte della cellula tumorale.

Recentemente, i ricercatori IEO hanno valutato, in modelli preclinici *in vitro* e *in vivo*, l'efficacia di una terapia di combinazione con Lonca-T e PARPi per il trattamento del linfoma a cellule B di alto grado (HGBCL), una neoplasia altamente eterogenea per cui ad oggi non sono disponibili delle terapie efficaci.

Antoine, puoi scrivere qualcosa sul linfoma di alto grado a cellule B?

Il linfoma a cellule B di alto grado (High-Grade B-Cell Lymphoma, HGBCL) è una forma aggressiva di linfoma non-Hodgkin (NHL) che origina dai linfociti B. Questa categoria comprende sottotipi quali il linfoma diffuso a grandi cellule B (DLBCL), il linfoma di Burkitt e il linfoma a cellule B di alto grado con riarrangiamenti di MYC, BCL2 e/o BCL6 (spesso definiti linfomi double-hit o

I loro risultati hanno mostrato che, impedendo il riparo del danno al DNA indotto da Lonca-T, la somministrazione dei PARPi aumenta l'efficacia della terapia con Lonca-T, risultando più efficaci rispetto ai due agenti somministrati singolarmente. Inoltre, l'analisi genomica dei dati dei pazienti suggerisce che le mutazioni in geni del sistema di riparo del DNA potrebbero rappresentare delle vulnerabilità delle cellule tumorali, aumentandone la sensibilità a questa terapia di combinazione in cui l'inibizione di sistemi di riparo del DNA, mediata da PARPi, e del danno al DNA indotto da Lonca-T, determinano la morte della cellula tumorale.

triple-hit). L'esame istopatologico, comprensivo di immunofenotipizzazione e analisi genetiche (come la FISH per i riarrangiamenti di MYC, BCL2 e BCL6), è fondamentale per una corretta diagnosi, classificazione e stratificazione prognostica. Il trattamento è intensivo e prevede generalmente un'immunochemioterapia. Nei casi di malattia recidivata o refrattaria può essere preso in considerazione il trapianto di cellule staminali. Terapie più recenti, come la terapia con cellule CAR-T e i farmaci a bersaglio molecolare, sono sempre più utilizzate, soprattutto nei casi più difficili da trattare. La ricerca è attualmente focalizzata sul miglioramento degli esiti clinici attraverso approcci di medicina personalizzata e lo sviluppo di nuove terapie.

(Antoine Imbert è un membro AI (Mistral) del team newsletter)

TELL ME MORE!

Innanzi tutto, analizzando dataset di pazienti, gli autori hanno notato una maggiore presenza di mutazioni in geni coinvolti nel riparo del danno al DNA (indotto dai legami tra le eliche di DNA), in pazienti HGBCL con alterazioni a livello del gene MYC rispetto ai pazienti che non mostravano alcuna alterazione di MYC. Inoltre, le cellule in cui MYC era alterato o sovraespresso erano maggiormente sensibili a Lonca-T rispetto alle cellule prive di alterazioni di MYC. Analogamente, le cellule in cui MYC era alterato o sovraespresso erano più sensibili ai PARPi (Talazoparib), suggerendo un ruolo delle alterazioni di MYC nella sensibilizzazione delle cellule tumorali a questi farmaci.

In vitro, il trattamento delle cellule con la combinazione Lonca-T/PARPi si rivelava più efficace rispetto ai due farmaci somministrati singolarmente, inducendo l'arresto del ciclo cellulare, l'inibizione della sintesi di DNA e l'aumento della morte cellulare. Infatti, impedendo il riparo del DNA danneggiato da Lonca-T, i PARPi aumentavano l'efficacia di Lonca-T.

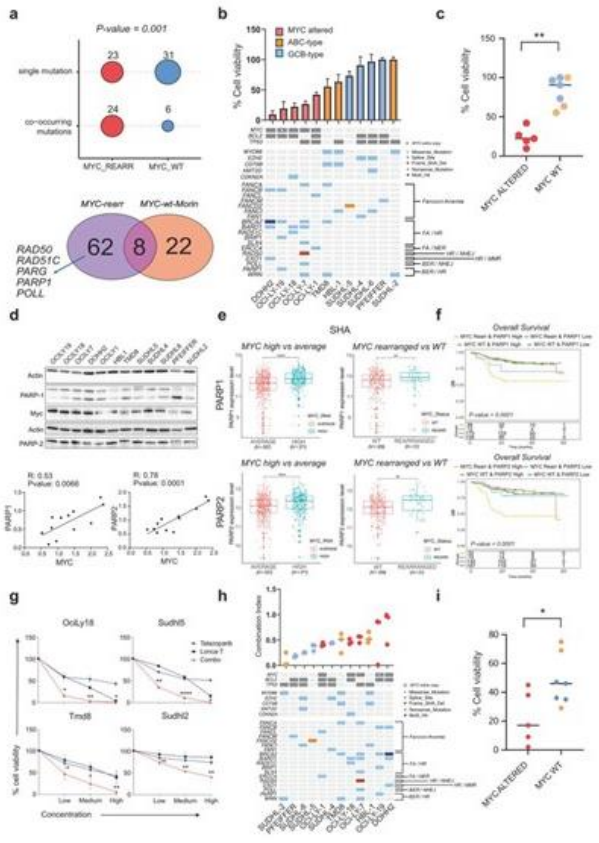


Image from Fusani et al. (an open access article under the CC BY NC ND license.)

Sebbene questo effetto si verificasse indipendentemente dalle alterazioni di MYC, la maggiore efficacia –alla minima dose– si osservava nelle cellule in cui MYC era alterato. Effetti analoghi si osservavano sostituendo Lonca-T con un altro cross-linker, come il cisplatino. E' interessante sottolineare che le cellule sane non erano influenzate dal trattamento combinato con Lonca-T e PARPi.

Successivamente, gli autori hanno valutato l'efficacia del trattamento combinato in modelli preclinici *in vivo*, utilizzando due modelli PDX. Così come in vitro, la somministrazione dei PARPi aumentava in maniera significativa l'attività antitumorale di Lonca-T, prolungando la sopravvivenza degli animali, rispetto ai due farmaci somministrati singolarmente. Gli autori hanno inoltre osservato una ridotta espressione di EGR1 dopo il trattamento. La ridotta espressione di EGR1 è stata precedentemente associata alla sensibilità a terapie a base di platino, mentre la sovraespressione di EGR1 è stata collegata alla resistenza agli inibitori della Bruton Tyrosine Kinase (BTKi). Questi risultati suggeriscono che la ridotta espressione di EGR1 indotta dal trattamento combinato con Lonca-T e PARPi possa rappresentare un marcatore di sensibilità alle terapie a base di platino e fornire un razionale per valutare strategie terapeutiche basate sulla tripla combinazione con Lonca-T/PARPi/BTKi.

Alex, puoi scrivere qualcosa su loncastuximab tesirine e sugli inibitori di PARP?

Il loncastuximab tesirine appartiene alla categoria degli anticorpi farmaco-coniugati (*antibody-drug conjugates*, ADC). Si tratta di una molecola costituita da un anticorpo monoclonale diretto contro CD19, una glicoproteina espressa sulla superficie dei linfociti B normali e della maggior parte delle neoplasie a cellule B, coniugato a un agente citotossico della classe delle pirrolobenzodiazepine (PBD), denominato tesirine. L'efficacia di Lonca-T deriva dalla combinazione tra la specificità dell'anticorpo monoclonale e la potente attività citotossica del payload. Dopo il legame con l'antigene CD19, il complesso viene rapidamente internalizzato mediante endocitosi. All'interno dei lisosomi, il linker viene degradato da proteasi intracellulari, liberando il dimero PBD (SG3199). Quest'ultimo si lega al solco minore del DNA formando cross-link interfilamento, che impediscono la replicazione e la trascrizione del DNA. L'accumulo di tali lesioni induce l'arresto del ciclo cellulare e l'apoptosi della cellula tumorale. È stato inoltre descritto un moderato effetto bystander, attraverso il quale il farmaco può esercitare attività anche su cellule vicine con espressione ridotta o eterogenea di CD19. Uno degli aspetti più interessanti di questo ADC è rappresentato dall'elevata potenza del payload PBD, capace di indurre danni irreversibili al DNA a concentrazioni estremamente basse, rendendo il trattamento efficace anche in cellule resistenti ad altre classi di chemioterapici. Loncastuximab tesirine è impiegato principalmente nel trattamento del linfoma diffuso a grandi cellule B (*Diffuse Large B-Cell Lymphoma*, DLBCL) recidivato o refrattario, nonché di altre forme aggressive di linfoma a grandi cellule B dopo almeno due precedenti linee di terapia sistemica. In questo contesto rappresenta un'importante opzione terapeutica per pazienti che non sono candidabili al trapianto autologo o che hanno fallito altre strategie, comprese, in alcuni casi, le terapie CAR-T.

Le PARP (Poly ADP-Ribose Polymerases) costituiscono una famiglia di enzimi coinvolti nei meccanismi di riparo del DNA. Tra queste, PARP1 e PARP2 svolgono un ruolo fondamentale nel riparo delle rotture a singolo filamento (*Single Strand Breaks*, SSB) mediante il sistema di *Base Excision Repair* (BER). Gli inibitori di PARP (PARPi) rappresentano una delle applicazioni più importanti del concetto di letalità sintetica, secondo cui la contemporanea alterazione di due vie di riparazione del DNA determina la morte cellulare, mentre la perdita di una sola via risulta compatibile con la sopravvivenza. Tra i principali farmaci appartenenti a questa classe si ricordano olaparib, niraparib, rucaparib, talazoparib. In condizioni fisiologiche, PARP1 riconosce rapidamente le rotture a singolo filamento del DNA e promuove il reclutamento delle proteine coinvolte nella loro riparazione. Gli inibitori di PARP bloccano tale attività attraverso due meccanismi principali: l'inibizione dell'attività catalitica dell'enzima, impedendo la sintesi delle catene di poli(ADP-ribosio); il PARP trapping, ossia il blocco dell'enzima direttamente sul DNA, determinando un ostacolo fisico alla progressione della forcella replicativa. Durante la replicazione cellulare, le rotture a singolo filamento non riparate evolvono in rotture a doppio filamento (*Double Strand Breaks*, DSB). Nelle cellule normali tali lesioni vengono corrette attraverso la ricombinazione omologa (*Homologous Recombination Repair*, HRR), un sistema altamente accurato che dipende principalmente dalle proteine BRCA1, BRCA2, PALB2 e da altri geni coinvolti nella riparazione del DNA. Quando tali geni risultano mutati o inattivati, come avviene nei tumori con deficit di ricombinazione omologa (*Homologous Recombination Deficiency*, HRD), la cellula non è più in grado di riparare efficacemente il danno genomico. L'inibizione di PARP determina quindi un accumulo progressivo di lesioni che porta all'instabilità genomica e, infine, alla morte cellulare. Questo fenomeno rappresenta il classico esempio di letalità sintetica, uno dei concetti cardine della moderna oncologia molecolare. Gli

inibitori di PARP trovano oggi impiego in numerosi tumori solidi caratterizzati da mutazioni dei geni BRCA1/2 o da HRD, tra cui il carcinoma ovarico, mammario, prostatico, pancreatico.

(Alexander Irwin è un membro AI (ChatGPT) del team newsletter)

Gli autori – **Stefania Fusani.**

Stefania Fusani è stata ricercatrice post-doc nel gruppo di Enrico Derenzini presso il Dipartimento di Oncologia Sperimentale di IEO. Ha conseguito una laurea magistrale in Biologia Molecolare presso l'Università di Parma e un dottorato di ricerca in Medicina dei Sistemi presso la Scuola Europea di Medicina Molecolare (SEMM). La sua attività di ricerca si è concentrata sull'immunoterapia e, in particolare, sullo sviluppo di strategie volte a potenziare la risposta immunitaria antitumorale nel linfoma.

Referenza. *Targeting DNA interstrand crosslinks repair with synthetic lethality in High-Grade B-Cell Lymphoma. Stefania Fusani, Alessandro Davini, Alessandra Rossi, Saveria Mazzara, Alessio Maria Edoardo Maraglino, Anna Vanazzi, Dorotea Salemi, Stefania Orecchioni, Paolo Falvo, Giovanna Talarico, Francesco Bertolini, Corrado Tarella, Enrico Derenzini. Leukemia 2026. doi: 10.1038/s41375-026-03042-w.*

MiTo – uno strumento computazionale che sfrutta i mitocondri per capire la progressione del tumore.

Durante la progressione del tumore, le cellule subiscono delle continue alterazioni del loro genoma e del loro epigenoma, che vengono selezionate e si accumulano, dando forma ad una cellula tumorale che, rispetto alle cellule circostanti, è più resistente e prolifera di più, sostenendo la crescita del tumore. Queste mutazioni (molte delle quali neutrali e semplicemente trasmesse da una cellula alla sua progenie) che normalmente emergono, si accumulano, vengono selezionate, possono essere utilizzate come dei "marcatori genetici" permettendo di seguire il destino delle cellule tumorali in un contesto nativo, senza il bisogno di ingegnerizzare le cellule.

In un articolo recente di Cossa, Dalmasso et al., i ricercatori IEO co-coordinati da Pier Giuseppe Pelicci – Direttore del dipartimento di oncologia sperimentale di IEO– e Yinxiu Zhan –coordinatore della Data Science Unit del dipartimento di oncologia sperimentale–, descrivono lo sviluppo di un nuovo strumento computazionale –MiTo– per "seguire", durante la progressione tumorale, i marcatori genetici rappresentati dalle mutazioni nel DNA mitocondriale. MiTo permette di dedurre, in maniera automatica e con una risoluzione di singola cellula, sulla base di varianti nel DNA mitocondriale, "l'evoluzione clonale" del tumore, ovvero in che modo una certa cellula, caratterizzata da –marcata con– una specifica alterazione del DNA mitocondriale, prolifera per dare origine ad una popolazione di cellule (un clone cellulare) che costituiscono una porzione della massa tumorale. Consentendo anche di analizzare l'espressione genica, MiTo permette di identificare i profili di espressione genica delle cellule nel tumore primario –gli autori lo hanno fatto nel tumore al seno– e nelle metastasi corrispondenti, caratterizzate da processi come la transizione epitelio-mesenchimale (EMT) e la proliferazione da un lato, e fosforilazione ossidativa dall'altro. Infine, analizzando il modo in cui i programmi di regolazione genica vengono ereditati dalle cellule figlie al momento della divisione cellulare, MiTo ha evidenziato l'esistenza di una "memoria cellulare", sottolineando cioè come determinati programmi di espressione genica vengano ereditati da una cellula all'altra al momento della divisione cellulare, contribuendo probabilmente, insieme alla risposta cellulare a stimoli ambientali, alla progressione del tumore.

Sebbene altri strumenti (come quelli basati su WGS o CRISPR) possano sembrare più adatti nel caso in cui le analisi richiedano una risoluzione elevata, MiTo fornisce uno strumento utile per analisi più semplici, meno costose e soprattutto che, non richiedendo di ingegnerizzare le cellule (non richiedono infatti l'espressione

di sequenze *barcode* per marcare le cellule), possono essere usati in contesti biologici nativi (eventualmente fuori dal setting puramente sperimentale).

TELL ME MORE!

I ricercatori IEO hanno precedentemente analizzato l'evoluzione clonale durante la progressione del tumore al seno applicando approcci di *lineage tracing*. Esprimendo delle brevi sequenze "*barcode*" nelle cellule tumorali per marcare/identificare ogni singola cellula tumorale e la sua progenie durante la crescita del tumore, insieme ad analisi omiche su singola cellula, hanno svelato informazioni chiave sulla progressione del tumore. Questo approccio richiede però l'ingegnerizzazione delle cellule tumorali, per l'espressione delle sequenze *barcode*.

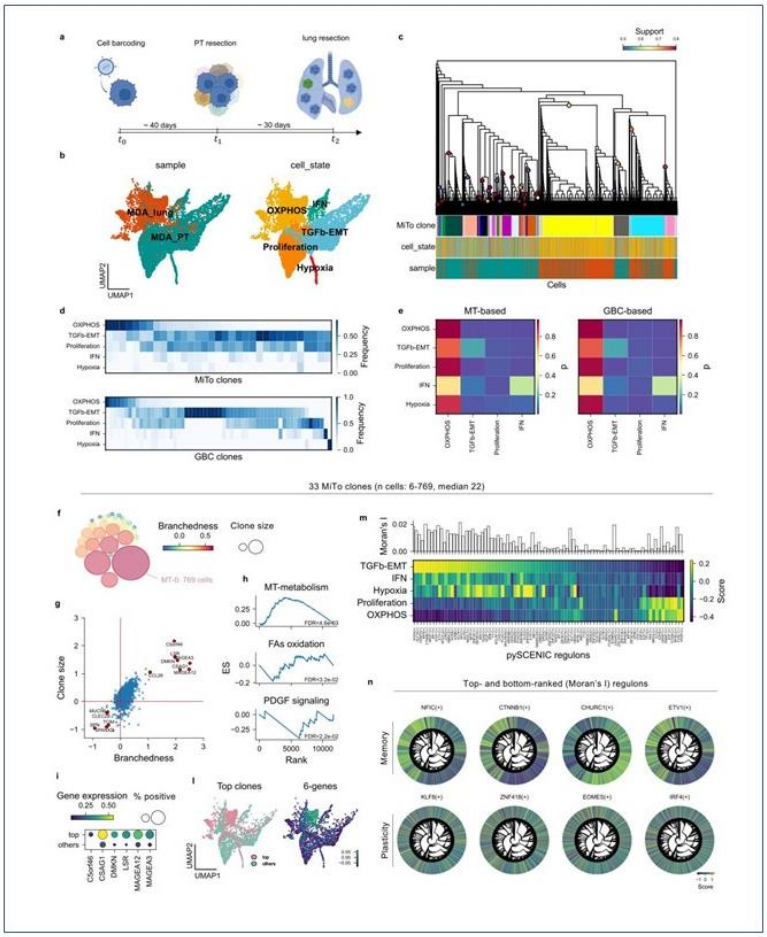


Figure from Cossa, Dalmasso et al. (an open access article under the CC-BY-NC-ND license.)

Le mutazioni endogene che vengono continuamente generate durante la progressione tumorale possono però essere sfruttate come marcatori genetici *endogeni* per approcci di *lineage tracing*.

Per poter utilizzare una mutazione endogena come marcatore genetico per il *lineage tracing*, questa deve però avere delle caratteristiche specifiche: *i.* deve essere endogena (ovvero manifestarsi in maniera naturale, senza richiedere l'ingegnerizzazione); *ii.* deve mutare rapidamente (per permettere di seguire da vicino ogni fase della progressione del tumore e dell'evoluzione clonale); *iii.* deve essere facile da sequenziare (così che la metodica non risulti troppo costosa). In questo contesto, le varianti del DNA mitocondriale (mtDNA) rappresentano una valida opzione. Il mtDNA infatti muta molto più velocemente del DNA nucleare ed è più piccolo (quindi più facile e veloce da sequenziare).

Eppure, ad oggi l'affidabilità delle varianti mitocondriali come marcatori genici e degli strumenti computazionali esistenti per identificarle rimane incerta.

Per questa ragione, i ricercatori IEO hanno sviluppato MiTo.

MiTo è composto da due componenti: *i.* nf-MiTo, che funziona in cinque fasi consecutive, dal pre-processamento dei dati, al filtraggio (per eliminare i dati di bassa qualità), all'inferenza, ovvero alla costruzione di un albero filogenetico che riproduca il modo in cui ogni data cellula tumorale, identificabile tramite un marcatore genetico/variante del mtDNA, dà origine alla sua progenie durante la progressione del tumore, formando una sottopopolazione all'interno della massa tumorale, e *ii.* un MiTo package per la successiva analisi. MiTo può essere integrato in workflow esistenti, e ampiamente utilizzati, per le analisi su singola cellula e permette di aggiungere facilmente delle nuove proprietà. La fase di pre-processamento così come quella di filtraggio sembrano essere cruciali per l'accuratezza dei risultati. Inoltre, la possibilità di modificare numerosi parametri permette il pieno controllo dell'intera pipeline analitica e di personalizzare l'analisi. Quando hanno confrontato MiTo con altri strumenti ampiamente utilizzati per il *lineage tracing* su

singola cellula, i risultati hanno mostrato che *i.* MiTo identificava un numero di cloni simile a quello reale in tutti i dataset analizzati; *ii.* mentre il WGS rimaneva la soluzione migliore per analisi ad elevata risoluzione, i costi elevati associati, il numero di cellule che possono essere analizzate e la limitata compatibilità con altre analisi omiche rappresentano un problema; *iii.* gli strumenti basati su Cas-9, pur essendo una buona soluzione in termini di risoluzione, necessitando di ingegnerizzare la cellula non sono utilizzabili in contesti nativi, limitandone l'utilizzo in ambito sperimentale. MiTo, invece, offre una soluzione semplice, poco costosa, facilmente scalabile, che, sfruttando alterazioni nel mtDNA che si manifestano naturalmente, rappresenta uno strumento adatto per studi in contesti nativi, fornendo sia informazioni sull'evoluzione clonale sia fenotipiche, sebbene ad una risoluzione lievemente inferiore (un limite che tuttavia condivide con i sistemi basati su metilazione del DNA). Una volta valutate le performance di MiTo, gli autori hanno applicato il loro strumento a contesti biologicamente rilevanti, sfruttando un dataset da loro generato ottenuto tracciando *a)* varianti mitocondriali (mtSNV, *mitochondrial single nucleotide variants*) e *b) barcode* espressi tramite vettori lentivirali, in *1)* linee cellulari di tumore al seno MDA-MB-231 trasdotte con vettori lentivirali esprimenti *barcode* unici. Dopo la trasduzione, le cellule sono lasciate proliferare per un breve periodo e poi unite in proporzioni definite per creare dei mix clonali (ovvero in cui ogni cellula con un determinato *barcode* genera una popolazione clonale di cellule derivante da una singola cellula fondatrice, che sono poi mischiate, in proporzioni definite, con cellule derivanti dall'espansione di un'altra cellula fondatrice marcata con un altro barcode); in *2)* cellule MDA-MB-231 trasdotte con *barcode* e trapiantate in animali riceventi. I tumori primari risultanti e le metastasi corrispondenti sono quindi resecati e analizzati.

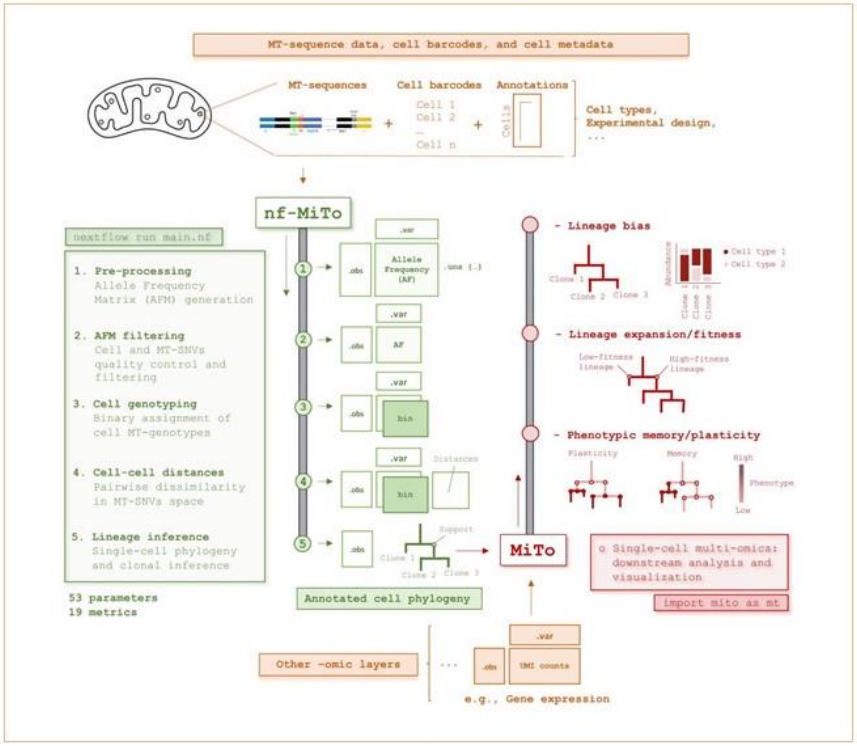


Figure from Cossa, Dalmasso et al. (an open access article under the CC-BY-NC-ND license.)

Tutti i campioni sono sottoposti a scRNAseq, per analizzare espressione genica, varianti mitocondriali (*a*) e *barcode* (*b*), in colture cellulari (*1*), tumori primari e metastasi corrispondenti (*2*).
Le analisi hanno evidenziato un'elevata corrispondenza tra inferenza clonale basata sui *barcode* e su mtSNV, supportando l'affidabilità di MiTo. Integrando i dati derivanti dall'analisi dell'espressione genica e dall'inferenza clonale, gli autori hanno evidenziato delle variazioni fenotipiche, tra il tumore primario – caratterizzato da EMT, risposta a interferone, ipossia, proliferazione– e la metastasi corrispondente – caratterizzata da fosforilazione ossidativa, un segno di adattamento del metabolismo mitocondriale durante la progressione metastatica. Inoltre, l'aumentata fitness clonale correlava con un aumentato metabolismo mitocondriale e con la riduzione dell'ossidazione degli acidi grassi e della signalling di PDGF. Hanno inoltre identificato sei geni il cui livello di espressione correlava (aumentava) con l'aumentare della fitness cellulare; alcuni di questi geni sono noti per essere collegati alla progressione del tumore, alcuni ad una scarsa prognosi dei pazienti.
Per verificare se questi programmi di espressione genica fossero ereditati dalle cellule figlie al momento della divisione cellulare, hanno correlato i network regolatori (ovvero gli elementi che regolano l'espressione

genica) con l'inferenza basata su mtSNV, scoprendo che molti erano infatti conservati in maniera significativa alla divisione cellulare, durante l'evoluzione del tumore.
I loro risultati mostrano quindi che MiTo rappresenta uno strumento valido che, permettendo di dedurre in maniera affidabile l'evoluzione clonale, correlarla con l'espressione genica e distinguere la "memoria", ereditata da cellula a cellula, dei programmi di espressione genica può permettere di definire, *in vivo*, i determinanti somatici dell'evoluzione.

Referenza. *MiTo: tracing the phenotypic evolution of somatic cell lineages via mitochondrial single-cell multi-omics. Andrea Cossa #, Alberto Dalmasso #, Guido Campani, Elisa Bugani, Chiara Caprioli, Noemi Bulla, Andrea Tirelli, Yinxiu Zhan, Pier Giuseppe Pelicci. Nat Commun 2026. doi: 10.1038/s41467-026-71607-5.*

Nuovi biomarcatori e target terapeutici nell'epigenetica dei tumori testa-collo indotti da papillomavirus umano.

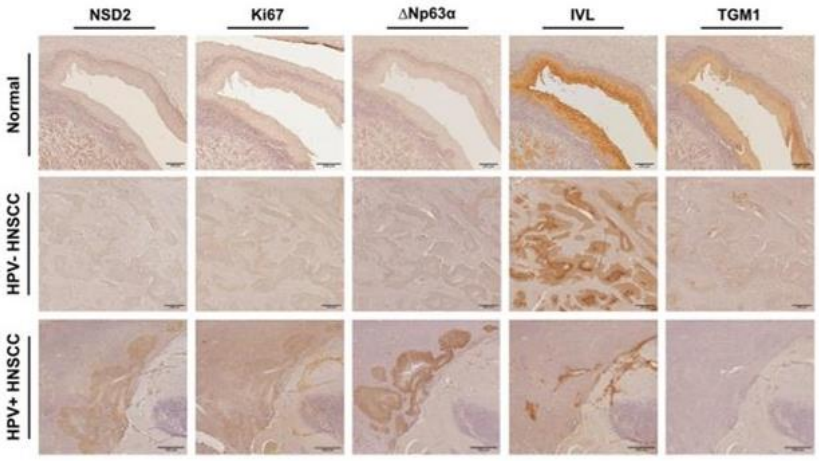
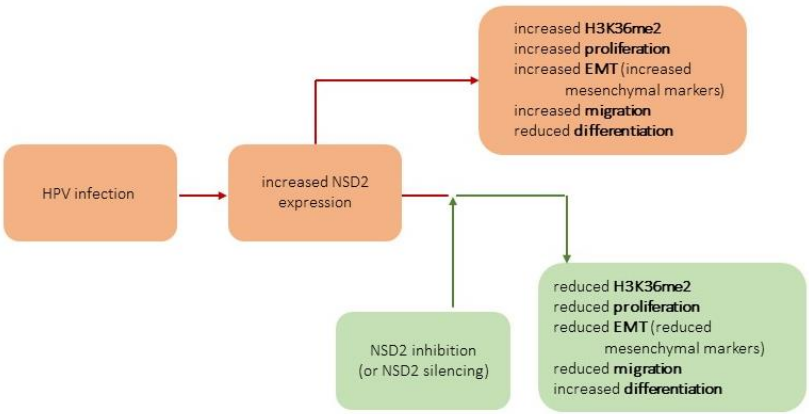


Figure adapted from Ghiani et al (an open access article under the CC BY license)

I tumori testa-collo (HNC) possono essere classificati in HPV+ e HPV-, ovvero indotti –oppure no– dall'infezione con papillomavirus umano (HPV). Eppure, nonostante le evidenti differenze molecolari e clinicopatologiche tra i due sottotipi, gli approcci terapeutici sono essenzialmente gli stessi e consistono principalmente in chemio-, radio- terapia e chirurgia. E' quindi necessaria una caratterizzazione molecolare approfondita per poter identificare nuovi biomarcatori e meccanismi di malattia da poter sfruttare in chiave terapeutica, per disegnare approcci terapeutici nuovi e più efficaci. Studi precedenti hanno descritto alterazioni epigenetiche nel HNC (in particolare, nel carcinoma squamocellulare), suggerendo l'esistenza di differenze epigenetiche tra i tumori HPV+ e i tumori HPV-.
In un articolo recente di Lavinia Ghiani et al., gli autori coordinati da Susanna Chiocca –PI del dipartimento di oncologia sperimentale di IEO–, in collaborazione con il gruppo di Tiziana Bonaldi, hanno caratterizzato il profilo epigenetico –in particolare, delle modificazioni post-traduzionali degli istoni, hPTM– nelle cellule di HNC HPV+ e HPV- e hanno osservato delle differenze –in particolare, nei livelli di di-metilazione a livello della lisina 36 dell'istone H3 (H3K36me2)–, suggerendo che i livelli di H3K36me2 potrebbero rappresentare un potenziale nuovo biomarcatore diagnostico per distinguere le cellule di HNC HPV+ dalle HPV-, ad esempio nel contesto di esami di biopsia liquida.

Inoltre, studiando i meccanismi molecolari coinvolti, hanno scoperto che l'infezione da HPV (nello specifico, le oncoproteine E6/E7 del HPV ad alto rischio HPV16 e HPV18) causa l'aumento dell'espressione della proteina NSD2, che a sua volta determina la metilazione dell'istone H3 (H3K36me2) e modula proliferazione, migrazione e differenziamento cellulare. Sebbene la maggiore espressione di NSD2 sia più accentuata nelle cellule HPV+ rispetto alle HPV-, è presente in entrambi i sottotipi rispetto ai tessuti normali e il silenziamento di NSD2 riduce proliferazione cellulare e migrazione (e transizione epitelio-mesenchimale, EMT) in entrambi i sottotipi molecolari.
I loro risultati mostrano quindi che NSD2 si trova in posizione strategica per controllare la plasticità cellulare, modulando migrazione e proliferazione (indotte dalla sovraespressione di NSD2 e limitate dall'assenza di NSD2) oppure differenziamento cellulare (indotto dall'assenza di NSD2, spento dalla sovraespressione di NSD2), indipendentemente dall'infezione da HPV (quindi sia nelle cellule HPV+ che in quelle HPV-). Hanno però osservato che colpire NSD2 potrebbe avere alcuni effetti specifici a seconda dell'infezione da HPV; il differenziamento cellulare è infatti indotto soprattutto nelle linee cellulari di HNC HPV+, suggerendo che inibitori di NSD2 potrebbero rappresentare un nuovo esempio di terapia di differenziamento nel HNC HPV+.

Molecole che inibiscono l'attività di NSD2 sono attualmente in sperimentazione nel contesto di clinical trial di fase I. Inoltre, il ruolo di NSD2 nella regolazione del danno al DNA suggerisce il potenziale di farmaci mirati contro NSD2 nel contesto di terapie di combinazione insieme a trattamenti che danneggiano il DNA come chemio- e radio-terapia.



TELL ME MORE!

Sfruttando approcci di spettrometria di massa quantitativa, gli autori hanno caratterizzato il profilo di hPTM dei tumori HPV+ e HPV- (sia in sezioni tumorali che in linee cellulari). Nonostante l'elevato grado di eterogeneità, hanno identificato alcune differenze nei livelli di hPTM, particolarmente evidenti per la H3K36me2, associate ai livelli di espressione delle oncoproteine E6/E7 di HPV e più marcate nelle cellule HPV+ che nelle HPV-.
Studi meccanicistici hanno rivelato che in cheratinociti primari umani, l'ospite naturale dell'infezione da HPV, l'espressione delle oncoproteine virali E6/E7 determinava l'upregolazione (a livello trascrizionale) di NSD2, un modificatore istonico responsabile della hPTM H3K36me2 (mentre il silenziamento di E6/E7 nelle cellule HPV+ ne determinava la downregolazione). Solo le proteine E6/E7 di specie virali HPV ad alto rischio –e non da HPV a basso rischio– inducevano l'upregolazione di NSD2. NSD2 era sovraespresso anche nelle linee cellulari di HNC HPV+ e HPV-, aumentando i livelli di H2K36me2, e in campioni di pazienti con HNC HPV+.
Analisi dei dati, derivanti dal dataset TCGA, di pazienti con HNC e campioni raccolti in IEO (Divisione ENT di IEO diretta da Mohssen Ansarin) hanno confermato che l'infezione da HPV correlava con una maggiore espressione di NSD2 rispetto sia ai tumori HPV- che ai tessuti sani, e hanno rivelato una correlazione tra l'elevata espressione di NSD2 e il grado tumorale. L'analisi dei dati TCGA ha mostrato anche che le alterazioni geniche di NSD2 erano rare e l'espressione anomala era quindi dovuta soprattutto alla presenza delle proteine E6/E7 (ovvero ad infezione da HPV).
Per esplorare le conseguenze, a livello funzionale, della upregolazione di NSD2 indotta da E6/E7, gli autori hanno silenziato NSD2 sia nelle linee cellulari HPV+ che nelle HPV- e hanno osservato *i.* una riduzione dei

livelli di H3K36me2; *ii.* una riduzione della proliferazione, *iii.* una ridotta espressione di marcatori di EMT; *iv.* una ridotta migrazione cellulare (sia nelle linee cellulari HPV+ che HPV-, quindi indipendentemente dai livelli di E6/E7). Al contrario, la sovraespressione di NSD2 *i.* aumentava i livelli di H3K36me2, *ii.* aumentava la proliferazione, *iii.* upregolava l'espressione di marcatori mesenchimali, *iv.* aumentava la migrazione. In linea con questi dati, esperimenti di RNAseq hanno rivelato che diversi pathway cellulari coinvolti in EMT e interazione cellula/substrato venivano influenzati dall'espressione di NSD2.
Mentre la modulazione di NSD2 avveniva soprattutto in maniera indipendente dall'infezione da HPV, alcuni geni collegati al differenziamento erano upregolati in maniera specifica nelle HPV+ (che sono di solito di alto grado) e non nelle HPV-. L'espressione di NSD2 influenzava anche i livelli di p63 (nello specifico, l'isoforma deltaNp63alpha), un regolatore cruciale del differenziamento cellulare. Il silenziamento di NSD2 riduceva infatti p63 –determinando il differenziamento cellulare–, mentre la sovraespressione di NSD2 upregolava p63.
La proteina NSD2 è stata precedentemente implicata nel differenziamento in altri contesti (ad esempio nel differenziamento dei linfociti e dei progenitori neurali), indicando il suo ruolo chiave nel differenziamento cellulare e suggerendo che la modulazione dell'espressione di NSD2 potrebbe contribuire a regolare il differenziamento cellulare –almeno in parte attraverso la sua attività su p63–, soprattutto nei tumori HPV+, proponendolo come un potenziale nuovo target di terapie di differenziamento. Ciò è particolarmente importante considerando che i tumori HPV+ sono solitamente di alto grado (ovvero, scarsamente differenziati).

Gli autori – Lavinia Ghiani

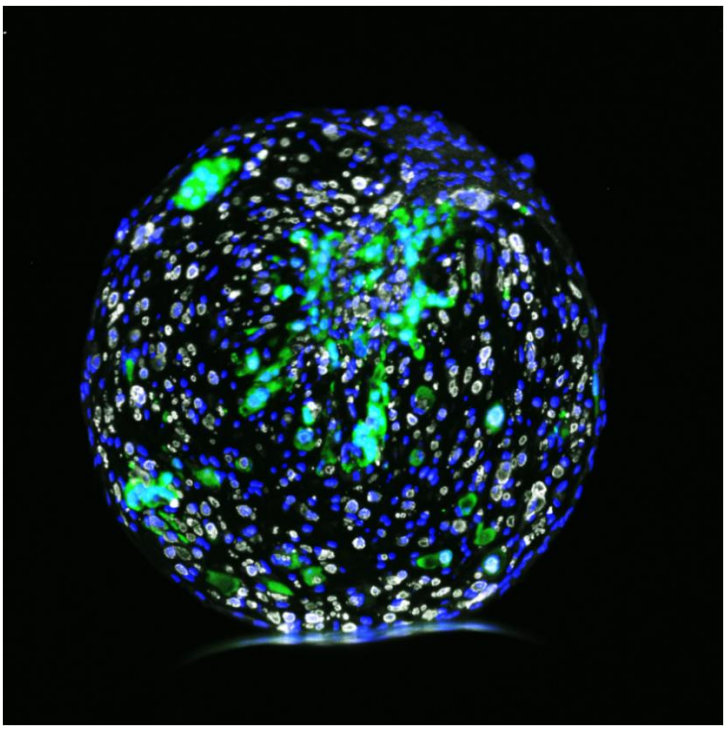
Lavinia Ghiani è una ricercatrice post doc in IEO, nell'unità "Viruses and cancer" diretta da Susannia Chiocca. Con una laurea in "Genetica e biologia molecolare in ricerca di base e biomedica" ottenuta all'Università di Roma La Sapienza, ha completato il suo dottorato in oncologia molecolare all'Università di Milano. Il suo lavoro di ricerca si focalizza sulla definizione dei meccanismi molecolari alla base dell'insorgenza e della progressione dei tumori testa-collo indotti da infezione da virus HPV, con particolare attenzione ai regolatori epigenetici, al fine di identificare nuovi biomarcatori di malattia e target terapeutici che possano migliorare l'attuale approccio terapeutico dei pazienti con tumore testa-collo.

Referenza. *NSD2 upregulation is driven by high-risk HPV E6/E7 and disrupts epithelial differentiation in HPV-associated head and neck cancer. Lavinia Ghiani, Simona Citro, Alessandro Medda, Mirko Doni, Farkhondeh Ghoryani, Roberta Noberini, Ottavio Croci, Fausto Maffini, Claudia Miccolo, Laura Monteleone, Marta Tagliabue, Rita De Berardinis, Stefano Campaner, Tiziana Bonaldi, Mohssen Ansarin, Susanna Chiocca. J Exp Clin Cancer Res 2026. doi: 10.1186/s13046-025-03631-0.*

Perché le cellule tumorali raramente metastatizzano nel cuore? Uno studio meccanicistico.

In un articolo recente, gli autori –tra cui i ricercatori IEO Pier Giuseppe Pelicci, Ivan Dellino, Lorenzo Ciacci– hanno sfruttato modelli preclinici *in vivo* ed *ex vivo* per studiare i meccanismi alla base della rara colonizzazione del cuore da parte delle cellule tumorali, mostrando che le forze meccaniche che agiscono sulle cellule tumorali limitano la proliferazione delle cellule tumorali.
Analisi trascrittomiche hanno svelato il coinvolgimento di meccanismi epigenetici, come i cambiamenti nella metilazione degli istoni e nel compattamento della cromatina, che a loro volta influenzano geni chiave coinvolti nella proliferazione cellulare, e hanno identificato la proteina Nesprina2 come fattore chiave nel tradurre gli stimoli meccanici esterni in cambiamenti dell'espressione genica e nella modulazione della proliferazione cellulare.

Le proprietà fisiche del microambiente nella modulazione di processi cellulari come la proliferazione e la migrazione sono ampiamenti studiati, soprattutto per quel che riguarda l'effetto della rigidità della matrice extracellulare sul comportamento cellulare. Questo studio ha dimostrato che sebbene altri meccanismi possano essere coinvolti, contribuendo alla limitata proliferazione –e successiva colonizzazione– delle cellule tumorali, nel cuore le forze meccaniche che agiscono sulle cellule tumorali influenzano il profilo epigenetico delle cellule (i livelli di metilazione degli istoni) e la proliferazione, prevenendo la colonizzazione del cuore. I meccanismi identificati potrebbero essere sfruttati in chiave terapeutica con specifici approcci di trattamento basati sulla modulazione di forze meccaniche.

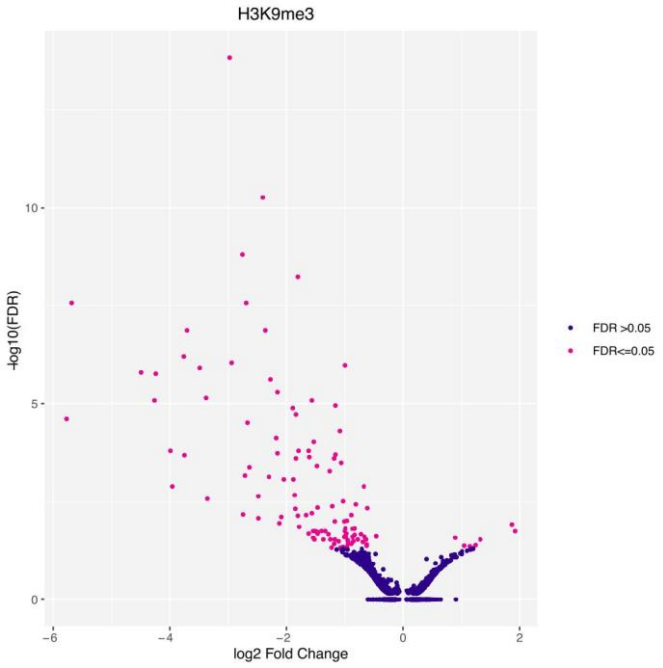


TELL ME MORE!

La colonizzazione del cuore da parte delle cellule tumorali è modulata da forze meccaniche esterne. Utilizzando modelli preclinici *in vivo*, gli autori hanno valutato il ruolo della pressione meccanica nella colonizzazione del cuore da parte delle cellule tumorali. In questo modello, la ridotta pressione meccanica ha portato ad una maggiore proliferazione delle cellule tumorali (ingegnerizzate al fine di indurre la perdita di p53 e l'espressione della forma mutata G12D di Kras) rispetto ai controlli, con le cellule tumorali che colonizzavano abbondantemente il cuore e inducevano la morte dei cardiomiociti. La colonizzazione era correlata in maniera specifica con la proliferazione delle cellule tumorali piuttosto che con un diverso tasso di attecchimento (engraftment) o di morte cellulare. I risultati sono stati confermati in sistemi *ex vivo*, in cui la modulazione (aumento) delle forze meccaniche (che simulavano il battito cardiaco) nelle colture tissutali cardiache arrestavano la proliferazione delle cellule tumorali. Inoltre, modificando la concentrazione extracellulare di calcio per modulare la contrattilità dei cardiomiociti e simulare il battito cardiaco, si otteneva (così come con la pressione meccanica applicata) l'arresto della proliferazione delle cellule tumorali. Le differenze osservate nella proliferazione cellulare non erano dovute ad un'alterata disponibilità di nutrienti.

Meccanismi alla base della scarsa colonizzazione del cuore, modulata dalla pressione meccanica, da parte delle cellule tumorali. Successivamente, gli autori hanno analizzato i meccanismi implicati, per valutare in che modo le cellule tumorali traducono gli stimoli meccanici (associati con il battito cardiaco) in una ridotta proliferazione cellulare. A questo scopo, hanno effettuato analisi di trascrittomica spaziale su tumori primari (di polmone, melanoma, colon) di origine umana rispetto alle metastasi cardiache ed extra-cardiache. Queste analisi hanno rivelato che, indipendentemente dal tumore di origine, le metastasi cardiache mostravano alcune caratteristiche associate con l'elevata espressione di geni coinvolti nella demetilazione degli istoni. In linea con questi dati, il livello di H3K9me3 e di compattamento della cromatina erano ridotti nelle metastasi cardiache rispetto alle extra-cardiache e ai tumori primari. I livelli differenti di metilazione degli istoni e di compattamento della cromatina determinavano un aumento dell'accessibilità di regioni del DNA coinvolte in processi come l'arresto del ciclo cellulare, la percezione degli stimoli meccanici, il citoscheletro.

L'associazione tra pressione meccanica, metilazione degli istoni e proliferazione cellulare non era puramente correlativa. Infatti, nelle colture tissutali cardiache, la pressione meccanica applicata, che simulava il battito cardiaco, riduceva la metilazione di H3K9 e il compattamento della cromatina e, soprattutto, il silenziamento delle demetilasi della lisina KDM4 e KDM5 determinava un aumento dei livelli di H3K9me3 e una maggiore proliferazione delle cellule tumorali, dimostrando una relazione causale.



Nesprina2 nella traduzione dei segnali meccanici. Infine, gli autori hanno identificato il fattore responsabile di tradurre la pressione meccanica in demetilazione degli istoni e nell'arresto della proliferazione. Hanno scoperto che nelle cellule tumorali in coltura con sezioni tissutali cardiache, il silenziamento della proteina Nesprina2 influenzava il livello di metilazione degli istoni e causava un aumento della proliferazione in condizioni in cui, per via della pressione meccanica, la proliferazione cellulare avrebbe dovuto arrestarsi. Ciò era vero in tutti i tre modelli tumorali (polmone, melanoma e colon), indicando che Nesprina2 potrebbe tradurre la pressione meccanica in proliferazione cellulare in diversi tipi di tumore. Inoltre, l'iniezione *in vivo* di cellule tumorali in cui Nesprina2 era silenziata determinava una proliferazione sostenuta delle cellule tumorali nel cuore.

Referenza. *Mechanical load inhibits cancer growth in mouse and human hearts. Giulio Ciucci #, Daniela Lorizio #, Nicoletta Bartoloni, Mauricio Budini, Andrea Colliva, Simone Vodret, Anh-Vu Nguyen, Lorenzo Ciacci, Bernhard Texler, Benno Cardini, Rupert Oberhuber, Sofia Bindelli, Ilaria Luciana Carlotta Del Giudice, Roman Vuerich, Francesco Riccitelli, Elena Zago, Henrik Nicolay Finsberg, Mattia Chiesa, Gianluca Lorenzo Perrucci, Rossana Bussani, Furio Silvestri, Manuel Maglione, Gaetano Ivan Dellino, Gianfranco Sinagra, Mauro Giacca, Thomas Eschenhagen, Paolo Golino, Giulio Pompilio, Pier Giuseppe Pelicci, Laura Andolfi, Maurizio Pinamonti, Matteo Dal Ferro, Samuel Wall, Francesco S Loffredo #, Serena Zacchigna #. Science 2026. doi: 10.1126/science.ads9412.*

Il microbioma tumorale – una descrizione approfondita.

Microorganismi diversi (virus, batteri, funghi, archea) abitano aree differenti del corpo che funzionano come "barriere" nei confronti dell'ambiente esterno, come la cute, il tratto respiratorio superiore, urogenitale, orodigestivo. Alterazioni in queste comunità di microorganismi sono associate con condizioni patologiche differenti, incluso il cancro. Il microbiota può colonizzare anche le lesioni tumorali e influenzare direttamente il comportamento delle cellule tumorali; nel tumore del colon-retto (CRC), alcune specie batteriche sono state precedentemente collegate alla malattia (ad esempio, *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Escherichia coli)*. Analizzare il microbioma intratumorale in lesioni situate in aree del corpo che non costituiscono delle barriere è complicato da questioni tecniche e questo rende i risultati a volte incerti e contrastanti.

Per ovviare a questi problemi, i ricercatori, tra cui Nicola Segata –Group leader del dipartimento di oncologia sperimentale di IEO e Professore ordinario all'Università di Trento–, hanno perfezionato uno strumento computazionale per l'analisi del microbioma –PathSeq-T2T– che, incorporando la sequenza completa del

genoma umano, permette di estrarre in maniera affidabile (per sottrazione) le sequenze del microbioma intratumorale. Applicando questo strumento ai dati di sequenziamento di tumori umani, hanno ottenuto un'immagine dettagliata del microbioma tumorale.

Usando questo strumento computazionale, innanzi tutto, i ricercatori hanno mostrato che, diversamente da quanto suggerito da studi precedenti, i tumori localizzati in aree del corpo differenti dalle barriere anatomiche non sono colonizzati dal microbiota, che sono invece abbondanti nei tumori del tratto orodigestivo. Inoltre, i ricercatori forniscono una descrizione dettagliata delle comunità microbiche all'interno di diversi tipi di tumore, in differenti aree del corpo, e identificano delle associazioni tra l'abbondanza e il tipo di specie microbiche presenti e il genoma tumorale, nello specifico con il numero di mutazioni (*tumor mutational burden*, TMB). Infine, i loro risultati hanno evidenziato una correlazione tra specifiche specie microbiche e CRC ad insorgenza precoce, suggerendo un ruolo di questi microorganismi nel processo di tumorigenesi

Nicola Segata

Studiare il microbioma tumorale ha rappresentato a lungo una sfida per i ricercatori in questo ambito. I ricercatori IEO hanno precedentemente sviluppato uno strumento computazionale per estrarre queste informazioni sul microbioma tumorale ottenute attraverso il sequenziamento del RNA (invece che WGS) di campioni di CRC di pazienti IEO, mostrando il potere prognostico della caratterizzazione del microbioma e, attraverso l'integrazione con altri dati omici (come dati di espressione genica, mutazioni, metilazione e caratteristiche microambientali metaboliche), fornendo una descrizione, con una definizione spaziale, di questi fattori, la loro correlazione, interazione e potenziale co-evoluzione come parte di un ecosistema tumorale (cfr. newsletter n. 4). Quei dati, insieme ai risultati raccolti in questo studio, enfatizzano ancora una volta il potere di questi approcci e le informazioni critiche, clinicamente rilevanti, che possono fornire.

TELL ME MORE!

PathSeq-T2T – come funziona? I dati ottenuti dalle analisi (di *whole genome sequencing*, WGS) dei campioni tumorali contengono sia informazioni genomiche specifiche del tumore che informazioni genomiche del microbioma associato al tumore (dati WGS = informazione genomica tumorale + informazione sul microbioma associato al tumore). PathSeq-T2T funziona sottraendo dai dati di WGS del tumore il genoma umano di riferimento (T2T-CHM13), così da ottenere l'informazione sul genoma microbico. Il genoma non umano (microbico) rimanente viene successivamente analizzato con strumenti computazionali come Kraken2, MetaPhlAn4, and Sylph, per quantificare i segnali del microbioma (cioè stimare l'abbondanza delle differenti specie microbiche nel campione) e identificare le varie specie.

Validazione di PathSeq-T2T. Gli autori hanno confermato la validità di PathSeq-T2T *i.* utilizzando dati *in silico* misti di DNA umano e microbico, osservando una migliore performance rispetto ad altri strumenti; *ii.* utilizzando i dati ottenuti dal sequenziamento di campioni *in vitro* (di origine umana, microbica e derivante da sostanze contaminanti), dimostrando un'elevata sensibilità (permettendo anche di stabilire un valore soglia di background per eventuali contaminanti anche in campioni quasi sterili); *iii.* in linee cellulari di CRC.

PathSeq-T2T in dati real world di pazienti. Una volta validato, hanno applicato PathSeq-T2T per l'analisi di dati WGS di campioni tumorali reali e germinali corrispondenti (sangue e saliva). Come atteso, PathSeq-T2T non ha rilevato alcuna sequenza di origine microbica in campioni sterili o dal basso carico microbico (cioè non sono rimaste sequenze microbiche dopo aver filtrato contro i dati del genoma umano di riferimento), come sangue e glioblastoma (GBM), rilevando invece sequenze di origine microbica nella saliva e nei campioni di CRC. Analizzando in maniera approfondita la specifica composizione delle comunità microbiche rilevate dopo il filtraggio ad opera di PathSeq-T2T, hanno identificato specie batteriche piuttosto differenti nei campioni di saliva e di CRC rispetto a quelli di sangue e GBM. Dato che le specie microbiche identificate nel sangue e nel GBM apparivano probabili contaminanti, presenti anche nei campioni di saliva (mentre le specie nella saliva non erano presenti nel sangue e nel GBM), sono andati avanti ad analizzare l'intero dataset (invece di limitarsi all'analisi di saliva, sangue, CRC, GBM) per identificare in maniera affidabile eventuali contaminanti in comune. A questo scopo, hanno sviluppato uno *score*, assumendo che se una data specie microbica era egualmente abbondante in tutti i campioni, era probabilmente un contaminante piuttosto che una reale specie microbica associata al tumore.

PathSeq-T2T identifica le specie del microbioma nei tumori del tratto orodigestivo e non. I tumori che, dopo la rimozione di probabili contaminanti, conservavano un segnale microbico oltre il valore soglia –ovvero associati al tumore– erano soprattutto localizzati nel tratto orodigestivo (tumori CRC, orofaringeo, esofageo, gastrico). I tumori localizzati all'esterno del tratto orodigestivo mostravano nel complesso livelli microbici bassi (sebbene oltre la soglia). Un livello microbico più alto era di solito collegato ad infezioni (*e.g.* influenza). Una ulteriore caratterizzazione dei campioni tumorali del tratto orodigestivo ha permesso, da un lato, di quantificare la generale abbondanza dei microrganismi nelle differenti aree del tratto gastrointestinale superiore e inferiore (quindi a seconda della posizione del tumore); dall'altro, ha consentito di identificare le diverse specie microbiche, che risultavano essere piuttosto differenti nelle diverse aree del corpo analizzate.

Batteri, virus, funghi, archea, parassiti nei campioni tumorali. Le loro analisi hanno anche rivelato la presenza di funghi, archea, parassiti, virus, oltre all'abbondanza di batteri, nelle lesioni tumorali in differenti aree del tratto gastrointestinale.

Microbioma tumorale e genoma tumorale. La correlazione tra microbioma tumorale e genotipo tumorale ha rivelato che il genotipo tumorale e il sito anatomico erano forti predittori della composizione del microbioma associato al CRC. Le specie del microbiota associate al tumore erano abbondanti nel CRC ipermutato (nel sottotipo *microsatellite-instable* –MSI– più che nel sottotipo *microsatellite stable* –MSS), sebbene si osservasse un minor numero di specie microbiche differenti. La correlazione tra instabilità genomica e abbondanza di specie del microbioma era conservata in altri tipi di tumore.

TMB e abbondanza di specie del microbiota. Le loro analisi hanno mostrato un'associazione del TMB e dell'area del corpo in cui era localizzato il tumore con *i.* l'abbondanza di specie del microbioma nel CRC (sia nel MSI che nel MSS) e nel tumore gastrico, indicando che il TMB sia un predittore chiave della colonizzazione microbica in tipi di tumore diversi, e coorti di pazienti diverse, e *ii.* le specie microbiche. Infatti, mentre alcune specie erano abbondanti nel CRC con alto TMB, altre lo erano poco; altre ancora erano associate con CRC con basso TMB. Altre specie non erano correlate con il TMB ma correlate con il sito anatomico. Infine, l'abbondanza di altre specie variava con lo stadio della malattia. Quindi, sebbene la posizione del tumore appariva essere il primo determinante della composizione del microbioma associato al tumore, interazioni tra fattori differenti potrebbero contribuire a determinare la composizione del microbioma ed eventuali alterazioni nel microambiente tumorale durante la progressione della malattia potrebbero favorire la colonizzazione da parte di altre specie microbiche.

Microbioma tumorale e CRC ad insorgenza precoce. Analizzando la correlazione tra età di insorgenza del CRC e composizione del microbioma, gli autori hanno scoperto che alcune specie (tra cui *Akkermansia muciniphila* e *Hungatella hathewayi)* erano assenti nel tumore precoce (nel colon distale, dove questi tumori sono più frequenti), suggerendo un loro possibile contributo nel processo di tumorigenesi.

Referenza. *Biodiversity and biogeography of the multi-kingdom cancer microbiome. Anders B Dohlman, Robin Mjelle, Henry M Wood, Kevin Jiang, Alaina Shumate, Iris Lee, Gianmarco Piccinno, Garazi Serna, Abdul-Rakeem Yakubu, Paolo Nuciforo, Phil Quirke, Curtis Huttenhower, Nicola Segata, Matthew Meyerson. Cell 2026. doi: 10.1016/j.cell.2026.04.015.*

Tamoxifene a basse dosi, in un contesto adiuvante, per ridurre il rischio di tumore al seno.

Sara Gandini

Le donne che si sono sottoposte alla rimozione chirurgica conservativa di un tumore al seno non invasivo (*ductal carcinoma in situ*, DCIS) rimangono ad aumentato rischio di recidiva, o di insorgenza di un tumore al seno invasivo. La terapia adiuvante a base di tamoxifene (20 mg, una volta al giorno) è quindi solitamente raccomandata in queste pazienti, per ridurre il rischio di malattia successiva. I significativi effetti collaterali associati con la somministrazione di tamoxifene ne limitano però l'utilizzo, portando a proporre una strategia terapeutica alternativa, con la somministrazione di tamoxifene a basse dosi (10 mg, a giorni alterni) al fine di ridurre gli effetti collaterali pur conservando i benefici associati con il tamoxifene, in termini di riduzione del rischio di malattia.

Uno studio appena pubblicato sulla rivista *Journal of Clinical Oncology* fornisce evidenze definitive a sostegno dell'utilizzo di tamoxifene a basse dosi come terapia di prevenzione, in un contesto adiuvante, dopo l'intervento chirurgico.

Il lavoro, co-coordinato da Sara Gandini –PI al dipartimento di oncologia sperimentale di IEO– e Andrea DeCensi –Direttore della Breast Unit della Fondazione Champalimaud di Lisbona (Portogallo)– combina i dati di tre studi clinici indipendenti, generando il più grande dataset mai realizzato sul tema: 1.545 pazienti seguite per oltre nove anni. I dati sono stati raccolti dalla Divisione di Prevenzione e Genetica Oncologica dello IEO, diretta da Bernardo Bonanni e Aliana Guerrieri Gonzaga, in collaborazione con l'Ospedale Galliera di Genova e la Fondazione Champalimaud.

I ricercatori hanno dimostrato che il tamoxifene a basso dosaggio conserva la stessa –duratura– efficacia dell'alto dosaggio, in termini di prevenzione della malattia, ma con meno effetti collaterali. Questi risultati supportano quindi strategie di riduzione del dosaggio, permettendo alle pazienti di aderire più facilmente alla terapia, senza comprometterne l'efficacia.

Lo studio evidenzia inoltre, per la prima volta, gli effetti della menopausa sull'efficacia preventiva del tamoxifene, mostrano un effetto protettivo maggiore nelle donne in menopausa. Non solo, le loro analisi hanno anche evidenziato una diversa efficacia a seconda della localizzazione del tumore, nella stessa mammella (ipsilaterale) del primo tumore, oppure nell'altra (controlaterale). Infatti, mentre i loro risultati hanno evidenziato una maggiore riduzione dei tumori al seno ipsilaterali nelle donne in menopausa, hanno anche osservato un effetto più pronunciato sull'incidenza di neoplasia controlaterale tra le donne non in menopausa, suggerendo un effetto diverso del farmaco sulla recidiva (probabilmente ipsilaterale) rispetto all'insorgenza di un nuovo tumore (probabilmente controlaterale).

"Questo studio rappresenta un passo avanti significativo nella prevenzione del tumore al seno –-commenta Sara Gandini, primo autore dello studio– e fornisce evidenze solide a supporto dell'integrazione di

tamoxifene a basse dosi nella pratica clinica per le donne trattate per carcinoma *in situ*, offrendo una strategie terapeutica efficace, più sicura e più tollerabile per ridurre il rischio di futuri tumori al seno".

TELL ME MORE!

I tre dataset sono stati ottenuti mettendo insieme i dati di tre coorti di pazienti con tumore al seno ER-positivo localizzato, che hanno ricevuto tamoxifene a basso dosaggio. Nel complesso, lo studio ha considerato i dati di 1545 pazienti, 803 trattate con tamoxifene, 742 controlli non trattati.

Efficacia. L'efficacia della terapia a base di tamoxifene è stata valutata in termini di intervallo di tempo in assenza di malattia (ovvero, il tempo tra l'arruolamento nello studio fino ad una qualsiasi manifestazione della malattia, a livello locale o distante) e a seconda dello stato menopausale (menopausa *vs* premenopausa) e la posizione del tumore (ovvero ipsi- *vs* contro- laterale).

Tamoxifene e menopausa. Gli effetti del trattamento erano significativamente influenzati dalla menopausa. Infatti, il tumore al seno si è manifestato in 40 delle 335 donne nel gruppo tamoxifene/postmenopausa, 93 delle 401 del gruppo di controllo/postmenopausa; in 127 delle 448 del gruppo tamoxifene/premenopausa; in 107 delle 335 del gruppo controllo/premenopausa. Ad un followup di 10 anni, il 13% delle donne del gruppo tamoxifene/menopausa avevano un tumore al seno, contro il 24% delle donne nel gruppo controllo/menopausa, quindi con una riduzione del rischio dell'11%. Gli effetti erano più pronunciati nel sottotipo DCIS (*ductal carcinoma in situ*, 13% di riduzione del rischio di malattia a 10 anni). Tra le donne in pre-menopausa, invece, la malattia si verificava nel 28% di quelle trattate con tamoxifene e nel 30% dei controlli; non si osservavano effetti nel sottogruppo DCIS.

Tamoxifene e tumore al seno ipsilaterale. Quando si sono focalizzati nello specifico sui tumori ipsilaterali, la menopausa appariva strettamente correlata con il trattamento. Infatti, tra le donne in menopausa, si osservava un tumore al seno ipsilaterale in 22 delle 335 donne trattate con tamoxifene e in 63 delle 401 donne del gruppo di controllo, mentre tra le donne in premenopausa si osservava un tumore al seno ipsilaterale in 102 delle 448 donne trattate con tamoxifene e in 72 delle 335 donne del gruppo di controllo. Ad un follow-up di 10 anni, l'incidenza era del 7% nel gruppo tamoxifene/postmenopausa, 22% nel gruppo controllo/postmenopausa –con una riduzione del rischio del 10%–, 22% nel gruppo tamoxifene/premenopausa, 20% nel gruppo controllo/premenopausa.

Tamoxifene e tumore al seno controlaterale. Per quanto riguarda i tumori controlaterali, gli effetti del tamoxifene erano evidenti solo nelle donne in premenopausa (e non in quelle in postmenopausa), ovvero in 21 di 448 donne del gruppo tamoxifene/premenopausa e 35 di 335 donne del gruppo controllo/premenopausa.

Tamoxifene e sopravvivenza libera da malattia. La sopravvivenza libera da malattia era nel complesso influenzata dal trattamento con tamoxifene nelle donne in menopausa ma non in premenopausa.

Sicurezza. In linea con risultati precedenti, con questo dosaggio di tamoxifene, gli eventi avversi collegati al trattamento si manifestavano raramente.

Gli autori – Sara Gandini.

Sara Gandini è group leader al Dipartimento di Oncologia Sperimentale di IEO e professore aggiunto in Statistica Medica all'Università di Milano, membro della faculty della Scuola di dottorato SEMM (Scuole Europea di Medicina Molecolare) e del comitato del Melanoma Group EORTC. Con una laurea in Statistica dall'Università di Bologna (Italia), una laurea specialistica in Biometria dall'Università di Birmingham (UK) e un dottorato in Studi Oncologici all'Università di Birmingham, ha lavorato come ricercatrice in IEO prima di diventare group leader nel 2018. In IEO, è direttrice dell'Unità di Epidemiologia Farmaco-Molecolare. La sua ricerca si pone l'obiettivo di integrare e valutare l'importanza di fattori epidemiologici nella ricerca traslazionale e clinica, per creare le basi per la prevenzione oncologica personalizzata e programmi terapeutici che sfruttano l'integrazione di fattori di rischio molecolari, genetici ed epidemiologici.

Referenza. *Low-Dose Tamoxifen in Noninvasive Breast Neoplasia: Long-Term Results From an Individual-Participant Data Pooled Analysis. Sara Gandini, Aliana Guerrieri-Gonzaga, Davide Serrano, Roberta Rizzo, Matteo Lazzeroni, Matteo Puntoni, Tania Buttiron Webber, Gaetano Aurilio, Harriet Johansson, Alessio Carbone, Livia Giordano, Maria Digennaro, Laura Cortesi, Francesco Millo, Katia Cagossi, Giuseppe Aprile, Patrizia Serra, Elisa Gallerani, Marcio Debiasi, Berta Sousa, Pedro Gouveia, Bernardo Bonanni, Andrea DeCensi. J Clin Oncol 2026. doi: 10.1200/JCO-26-00841.*

In IEO l'evento organizzato da Motore Sanità "il futuro dell'oncologia è già qui".

Dal 20 al 22 maggio, IEO ha ospitato l'evento organizzato da *Motore Sanità* focalizzato sui recenti progressi nella diagnostica e nella terapia del cancro.

In un contesto di prevenzione, ricerca e cura oncologica, alla luce delle più recenti innovazioni, gli speaker della comunità medica e di ricerca e personalità del mondo politico hanno discusso i notevoli progressi degli ultimi decenni nella diagnostica e nella terapia oncologica, ottenuti sfruttando i più avanzati strumenti, enfatizzando come, nonostante le sfide poste dall'oncologia, la scienza stia procedendo rapidamente, rendendo il cancro una malattia sempre più gestibile, cronica –in alcuni casi persino curabile– e sottolineando che ancora di più può –e deve– essere fatto, con il lavoro congiunto delle comunità medico-scientifiche e istituzionali.

Il futuro della prevenzione oncologica. In termini di prevenzione, gli ospiti hanno sottolineato l'importanza di un futuro approccio di prevenzione personalizzata, sia in termini di prevenzione primaria (con un corretto stile di vita, esercizio fisico, e una dieta sana, che di per sé può ridurre il rischio di malattia del 50%, insieme ad un microbioma intestinale equilibrato) che di prevenzione secondaria, farmacologica, in individui ad alto rischio, sostenuta da una ricerca volta a stabilire la dose minima efficace e a valutare l'efficacia di nuove combinazioni terapeutiche o differenti regimi di trattamento (come la somministrazione intermittente). In questo scenario, l'analisi genomica delle alterazioni germinali può permettere di sviluppare approcci di prevenzione basati sul rischio, che includono chemio-prevenzione, chirurgia profilattica, monitoraggio o somministrazione di farmaci, sulla base di singole mutazioni a basso, moderato, o alto rischio o sulla base del rischio cumulativo dovuto a mutazioni geniche multiple, attraverso l'utilizzo di punteggi di rischio poligenico.

La combinazione di entrambi gli approcci di prevenzione (primaria e secondaria) insieme a screening più efficaci –utilizzando approcci diagnostici di ultima generazione (come la biopsia liquida, le analisi del microbioma, l'integrazione di strumenti di AI)– volti ad identificare il rischio di malattia nella popolazione generale e una diagnosi precoce, permetteranno di definire strategie di prevenzione personalizzate. Lo sviluppo di strumenti di screening di ultima generazione, non invasivi, possono infatti permettere, in futuro, lo sviluppo di test per la diagnosi precoce multi-tumore e screening sulla popolazione sana, permettendo così di *intercettare* la malattia. In questo scenario, aspetti fondamentali sono la sostenibilità e l'accessibilità di questi approcci innovativi, così come la formazione dei cittadini ed una comunicazione efficace, che permetta la presa in carico da parte dei cittadini della propria salute. Sebbene gli approcci di prevenzione rappresentino dei costi a livello nazionale, l'impatto su ogni individuo, sul sistema sanitario e sulla società intera li rende un investimento vantaggioso.

Approcci diagnostici di ultima generazione. In campo diagnostico, gli ospiti hanno discusso il potere della biopsia liquida basata su DNA tumorale circolante (ctDNA) che, grazie ai sofisticati approcci genomici attualmente disponibili, permette di rilevare quantità estremamente basse di DNA circolante (nel range del nano e pico molare), trasformando questa tecnologia in uno strumento diagnostico altamente sensibile, integrato nella pratica clinica in diversi, specifici contesti (soprattutto nel caso di malattia metastatica, sulla base di linee guida cliniche ben definite). La biopsia liquida basata su ctDNA è attualmente utilizzata di routine nella gestione del tumore al seno, soprattutto nella terapia di seconda linea, per decisioni riguardanti un eventuale aumento del dosaggio. Attualmente la ricerca si concentra sul possibile futuro impiego di questo approccio anche nella riduzione del dosaggio. Nel tumore al polmone, sebbene il suo uso sia, in alcuni casi, limitato, la biopsia liquida è utilizzata di routine nella scelta terapeutica e rappresenta uno strumento estremamente utile per la caratterizzazione molecolare del tumore. Sebbene in alcuni tipi di tumore –come il melanoma e il sarcoma– siano necessari studi ulteriori per integrare la biopsia liquida nella pratica clinica, e il suo utilizzo sia attualmente limitato ai clinical trial, nei tumori ematologici –pur non essendo ancora utilizzata di routine– rappresenta un valido strumento nel contesto di malattie in cui la diagnosi con gli approcci di biopsia convenzionale è difficile, e per definire la durata del trattamento.

Terapie antitumorali di ultima generazione. Per quanto riguarda la terapia, gli ospiti hanno evidenziato gli effetti trasformativi delle più recenti scoperte scientifiche, che hanno portato allo sviluppo e al crescente impiego dell'immunoterapia – anticorpi farmaco-coniugati (ADC), anticorpi bi-specifici, inibitori dei checkpoint immunitari (ICI), vaccini, terapie cellulari.

In numerosi contesti clinici, adiuvanti e neoadiuvanti, questi strumenti oggi rappresentano la pratica clinica. Ad esempio, nel melanoma, dall'introduzione di ipilimumab, seguita poco dopo da nivolumab e pembrolizumab, gli ADC sono ormai diventati la terapia standard in diversi setting e la ricerca attuale è principalmente volta a definire in maniera più precisa le sottopopolazioni di pazienti che potrebbero meglio beneficiare di questi approcci. Nel polmone –nonostante l'attesa eterogeneità nella risposta alla terapia tra diversi sottogruppi di pazienti caratterizzati da diverse proprietà molecolari e istopatologiche– l'immunoterapia –così come la terapia molecolare– hanno trasformato un tumore storicamente "big killer" in una malattia più gestibile, con un aumento significativo della sopravvivenza. Studi

ulteriori in questo contesto sono focalizzati sulla definizione di biomarcatori solidi per guidare le scelte terapeutiche, insieme alla ricerca su nuovi composti e combinazioni di farmaci più efficaci. Nel tumore al seno, generalmente considerato un tumore "*cold*" (ovvero caratterizzato da una scarsa infiltrazione immunitaria e quindi associato con una scarsa risposta ad immunoterapia), l'immunoterapia ha mostrato, nel contesto neoadiuvante, risultati notevoli soprattutto nel sottotipo di tumore al seno triplo negativo, il meno diffuso ma il più aggressivo. Nel sarcoma, ad oggi l'immunoterapia ha mostrato una scarsa efficacia, probabilmente per via degli studi limitati ad oggi disponibili su questo tumore raro. Infine, gli ospiti hanno sottolineato i risultati notevoli osservati in ambito emato-oncologico con gli approcci di immunoterapia: ADC, anticorpi bi-specifici e cellule CART (queste ultime impiegate principalmente per il trattamento delle neoplasie ematologiche) hanno profondamente rivoluzionato il panorama terapeutico, permettendo anche, in alcuni casi, di evitare del tutto la chemioterapia. Infine, sono stati discussi gli sviluppi futuri relativi agli approcci di trasferimento genico *in vivo*, che porteranno verosimilmente, in un prossimo futuro, all'ingegnerizzazione i*n vivo* di cellule CART con nanoparticelle lipidiche, sfruttando metodologie oggi utilizzate per il trattamento di altre malattie ematologiche (come la talassemia o l'anemia falciforme).

L'approccio IEO per ottimizzare le cure dei pazienti. Gli speaker hanno evidenziato il lavoro di IEO nell'implementazione di questi approcci avanzati per fornire ai pazienti i maggiori benefici: nell'ambito della ricerca, selezionando attentamente e dando priorità agli studi più clinicamente rilevanti (sulla base delle necessità specifiche dei pazienti IEO); in ambito terapeutico, sottolineando l'importanza di una gestione ottimizzata –della malattia e degli eventi avversi collegati al trattamento– e multidisciplinare dei pazienti oncologici, che permetta di massimizzare i benefici (anche in tumori rari per cui non sono ad oggi disponibili approcci terapeutici molecolari e immunoterapici), attraverso la collaborazione all'interno e tra le diverse divisioni cliniche IEO, e con collaboratori esterni. In questo contesto, è stato discusso anche il ruolo della farmacia ospedaliera, come attore chiave nella gestione dei pazienti lungo-sopravviventi così come nella gestione dei farmaci sperimentali, rimanendo un punto di riferimento per i pazienti dopo la dimissione.

La ricerca – il motore del progresso clinico. In termini di ricerca, sono stati evidenziati due concetti principali: l'importanza dell'interazione pubblico-privato e lo sviluppo di reti oncologiche. Infatti, primo, i complessi problemi attuali richiedono collaborazione, sforzo congiunto, risorse ed expertise, per gli interessi di tutti e quindi di ogni singolo individuo, guidati da linguaggi comuni e obiettivi condivisi. Secondo, nell'attuale scenario scientifico, la creazione di reti di centri oncologici è diventata una priorità nazionale ed europea, per superare le questioni collegate all'informazione frammentata e accelerare così gli studi clinici, l'innovazione, l'accesso alle nuove terapie, aumentare la competitività ed attrarre eccellenze in ricerca e finanziamenti. In questo scenario, è stato sottolineato il lavoro eccellente di Alleanza Contro il Cancro (ACC, la rete di centri oncologici italiani di eccellenza, finanziata dal Ministero della Salute, di cui fa parte IEO). Lanciata oltre vent'anni fa, sponsorizzata e sostenuta dal Ministero della Salute, il primo obiettivo di ACC è stato il programma di genomica medica, finalizzato alla messa a punto di screening genomici basati su *next-generation sequencing* (NGS) per la medicina personalizzata nei centri ACC, e lo sviluppo di infrastrutture adeguate per la raccolta, la conservazione e l'utilizzo dei dati. Oggi, uno dei principali obiettivi di ACC è il progetto *Health Big Data*, volto a raggiungere una piena interoperabilità dei dati –fondamentale per le analisi successive e per la valorizzazione dei dati– e lo sviluppo di infrastrutture per la conservazione e la gestione dei dati. In parallelo, sono affrontate anche questioni come la privacy dei dati e la creazione di un *Molecular Tumor Board* all'interno di ACC, che contribuisca a rafforzare la rete e il valore dei dati raccolti.

Infine, gli speaker hanno evidenziato il ruolo, l'integrazione e la collaborazione tra i diversi uffici (grant office, technology transfer office, clinical trial office) a sostegno della traduzione di idee scientifiche in benefici per i pazienti.

AI nella ricerca e nella pratica clinica. E' stata inoltre ampiamente discussa la crescente integrazione dell'AI nella ricerca e nella clinica. Pur non essendo integrata in maniera omogenea in tutti i workflow clinici, in alcuni contesti (come la mammografia, o nell'analisi di biomarcatori computazionali) gli strumenti di AI sono infatti oggi ampiamente utilizzati, aiutando i clinici nell'interpretazione delle immagini diagnostiche. Inoltre, al fine di sfruttare al massimo il valore dei dati clinici dei pazienti, IEO ha sviluppato una *Data Platform*, creando un ecosistema di dati sanitari che consente l'integrazione di dati multimodali –inclusi i dati non strutturati, analizzati tramite algoritmi di AI– da fonti differenti, a beneficio dei pazienti IEO. La Data Platform IEO raccoglie e organizza, in linea con gli standard di interoperabilità, in un singolo bacino di dati (data lake) tutti i dati dei pazienti IEO estratti dalle cartelle cliniche elettroniche, dalle immagini diagnostiche, dal sequenziamento genomico, dalla biobanca digitale, le informazioni sui marcatori di patologia, i parametri vitali, i dati su abitudini e stili di vita, trasformando dati sanitari eterogenei in una "intelligenza clinica" utilizzabile, sostenendo i medici nelle decisioni terapeutiche. Dati di qualità, impegno ed expertise multidisciplinare di professionisti qualificati rappresentano gli strumenti in grado di accelerare la progressiva e completa integrazione dell'AI in ambito biomedico, plasmando i medici del ventunesimo secolo.

La comunicazione a beneficio del paziente. Uno degli aspetti critici evidenziati è stato la necessità di cambiare il modo in cui i risultati degli studi scientifici vengono presentati, *i.* umanizzandolo, evitando numeri e termini tecnici (come curve di sopravvivenza e hazard ratio), *ii.* attraverso il coinvolgimento (*engagement*) e *iii.* la formazione (*empowerment*)

del paziente, così da sostenerli verso la scelta del miglior approccio terapeutico, discutendo con loro le numerose opzioni terapeutiche disponibili, gestendo con un approccio professionale sentimenti come ansia e depressione, speranze e illusioni, insegnando loro come vivere il momento e gestire le loro emozioni nel mezzo degli eventi avversi e le incertezze collegate alla malattia. In questo contesto, l'adeguata integrazione degli strumenti di AI nelle discussioni paziente-dottore può contribuire a semplificare questa interazione.

Vent'anni di chirurgia robotica in IEO – il futuro è già qui. L'ultima giornata dell'evento è stata dedicata alla chirurgia robotica, come esempio di tecnologia che negli ultimi vent'anni è stata completamente integrata nei percorsi di cura in IEO, a beneficio dei suoi pazienti.

In linea con la visione di Umberto Veronesi di un'innovazione e una ricerca pienamente integrati nei percorsi di cura, nel 2006 l'IEO scelse di introdurre profondi cambiamenti nella chirurgia convenzionale e laparoscopica, immaginando il valore e le implicazioni della chirurgia robotica per la cura dei pazienti. Diventando una priorità strategica di IEO, guidata da una governance multidisciplinare dedicata, grazie ad investimenti nella formazione dei medici tanto quanto nella tecnologia, inserita in un programma multidisciplinare, il 2006 ha segnato l'anno della "rivoluzione chirurgica" in IEO, trasformando una strategia in pratica quotidiana. Affrontando sfide come l'iniziale scetticismo, i costi elevati e le questioni organizzative, la chirurgia robotica è diventata una tecnologia ampiamente utilizzata –nel giusto contesto e per pazienti accuratamente selezionati– in tutte le divisioni chirurgiche di IEO, contribuendo così alla sua sostenibilità.

Oggi, la crescente integrazione degli strumenti digitali segna l'inizio di una nuova era della chirurgia robotica. L'utilizzo di tecnologie avanzate permette la costruzione di sale operatorie digitali, in grado di integrare dispositivi medici, immagini e dati in tempo reale, consentendo l'immediata disponibilità di dati e immagini, la comunicazione e la collaborazione remota dentro e fuori la sala operatoria, così come la generazione di dati da poter ulteriormente sfruttare a scopi di ricerca, rendendo l'ospedale una piattaforma di ricerca traslazionale, sostenendo il progresso medico, verso la prossima innovazione tecnologica.

Identificando la chirurgia robotica digitale come una delle priorità strategiche di IEO, che ha recentemente portato all'inaugurazione di IEO3 –dotato di quattro sale operatorie digitali di ultima generazione–, IEO è pronto a fare da pioniere nella chirurgia digitale come ha fatto per la chirurgia robotica 20 anni fa, navigando questo campo altamente competitivo e perseguendo quell'eccellenza che permette di offrire ogni giorno ai suoi pazienti le migliori cure disponibili.

Anti-netrin antibodies against pancreatic cancer – results of a phase I clinical trial.

Typically expressed during development, and with a well-known role in axon guidance, netrin1 expression increases in different tumor types and has been previously shown to promote epithelial-to-mesenchymal transition (EMT), a crucial process in metastatic dissemination and chemoresistance. Previous studies showed, in preclinical *in vivo* models, that the anti-netrin1 antibody NP137 is able to revert EMT.
Can netrin1-targeted antibodies be clinically exploited to interfere with EMT and hence represent a novel antitumor treatment?
To answer this question, in the frame of a phase I clinical trial, researchers assessed efficacy and safety of the anti-netrin1 antibody NP137 in combination with chemotherapy (mFOLFIRINOX), as first line therapy, for the treatment of locally advanced pancreatic cancer.
Their results showed clinical benefits –in terms of survival– of the NP137/chemotherapy combination, and revealed the underlying mechanism, involving EMT inhibition through an antibody targeting a protein usually not expressed in adult healthy tissue but whose levels increase with tumorigenesis: Netrin1. Moreover, they propose netrin1 receptor neogenin as a potential biomarker identifying patients likely to respond to therapy.
Currently, the therapeutic options for these patients are limited, also in experimental contexts, as they are not eligible neither for clinical trials in the metastatic setting nor in the neoadjuvant/perioperative setting (indeed, these tumors are often unresectable). If confirmed within larger patient cohorts, this study may offer to these patients a new therapeutic option.

TELL ME MORE!

Clinical study. The study enrolled 43 patients in 9 different centers. Patients were treated with chemotherapy (mFOLFIRINOX) and anti-netrin1 antibody NP137. Safety analyses showed that NP137 was well tolerated, with manageable NP137-related adverse events of >3 grade manifesting in 12% of the patients, and no new adverse events than what expected for chemotherapy-only toxicity profile. Regarding efficacy, at a median followup of 13 months, 12 out of the 42 enrolled patients achieved a partial, durable, response, 27 out of 42 had a stable disease. At 6 months, PFS was 88%, OS was 91%; at 12 months, PFS was 45%, OS was 62%.
Functional study: mFOLFIRINOX-treated pancreatic cancers have been previously shown to undergo EMT, likely resulting in therapy resistance, which can be reverted by anti-netrin1 antibodies. Therefore, the authors evaluated whether NP137 antibody can synergize with chemotherapy, countering chemotherapy-induced EMT. RNAseq analyses of patient-derived pancreatic cancer tissue at diagnosis and after treatment revealed a number (260) of genes differentially (232 up-, 28 down- regulated) regulated after therapy, including post-therapy down-regulation of inflammatory pathways and 45 genes involved in EMT. Notably, in patients responding to chemotherapy+NP137 treatment (achieving partial response or stable disease), the 45-gene EMT signature was strongly down-regulated after therapy, whereas patients from previous studies who only received chemotherapy displayed an up-regulation of the 45-gene EMT signature. Furthermore, EMT pathway was the main differentially activated pathway both in post- vs pre-chemotherapy alone and in post- vs pre- NP137+chemotherapy.
Molecular analysis: Analyses of the molecular factors linked to treatment response and PFS showed that *i.* in chemotherapy only patients, the expression of the netrin1 receptor neogenin anti-correlated with PFS (that is, high neogenin expression correlated with poor prognosis), in line with the notion that high neogenin expression would result in netrin1-neogenin-modulated EMT; *ii.* in chemotherapy+NP137-treated patients, neogenin expression was strongly correlated with PFS, meaning that high neogenin expression resulted in better response to combined therapy and improved PFS. These results suggest that neogenin may be a factor

predicting response to chemotherapy+NP137 combination, representing a biomarker for patient stratification, capable of identifying patients likely to benefit from this treatment approach.
Finally, the authors showed, in cellular assays, that netrin1-neogenin were involved in pancreatic cancer progression. Indeed, in *in vivo* preclinical models, NP137 antibody countered cell migration (as a proxy of EMT), only when neogenin was expressed, while it did not when neogenin was silenced.

Reference. Netrin1 blockade alleviates resistance to chemotherapy in pancreatic cancer. Gael Roth, Pascal Artru, Olivier Bouche, Nicolas Williet, Julien Ghelfi, Anthony Turpin, Astrid Lievre, Jean-Frédéric Blanc, Camille Evrard, Jean-Baptiste Bachet, Pauline Parent, Marc Manceau, Matthieu Roustit, Anna Borowik, Victoire Granger, Aurélie Durand, Christelle d'Engremont, Edouard Girard, Mircea Chirica, Nicolas Braissand, Nicolas Rama, Eugénie Modolo, Hector Hernandez-Vargas, Elise Georges, Jean-Yves Scoazec, Jerome Cros, Sébastien Hazard, Benjamin Ducarouge, Thomas Decaens, Agnès Bernet, Patrick Mehlen. Nature 2026. doi: 10.1038/s41586-026-10436-4.

In blood metabolites and in the gut microbiota, factors predicting response to immunotherapy.

Despite the increasingly diffused immunotherapy in the oncology field, the metabolic factors determining patient response to therapy are unknown.
Through the metabolomic analysis of blood specimens and the metagenomic analysis of fecal specimens of over 1700 patients (from different independent cohorts), with five different tumor types, longitudinally sampled, at different clinical stages, treated with different therapy approaches, and thanks to a machine learning model integrating metabolic data and clinical information, researchers have recently identified metabolites and patient features linked to therapy outcome.
Their findings revealed that higher blood and gut levels of histidine had an immunostimulatory effect – through increased mitochondrial activity and reduced T cell exhaustion–, resulting in antitumor efficacy (with significantly longer progression-free survival, PFS). Furthermore, in preclinical *in vivo* models, histidine supplementation exhibited antitumor effects, indicating a causal relationship rather than a simple correlation. Finally, in patients with chronic inflammatory disease at high risk of cancer, dietary intake of histidine, along with a favorable gut microbiota (previously shown to be positively correlated with efficacy of immune checkpoint inhibitor-based therapy), associated with better therapy outcome (increased progression-free survival). Conversely, gut microbiota alterations (dysbiosis) were linked with high level of immunosuppressive histidine end-products in the blood, suggesting gut microbiota influence on circulating histidine and, hence, on its immunostimulatory effects.
Although prospective clinical trials are needed to enable to generalize the data and definitively establish the prognostic relevance of histidine levels and its therapeutic potential, a controlled histidine supplementation –which has been previously shown to be safe–, in patient subgroups selected on the basis of their histidine-modulating gut microbiota composition, may be worthy of further investigation, possibly allowing to define a novel strategy to prevent or delay cancer onset in high risk patients.

TELL ME MORE!

A 6-metabolite signature predicting patient outcome. The authors analyzed over 4000 plasma samples and 620 fecal samples of more than 1700 patients from several different independent patient cohorts. Mass spectrometry-based metabolomic analyses enabled the generation of a dataset containing 154 metabolites, which allowed for the development of a machine learning model. Leveraging this machine learning model, the authors identified a 6-metabolite signature (histidine, succinic acid, carnitine, docosatrienoic acid, hexadecanedioic acid and creatinine) and two clinical traits (age and body mass index) associated with

patient outcome (progression-free survival, PFS) under cancer therapy. Among the six metabolites emerging from the analysis, histidine was the most robust predictor, although other metabolites, including long chain fatty acids and succinate, appeared (negatively) associated, though to a lower extent, with patient outcome. The metabolite signature was further validated in multiple cohorts and experimental models.

Histidine predictive value. Next, the authors found that patients could be stratified according to PFS or overall survival (OS) on the basis of plasma histidine levels: Higher histidine, before therapy, correlated with better patient outcome (longer PFS, OS or recurrence-free survival –RFS–, in the different cohorts). Notably, in one of the patient cohorts analyzed, histidine levels were greater in high risk group as well as in intermediate risk vs low risk patients. Moreover, in healthy individuals at high risk of (tobacco-associated) cancer, high histidine levels were linked to lower cancer incidence. The predictive value of histidine was independent from the specific type of therapy. During treatment, responders exhibited increasing histidine levels. Overall, their data indicated that high levels of plasma histidine correlate with reduced risk of developing cancer in smokers, and better chance of response to immunotherapy in patients with different cancer types.

Histidine levels and patient outcome – is there a therapeutically exploitable causal link? In order to assess the existence of a causal relationship between histidine levels and patient outcome, the authors characterized circulating immune system cells (peripheral blood mononuclear cells) of untreated and, since histidine can be metabolized by the microbiome, fecal microbiota transplantation (FMT)-treated patients. They found more activated immune cells (CD4 and helper T cells, B cells, monocytes) in high circulating histidine patients, indicating an immunostimulatory role of plasma histidine.

In preclinical *in vivo* models, histidine resulted in enhanced proliferation of pre-effector CD8 T cells, increased T cell mitochondrial activity, in a fatty-acid oxidation (FAO)-dependent manner, and improved ability to resist exhaustion. Moreover, dietary histidine supplementation displayed both a therapeutic and a prophylactic effect, increasing immunotherapy efficacy and preventing tumor development. Interestingly, histidine increase was parallel to reduced levels of immunosuppressive metabolites (such as tryptophan). Overall, their data indicate that, after oral histidine intake, the increase of plasma and tumor histidine concentrations could modulate lymphocyte function.

The gut microbiota modulates histidine immunostimulatory effects. The authors showed that the gut microbiota is involved in the immunostimulatory effects of dietary histidine. Indeed, they found a correlation between blood histidine level, at baseline, patient dietary habits, and (shotgun metagenomics-based analysis of) gut microbiota composition: High histidine levels correlated with ingestion of protein-rich food, and with a favorable microbiota, previously shown to be linked with ICI-based therapy efficacy. Conversely, dysbiosis was linked with high levels of immunosuppressive histidine end-products in the blood, suggesting an effect of gut dysbiosis on histidine recirculation, and indicating that histidine levels and ensuing immunostimulatory effects are likely to be the result of both dietary intake and microbiota production and metabolization.

Histidine levels and therapy toxicity. Is there a correlation between histidine and therapy-related side effects? While they found no association between plasma histidine levels and therapy toxicity, they did find a correlation with fecal histidine level, with higher histidine being linked to less severe/less frequent adverse events.

Reference. *Metabolic determinants of cancer immunotherapy outcomes identified by plasma profiling. Suissa D, Fidelle M, Reich E, Pham TN, Thomas S, Björk JR, Liu P, Zhao L, Kitaoka K, Piard E, Lebhar I, Tian AL, Thelemaque C, Alves Costa Silva C, Deutsch E, Loriot Y, Segata N, Piccinno G, Hospers GAP, Maleki Vareki S, Silverman MS, Lenehan JG, Bataille V, Boulate D, Kuznetsova T, Weersma RK, Messaoudene M, Durand S, van der Aalst CM, de Koning HJ, Schuler-Thurner B, de Vries IJM, Rafie E, Saliby RM, Machaalani M, Haferkamp S, Schilling B, Porcari S, Ciccarese C, Iacovelli R, Cremolini C, Choueiri TK, Elkrief A, Kroemer G, Heinzerling L, Chamoto K, Ianiro G, Routy B, Derosa L, Paragios N, Zitvogel L. Nat Med 2026. doi: 10.1038/s41591-026-04481-9.*

Proton therapy *vs* photon-based radiation therapy – results of a phase III clinical trial.

Radiation therapy is a quite diffused treatment approach, with limited cost and low cost-effectiveness ratio, which is rapidly evolving offering to patients increasingly precise and personalized treatments, with positive effects on quality of life.
Head and neck cancer (HNC) is commonly treated with different approaches, including radiation therapy, systemic therapy and surgery. Employed radiation therapy usually consists of photon-based intensity-modulated radiation therapy (IMRT) which, by modulating beam intensity, allows to reduce exposure of surrounding tissues, resulting in significantly increased precision, and making this approach the standard of care for this tumor type. However, toxicity still persists, mainly for tissues on the path of the beam.

Photon-based radiation therapy and proton therapy.
Radiation therapy can be "conventional", that is based on photons, or can exploit charged particles. Charged particle radiation therapy includes proton-based therapy and heavier ions (typically carbon)-therapy. Protons are positively charged subatomic particles which, due to their specific physical features, interact with biological tissues differently from photons. Due to the specific characteristics of charged particles, proton therapy enables to more carefully direct the energy beam to a restricted tissue area, thus more precisely targeting tumor cells while mostly sparing surrounding healthy cells, which receive lower doses. That results in reduced treatment-associated toxicity. Moreover, proton therapy can penetrate deep in tissues, thus allowing to safely reach even tumors located deep in the body.

In this scenario, proton therapy has emerged as a valid alternative, using protons instead of high energy x-rays of the photon-based therapy. Moreover, intensity modulation can allow to further reduce dose and, hence, toxicity.
In the frame of a recent phase III, randomized clinical trial, researchers have compared efficacy and toxicity of IMRT *vs* IMPT, in oropharyngeal cancer patients.
Results showed that IMPT was not inferior to IMRT; progression-free survival (PFS) was indeed comparable with the two approaches; high grade toxicity was instead reduced. Furthermore, overall survival (OS) resulted increased in IMPT-treated patients as compared to IMRT, possibly due to less severe treatment-related toxicities or better survival after disease progression.
For the first time a randomized phase III clinical trial demonstrated that IMPT was superior to IMRT in the treatment of oropharyngeal cancer patients.
Mechanisms underlying the improved OS observed are still under investigation; an involvement of a long term effect due to radiation-induced overactivation of the immune system, chronic inflammation and ensuing T cell exhaustion, or immune-cancer-microbiome axis have been hypothesized.
Although long term follow-up studies will be important to draw a more complete understanding, these results support IMPT as a new valuable treatment option for oropharyngeal cancer patients.

TELL ME MORE!

The trial was carried out in 21 care centers in US, and enrolled 439 patients (221 in the IMPT group, 219 in the IMRT group) with stage III or IV cancer, randomly (1:1) assigned to receiving either IMPT or IMRT together with systemic therapy. The majority of patients (91%) were males.
Efficacy. Efficacy was evaluated in terms of PFS (that is, time to first event of disease progression/recurrence, either locally or systemically), as well as OS. Among IMPT-treated patients, PFS was 83% at 3 years, 81% at 5 years; while in the IMRT-treated group it was 83% at 3 years and 76% at 5 years. OS was 92% at 3 years and 91% at 5 years in the IMPT group, and 90% at 3 years and 81% at 5 years in the IMRT group. Deaths due to disease were more common in the IMRT group (18) *vs* IMPT (9); treatment-related deaths (in the acute phase of treatment) were more common in the IMRT (6) *vs* IMPT (3). Overall efficacy assessment showed a non-inferiority of IMPT as compared to IMRT in terms of PFS, and even a greater efficacy of IMPT as compared to IMRT in terms of OS.

Safety. Treatment-related adverse events were overall more frequent or more severe in the IMRT group than in the IMPT. In particular, xerostomia (a medical condition in which salivary glands do not produce sufficient saliva), which is usually permanent and can affect quality of life, was less frequent in IMPT-treated patients.

Reference. Proton versus photon radiotherapy for patients with oropharyngeal cancer in the USA: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Steven J Frank, Paul M Busse, J Jack Lee, David I Rosenthal, Mike Hernandez, David M Swanson, Adam S Garden, G Brandon Gunn, Samir H Patel, James W Snider, Daniel J Ma, Jason K Molitoris, Nancy Y Lee, Upendra Parvathaneni, Mark W McDonald, Noah S Kalman, Alexander Lin, Nasiruddin Mohammed, Christina Henson, Christian Hyde 16, Gopal K Bajaj 17, Sanford R Katz 18, Roi Dagan 19, William H Morrison 4, Jay P Reddy 4, C David Fuller 4, Shalin J Shah 4, Jack Phan 4, Gregory M Chronowski 4, Lauren Mayo 4, Erich M Sturgis 20, Renata Ferrarotto 21, Xiaorong R Zhu, Xiaodong Zhang, Li Wang, Katherine A Hutcheson, Adel K El-Naggar, Amy C Moreno, Anna Lee, Michael T Spiotto, Neil D Gross, Stephen Y Lai, Jay J Liao, Jonathan Paly, Zhongxing Liao, Robert L Foote; University of Texas MD Anderson Cancer Center Clinical Trial Consortium. Lancet 2026. doi: 10.1016/S0140-6736(25)01962-2.

Biological mechanisms of cancer immune evasion – A look beyond neoantigens.

Immunotherapy has remarkably changed the therapy landscape of cancer patients, leveraging the patients' own immune system to attack abnormal cancer cells. Widely used immunotherapeutics such as anti-PD1 or antiCTLA4 antibodies, or the more recent bispecific antibodies, potentiate anticancer immune activity. However, despite the remarkable clinical efficacy of these treatments, not all tumors are sensitive to immunotherapy. For instance, differently from the MSI (microsatellite instable) subtype of colorectal cancer (CRC), the MSS (microsatellite stable) subtype, which represents the high majority of CRCs, has shown poor response to immunotherapy. This behavior of MSS CRC has been linked to a low tumor mutational burden (TMB). Indeed, while a high TMB leads to the generation of a high number of the so-called neoantigens ("new" mutations-derived cancer-specific proteins) that, once expressed on the membrane, make cancer cells "visible" and targetable by the immune system, a low TMB fails to do so. MSS tumors are overall genomically more stable, and have a lower TMB than the MSI subtype that has, instead, a higher TMB and is more sensitive to immunotherapy.

On this line, previous research efforts have focused on increasing the TMB of MSS tumors, through the use of mutation-inducing drugs, in order to make cancer cells visible to the immune system. However, although some patients did benefit from this therapeutic approach, some remained refractory to the treatment, suggesting the involvement of other unknown biological mechanisms.

Indeed, researchers recently demonstrated the existence of an additional mechanism involved in MSS tumor resistance to immunotherapy, involving factors secreted by cancer cells.

Their data show that, independently from neoantigens expressed on the cell surface, tumor cells are intrinsically resistant to immune clearance due to the release of factors in the extracellular space.

Antoine, can you briefly explain what is microsatellite instability?

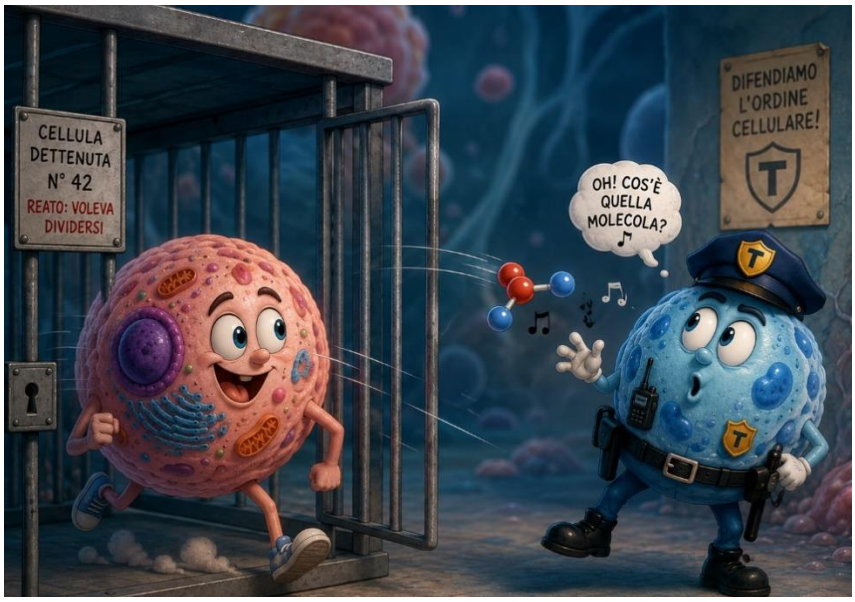
Bien sur! Colorectal cancers (CRC) are highly heterogeneous at the molecular level. One of the most important classifications is based on the status of microsatellites, which divides tumors into MSS (Microsatellite Stable) and MSI (Microsatellite Instable). This distinction has fundamental implications for prognosis, treatment response, and therapeutic choices. Microsatellites are short, repeated DNA sequences (1–6 bases) scattered throughout the genome. Normally, during DNA replication, the MMR (Mismatch Repair) system corrects errors that occur in these sequences. If the MMR system is defective, errors accumulate, leading to microsatellite instability (MSI). In MSS (Microsatellite Stable) tumors, the MMR system works correctly and cancers do not exhibit microsatellite instability. They represent the majority of colorectal cancers (about 85% of cases). With the advent of precision oncology, the MSI/MSS classification is becoming increasingly important. In fact, the distinction between MSI and MSS is crucial for the management of patients with colorectal cancer: While MSI tumors are less common but have a better prognosis and respond to immunotherapy, MSS tumors are more frequent, have a worse prognosis, and require traditional or targeted therapeutic approaches.

(Antoine Imbert is an AI member -Mistral- of the newsletter team.)

Specifically, they found that MSS tumors secrete molecules interfering with T cell recognition and T cell-tumor interaction, making cancer cells resistant to T cell-mediated killing. The released molecules work by altering glycosylation of proteins expressed on the cancer cell membrane, thus making them capable of evading immune clearance.

Their results explain why even when TMB of MSS cancers is experimentally increased, cancer cells find their way to escape immune surveillance, through the modulation of surface proteins.

By unraveling a new mechanism of cancer immunoresistance, with this work the authors suggest a potential new therapeutic approach to be further explored, through the targeting of these secreted factors, to overcome MSS tumor resistance to immunotherapy, in the frame of combination therapies targeting both TMB/neoantigens and the tumor-derived immunomodulatory secreted factors. Moreover, these findings hold a diagnostic potential, proposing the profiling of these secreted molecules to distinguish immunotherapy-refractory patients from immunotherapy-sensitive patients. Finally, they provide a technological platform exploitable in immunoresistance studies in different tumor types.



Exploiting secreted molecules to evade immune surveillance (image generated by ChatGPT)

TELL ME MORE!

The technological platform. To explore the tumor resistance mechanisms underlying the refractoriness of some (high TMB-induced) patients to immunotherapy, the authors developed a technological platform allowing both MSS and MSI tumors to express the same levels of a given antigen recognized by T cells. This approach enabled them to rule out a TMB/neoantigen-related effect. What happens in these conditions?

Beyond the TMB. Firstly, exploiting this system, they observed that even when TMB-linked effect was annulled, T cell reactivity against MSI and MSS tumor cells was different, with a significantly lower T cell activity against MSS tumors: While MSI cells were abundantly killed by T cells, MSS cells were not, indicating the involvement of a TMB/neoantigen-unrelated mechanism.

The secretome. When they analyzed the ensemble of molecules released in the extracellular space (the secretome) they found a significant different set of molecules in MSI *vs* MSS cultures, some secreted by T cells, and some secreted by the tumor cells, indicating that tumor-derived signals may contribute to modulate the immune system antitumor activity; these signals are deployed by tumor cells to protect themselves from the immune system. Interestingly, MSS tumor-derived factors (in the cell medium) were sufficient to significantly impair T cell reactivity against MSI tumors.

The mechanism. In-depth functional analyses showed that tumor-derived factors did not act by broadly inhibiting T cell response (namely, they did not impact on T cell viability or activation), but they rather *specifically* affected the distribution of proteins on the cell surface, ultimately weakening the physical interaction between T cells and tumor cells, and promoting cancer cell immune evasion. Finally, they found that this occurred via post-translational modification –specifically, glycosylation– of membrane proteins. Indeed, inhibiting glycosylation restored T cell-tumor interactions.

Reference. *Mismatch Repair-Proficient Colorectal Cancer can evade Immune Surveillance Through an Intrinsic Suppressive Program. Chiara Maria Cattaneo*, Sharon Scardellato*, Gianluca Mauri, Vittoria Matafora, Veera Ojala, Costanza Cannariato, Rosaria Chilà,*

Zulma Irene Magnani, Wouter Scheper, Luca Lazzari, Emile E. Voest, Maria Chiara Bonini, Angela Bachi, Salvatore Siena, Silvia Marsoni, Giovanni Germano, Alberto Bardelli. Cancer Discovery 2026. doi:. 10.1158/2159-8290.CD-26-0542.

In silico simulations – A new approach to preclinical and clinical research.

The journey of a new drug from the discovery phase until final approval and ensuing integration in the clinical setting is long and expensive, and the percentage of approved drugs is low. Indeed, the process requires extensive preclinical testing in *in vitro* and *in vivo* models, followed by human testing in large patient cohorts. In this frame, the recent technological advances have been leading a profound change, actively supported by regulatory bodies (such as FDA and EMA), revolutionizing the current approach to drug testing, with the introduction of digital twins and in silico clinical trials, to ultimately minimize animal and human testing.

Digital twins are digital representations of patients, meaning that, through the analysis of multimodal data (genomic, transcriptomic, proteomic, biomarkers, lab results, imaging, lifestyle, real world electronic health record data), they collect parameters describing patients' health, to be exploited, along with knowledge of drug interactions and disease progression, to predict disease outcome or response to treatment, in a personalized manner (that is, taking into consideration the specific features of each person, computationally "coded"). These *in silico* models allow to predict the response of a given treatment. *In silico* clinical trials refer to the testing of new compounds in virtual patient cohorts, obtained by assembling "digital patient" data and describing the disease features in computational terms.

These *in silico* models and simulations can be achieved by two alternative computational approaches: *i.* by "mechanistic modelling", or *ii.* by "statistical modelling". In mechanistic modelling, the underlying biological knowledge is used to generate models that simulate the actual biological, physiological, pharmacological processes upon simulation of drug administration; in statistical modelling, response to therapy is estimated directly based on the data, leveraging machine learning approaches to find patterns and infer relationships (drug-response).

Digital twins and *in silico* trials have been typically used in parallel to conventional clinical studies, to optimize clinical trial design; however, more recently their use is being considered for additional purposes, such as to support drug evaluation for regulatory approval. Indeed, the advantages of digital twins and computational clinical trials are multiple: They can be used to predict reaction to drugs before administering them to patients, within "personalized clinical trials", allowing to test, on the virtual twin of a given patient, efficacy and potential toxicity of a therapeutic before patient treatment; to evaluate multiple drug doses at the same time, thus accelerating the testing process; to explore not otherwise testable –involving underrepresented or high risk populations– or unethical scenarios; to provide virtual "control" arms for conventional patient-based clinical trials, either on the basis of real world evidence or synthetic data; to allow for the reduction of the number of patients required for a clinical trial.

The possibility of testing new compounds in virtual patients or patient cohorts allows to shorten the experimental phase, reducing also the associated costs, and accelerate the introduction of new drugs in the clinical setting. Moreover, allowing to avoid, or at least reduce, patient inclusion in the experimentation phase, unnecessary risks for patients can be avoided. Testing potential new drugs by means of rigorously validated computational models, simulating their activity and estimating potential toxicity, can allow for an efficient pre-selection phase, thus enabling to advance (to clinical testing, in limited patient cohorts) only the most promising compounds, and avoiding the current high number of failures when compounds reach the late stage of testing.

Despite their usefulness, issues remain to be addressed in relation to their prediction accuracy. Indeed, while some degree of uncertainty in model prediction of treatment outcome is acceptable/accepted, the extent of uncertainty, whose variability relates to the computational model employed, should be considered. Moreover, in case of different results as compared to data collected with conventional experimental data, strategies to handle conflicting results must be defined. Furthermore, the existence of potential biases in the training phase

of the models must be carefully evaluated, to ensure applicability to large and diverse patient populations, as well as the need to guarantee that patient consent for data reuse is properly obtained.
Although their employment in research is still limited, it is likely to become major in the coming years, sustained by the technological advances and the increasing exploitation of machine learning approaches, towards their increasing accuracy and reliability.
A collaborative effort would accelerate "the digital twin and *in silico* transition", aimed at, if not completely replacing animal and human research, significantly flanking the conventional approach to preclinical and clinical research.

Antoine, can you briefly summarize the main European initiatives aimed at supporting the implementation of digital twins in the biomedical field, specifically in oncology?

The EU is advancing digital twins in oncology through key initiatives. ***The European Cancer Imaging Initiative*** aims to deploy AI and imaging-based algorithms for personalized cancer prevention, diagnosis, and care, targeting 60 million cancer images accessible by the end of 2026. ***The 1+ Million Genomes*** project enables secure access to genomic and clinical data across 26 member states, with 15 operational structures expected by late 2026. Programs like ***ON-COME*** (EU4Health) and ***JANE2*** focus on innovative care models and expert networks for high-risk cancers, integrating big data and multi-omics diagnostics. Projects such as ***BIANCA*** (IEO-Laife Reply) digitize biobanks and train AI on histopathological samples, optimizing oncological diagnostics.

Can you write something more about the BIANCA project?

The ***BIANCA*** project, launched in late 2024 and developed by ***IEO*** and ***Laife Reply***, marks a significant leap in applying digital twins to oncology. It focuses on ***digitizing IEO's biobank***, transforming the physical archive of histopathological samples into an end-to-end digital ecosystem. Using ***artificial intelligence***, BIANCA trains algorithms to auto-annotate pathological images, reducing clinicians' manual workload and improving diagnostic accuracy and scalability.
BIANCA's importance lies in its ability to ***integrate research and routine diagnostics***, creating a scalable model. This approach not only speeds up data analysis but also enables the creation of ***digital twins*** for cancer patients, simulating personalized therapeutic scenarios and optimizing clinical decisions. In a context where precision medicine is increasingly central, BIANCA stands as a concrete example of how digitization and AI can revolutionize cancer care.

(Antoine Imbert is an AI member -Mistral- of the newsletter team.)

References. ***1.*** *The arrival of digital twins and in silico trials in drug development. Ashley L. Eadie, Holly Fernandez Lynch, Naomi Scheinerman & Ravi B. Parikh. Nature Medicine 2026. doi: 10.1038/s41591-026-04344-3.* ***2.*** *In Silico Research Is Rewriting the Rules of Drug Development: Is It the End of Human Trials? Lakhan S E. Cureus 2026. doi:10.7759/cureus.84007.*

Distinguishing head and neck cancer patients at high *vs* low risk of recurrence – evaluation of HPV infection and tumor spreading.

Human papilloma virus (HPV)-driven head and neck cancer (HNC) is clinically different and has a different prognosis as compared to HPV-negative HNC. Moreover, tumor spreading over the colonized lymph node, into the surrounding tissue (so-called extranodal extension, ENE), assessed either histologically on bioptic tissue or by imaging, represents an additional prognostic factor.

An accurate evaluation of patient prognosis, taking into consideration both prognostic factors –HPV infection and ENE–, can allow to more precisely tailor the treatment to each patient, de-escalating therapy in case of low risk disease or intensifying treatment if needed.

To this end, in the frame of a retrospective, multicenter, clinical study, researchers, including Mohssen Ansarin –Director of the Department of Otolaryngology Head and Neck Surgery at IEO–, assessed the impact of HPV infection on ENE-based prognosis in surgically treated HNC patients; in other words, was an ENE-based bad prognosis worsened by HPV infection, or HPV infection rendered ENE-based prognosis more favorable?

Mohssen Ansarin

Their results showed that the prognostic impact of ENE –that is, a better or worse patient prognosis– is different in HPV+ vs HPV- tumors. Indeed, while in HPV+ tumors, ENE does not influence neither patient survival nor tumor recurrence, in HPV- tumors a positive ENE is linked to worse survival and higher probability of recurrence, indicating that HPV status should be assessed along with ENE in these patients in order to more accurately distinguish patients at high risk of disease recurrence, who may need more intense adjuvant therapy after surgery, from those who, being at lower risk of disease relapse, may undergo less intensive post-surgical therapy.

Therefore, on one side, these findings highlight the need for performing HPV evaluation in surgically treated HNC patients, to refine ENE-based risk classification; on the other side, they underline the importance of further translational studies that, by clarifying the biological bases of ENE, may shed light on key mechanisms to be clinically targeted in the context of personalized medicine approaches.

TELL ME MORE!

The study included the retrospective analysis of data from 450 tonsil or tongue cancer patients recruited in 10 different care centers in Europe, with untreated, surgically resectable, histologically (by

Immunohistochemistry, IHC) diagnosed HNC, for which information about HPV status was available. HPV status is typically assessed by IHC of the viral p16 protein. Patients were thus separated in four different groups according to HPV infection (positive or negative) and ENE (positive or negative, namely present or absent). All patients underwent surgery and, according to the pathological assessment of bioptic tumor tissue, adjuvant therapy. Patient were then followed up for up to 5 years.
Clinical outcome was assessed in terms of overall survival (OS) and disease-free survival (DFS). 44% of the recruited patients were HPV+ (284).
Pathological examination of the tumor tissue revealed positive ENE in 25% of the patients (which was not related to factors such as age, sex, smoking status, alcohol consumption, tumor location, surgical approach, resection margin status, and clinical staging.)
At a median follow-up period of 51 months, 5-year DFS was 67% in HPV+/ENE+, *vs* 68% in HPV+/ENE-; OS was 72% in HPV+/ENE+, 76% in HPV+/ENE-. Among HPV- patients, instead, DFS was 36% in ENE+ *vs* 44% in ENE-; OS was 43% in HPV-/ENE+ *vs* 52% in HPV-/ENE-.
Recurrence (either local or distal) was more frequent in HPV- than in HPV+, yet, it differed according to positive or negative ENE; indeed, it was 20% in HPV+/ENE+ *vs* 56% in HPV-/ENE+ and 18% in HPV+/ENE- *vs* 37% in HPV-/ENE-.

Reference. *Recurrences and Survival in Oropharyngeal Squamous Cell Carcinoma According to p16 Status and Extranodal Extension. Paolo Boscolo-Rizzo, Fabiola Giudici, Jerry Polese, Marta Tagliabue, Egidio Sia, Vittorio Rampinelli, Marco Stellin, Enzo Emanuelli, Luigi A Vaira, Simone Zucchini, Pawel Golusinski, Didier Dequanter, Carlos Chiesa-Estomba, Antonino Maniaci, Mario Lentini, Rita De Berardinis, Mateusz Szewczyk, Jerome R Lechien, Cesare Piazza, Piero Nicolai, Mohssen Ansarin, Giancarlo Tirelli. Otolaryngol Head Neck Surg 2026. doi: 10.1002/ohn.70234.*

A new treatment option for gastroenteropancreatic neuroendocrine tumors: Results of a phase III clinical trial.

Gastroenteropancreatic (GEP) Neuroendocrine tumors (NET) are highly heterogeneous neoplasms. Patients are typically treated with somatostin analogues in first line therapy, and after progression they can receive peptide receptor radionuclide therapy (PRRT), chemotherapy or targeted therapy, such as mTOR inhibitors (everolimus), tyrosine kinase inhibitors, in later therapy lines. The only PRRT radiopharmaceutical approved so far for the treatment of somatostatin receptor-positive GEP NETs is Lu-177-oxodotreotide (Lu-177-DOTATATE). Lu-DOTATOC is a novel radiopharmaceutical.
In the frame of the multicenter COMPETE clinical trial, whose results have been recently published in *The Lancet*, researchers, including IEO clinician Chiara Maria Grana –Director of Radiometabolic Therapy Unit of IEO Division of Nuclear Medicine– , Lu-177-DOTATOC was compared with everolimus in advanced, progressive, unresectable GEP NETs in order to evaluate efficacy and safety of this new

Antoine, can you briefly summarize the mechanism of action of radionuclide-based therapy and provide details about Lu-DOTATOC?

Radionuclide therapy uses radioactive isotopes to deliver targeted radiation to tumor cells, especially in oncology. The mechanism involves *i.* targeting: Radionuclides are linked to molecules (*e.g.*, peptides, antibodies) that bind specifically to receptors or antigens overexpressed on cancer cells. *ii.* internalization: After binding, the complex is internalized, exposing the cell to localized radiation. *iii.* radiation emission: The radionuclide emits radiation, damaging DNA and inducing cell death. The radiation's short range minimizes damage to surrounding healthy tissue.
Lu-DOTATOC (Lutethium-177 DOTATOC) is a radiolabeled somatostatin analog used for neuroendocrine tumors (NETs). It binds somatostatin receptor subtype 2 (SSTR2), which is highly expressed in NETs; Lutetium-177 emits low-energy gamma rays for imaging and it can be used for therapeutic purposes to deliver cytotoxic radiation directly to tumor cells, sparing healthy tissue.

(Antoine Imbert is an AI member (Mistral) of the newsletter team)

PRRT. Their results highlighted, in these patients, a superior efficacy of Lu-DOTATOC as compared to everolimus in terms of survival (with a significantly longer progression-free survival and greater objective response), along with reduced toxicity. Although patient follow-up is still ongoing in order to get reliable results in terms of overall survival, COMPETE was the first phase III clinical trial demonstrating a greater efficacy of Lu-DOTATOC as compared to everolimus, with a more favorable toxicity profile, thus providing patients with an additional valid therapeutic option. The authors underline that, based on these results, Lu-DOTATOC should be recommended for the treatment of GEP NET patients, especially for those who progressed under previous therapies, which represent a common real-world scenario.

TELL ME MORE!

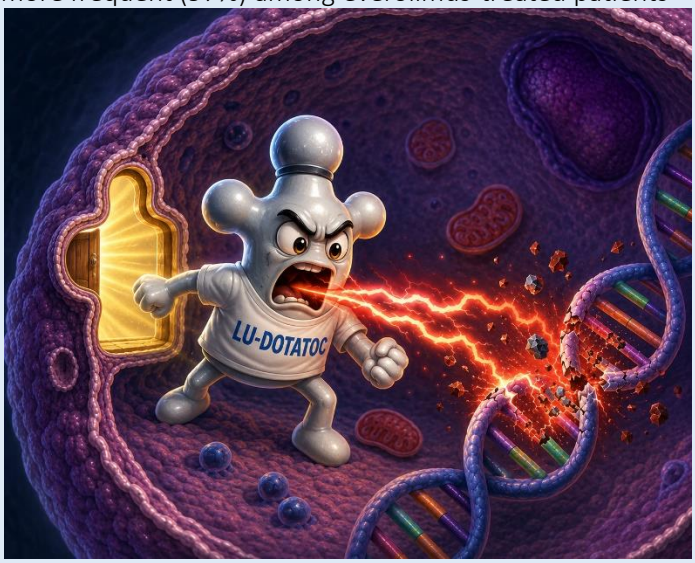
COMPETE was a prospective, multicenter, international, phase III trial aimed at assessing superiority of the radionuclide Lu-DOTATOC as compared to everolimus in patients with advanced, unresectable or metastatic, progressive, somatostin receptor-positive, treatment-naïve or progressing under previous therapy, GEP NET patients. The 309 patients enrolled across 49 cancer centers in 14 different countries were randomly assigned to receiving either the PRRT (207) or everolimus (102.)

Efficacy. Treatment response was assessed by imaging (MRI or CT) and efficacy was measured in terms of progression-free survival (PFS, namely time from randomization to disease progression) as well as objective response rate (ORR; namely the proportion of patients achieving complete or partial response) and overall survival (OS). At the end of the study, median PFS was 23.9 months for Lu-DOTATOC *vs* 14.1 months for everolimus, underlining a greater efficacy of Lu-DOTATOC. Notably, the superior efficacy of Lu-DOTATOC was observed also in most of the (exploratory) subgroup analyses, including grade 2 tumors, second line administration, body mass index.

Regarding OS, although at the time of analysis data were not mature, median OS was 63.4 months for Lu-DOTATOC *vs* 58.7 months for everolimus, further indicating Lu-DOTATOC superiority. However, administration of additional post-study treatments may have affected the OS data.

ORR was significantly greater for Lu-DOTATOC than everolimus, being 22% vs 4%, respectively, and duration of response was longer with Lu-DOTATOC than with everolimus (being 27 vs 13 months, respectively.)

Toxicity. Treatment-related adverse events were more frequent (97%) among everolimus-treated patients than in the Lu-DOTATOC group (82%), leading to treatment discontinuation in 6% of the Lu-DOTATOC-treated patients and 23% of the everolimus-treated patients. In addition, serious adverse events were more frequent in everolimus-treated (15%) than in Lu-DOTATOC-treated (3%) patients. Anyway, no treatment-related adverse events led to death in both groups. Patient follow-up is still ongoing. Changes in quality of life (QoL score) were small for Lu-DOTATOC-treated patients and actually indicating a slight decline for those receiving everolimus. Moreover, for those patients who experienced an improvement in QoL, this was more durable for Lu-DOTATOC-treated than for everolimus-treated.



Lu-DOTATOC damaging the DNA (image generated by ChatGPT.)

Reference. *[(177)Lu]Lu-edotreotide versus everolimus for gastroenteropancreatic neuroendocrine tumours (COMPETE): a phase 3, multicentre, randomised, open-label, superiority trial. Walter T, Jann H, Ansquer C, Deshayes E, Garcia-Carbonero R, Teulé A, Baum RP, Verberne HJ, Ćwikła JB, Srirajaskanthan R, de Mestier L, Grana CM, Buck A, Hörsch D, Pavel M, Dierickx LO, Michael M, Strosberg*

J, Kollár A, Jimenez-Fonseca P, Rinke A, Del Olmo-García M, Flaus A, Hernando J, Kluge A, Breuninger M, Melnyk S, Zhernosekov K, Capdevila J; COMPETE Investigator Team. Lancet 2026. doi: 10.1016/S0140-6736(26)00604-5.

Molecular characterization of primary-metastatic lesions in lung cancer.

Tumor genomic profiling leveraging next-generation sequencing (NGS) approaches has profoundly changed the treatment of lung cancer patients, allowing for the identification of targetable tumor-driving gene alterations. Since genomic characterization of primary lung cancer lesions is often difficult, metastases usually remain the only available option. However, it is not known whether metastases and primary tumors share the same genomic profile and carry the same driver mutations, or whether metastases have acquired –or lost– genomic alterations distinguishing them from the primary lesions. This information is crucial for the selection of the proper targeted therapy. Therefore, defining the concordance between genomic alterations in primary tumors and metastases is needed to continue using metastases as the "genomic mirror" of the primary tumor to guide therapy selection.

Lorenzo Spaggiari

To address this issue, in the frame of a prospective, monocentric study, IEO researchers headed by Lorenzo Spaggiari –Director of the Lung Program at IEO– analyzed matched primary tumor and metastatic samples (isolated during diagnosis) from lung cancer patients, to describe their molecular profile and assess whether metastases can be used as a proxy for primary tumor genomic profiling. To this end, they used advanced highly sensitive NGS approaches for sequencing; moreover, the prospective nature of the study allowed to focus on primary and metastatic samples isolated at the same time (so to rule out potential differences linked to tumor evolution), in untreated patients (to rule out potential therapy effects).

Their results showed that all tumor-driving genomic alterations found in the primary tumors were also found in the matched metastases, indicating that genome profiling of the metastases can be reliably used –in alternative to more extensive spatial molecular characterization– in the clinical-diagnostic setting to identify the actionable alteration and select the targeted therapy approach.

Although the number of samples included in this pilot study are limited, conclusions robustly support the use of this approach for the identification of targetable mutations guiding therapy decision; yet, additional genomic modifications acquired during tumor evolution, not captured by the gene panel-based analysis, likely contributing to shape tumor heterogeneity and supporting tumor growth, cannot be excluded. Moreover, further studies focusing on metastatic lesions in different organs other than the lung may provide additional insights into the metastatic process.

TELL ME MORE!

The analysis included samples from 27 patients with lung cancer and metastases. The typical panel of main genomic driver alterations in lung cancer were tested. 63% of the patients had at least one driver mutation.

EGFR was the most common mutated gene found in primary tumors, followed by KRAS. About half of the patients also exhibited concurrent mutations in p53. When primary tumor genomic characterization was compared with that of metastatic samples, they observed that all metastases retained the driving genomic event of the primary tumor (100% concordance), indicating that actionable driver alterations represent stable clonal events during early metastatic dissemination. Concordance was high –though not 100%– also for p53, and for copy number alterations, suggesting that these may represent genomic changes acquired later on during tumor evolution, likely contributing to overall metastasizing cancer cell fitness and therefore positively selected and retained.

The authors – **Lorenzo Spaggiari.**

Lorenzo Spaggiari is Director of the Lung Program at IEO and head of the Division of Thoracic Surgery. He is also full professor of Thoracic Surgery at the University of Milan. With a medical degree, a PhD in Surgical Cardio-thoracic surgery, a specialty in General Surgery (University of Parma), and one in Thoracic Surgery (University of Modena), he enriched his work experience in different institutions in Italy (Parma) and abroad (Madrid, Paris, Bordeaux). Since 2003, is director of the Thoracic Surgery Division at IEO, and since 2014 is also Director of the IEO Lung Program.

Reference. *Concordance of Actionable Driver Alterations Between Primary Lung Adenocarcinoma and Paired Thoracic Metastases: A Prospective Next-Generation Sequencing Study. Luca Bertolaccini, Mariano Lombardi, Matteo Chiari, Alessandra Rappa, Monica Casiraghi, Marianna D'Ercole, Antonio Mazzella, Giorgio Lo Iacono, Shehab Mohamed, Valeria Midolo De Luca, Nicola Fusco, Elena Guerini Rocco, Lorenzo Spaggiari. Cancers (Basel) 2026. doi: 10.3390/cancers18111773.*

Liquid biopsy - Extracellular vesicles for brain tumor diagnosis and monitoring.

Liquid biopsy is increasingly used for the non-invasive cancer diagnostics and molecular characterization, or for the monitoring of disease progression and response to therapy, allowing for the design of tailored treatment approaches, without the need of tissue biopsy. Liquid biopsy includes the analysis of circulating free DNA (cfDNA), proteins, metabolites, as well as extracellular vesicles (EVs) released in the bloodstream by cells, including tumor cells. EVs can cross the blood-brain barrier and be released in the circulation, where they can be collected and analyzed. IEO researchers have previously shown that EV abundance in the blood is higher in glioblastoma (GBM) patients than in healthy subjects or other brain tumors, decreases after tumor resection, and re-increases in case of relapse. Due to EV clinical potential, methodologies to artificially and transiently increase the release of EVs (and cfDNA) in the blood are being explored, to facilitate collection and improve analytical accuracy. To this end, approaches such as FUS-BBBO (Focused Ultrasound-mediated Blood-Brain Barrier Opening) aimed at transiently increasing the permeability of the blood-brain barrier to enhance the release of EVs as well as cfDNA in the circulation are being investigated, both in preclinical *in vivo* setting and in the frame of clinical prospective trials. Previous studies have shown that the extent of increase of cfDNA release induced by FUS-BBBO varies among patients and according to disease state; however, the effects of FUS-BBBO on EVs remains largely unknown.

In the frame of a collaboration with the Fondazione Istituto Neurologico Carlo Besta, researchers coordinated by Giuliana Pelicci –Pi at the department of experimental oncology of IEO– together with Massimilano Del Bene, whose research program originated at IEO and continues through a close scientific collaboration between the two institutions, specifically investigated the effects of FUS-BBBO on released EVs and cfDNA in GBM patients, to gain insights into the effects of this procedure on these two disease biomarkers, to ultimately facilitate interpretation of results and integration of liquid biopsy in the clinical neuro-oncology setting.

Their results showed that while FUS-BBBO did not affect the release of EVs, it did influence the overall size of the released EVs, selectively clearing large EVs from the circulation. Furthermore, although the procedure

did not significantly alter cfDNA concentration in the blood (and fragmentation profile), in some cases, in some patients, when FUS-BBBO was set to specific parameters, it did increase at later time points, suggesting that, in this setting, cfDNA longitudinal sampling may be more informative than a single measurement.
Despite the limited patient cohort included in the study, with this work the authors provide evidence that although FUS-BBBO safety is well established, it may not be indiscriminately adoptable for all circulating biomarkers, but its usefulness should be thoroughly investigated. Indeed, while it may be useful to increase cfDNA abundance, whose release in the blood is known to be related to the transient blood-brain barrier opening, allowing for easier sampling and accurate analysis, their findings indicate that this may not be the case for EVs whose release in the bloodstream might rely also on additional biological mechanisms. The processes underlying the selective clearance of larger EVs will require further investigation; the implications may span from accurate biomarker analysis in disease diagnostics and monitoring, to potential involvement in pro-tumorigenic intercellular communication, paving the way to a potential additional exploitation of FUS-BBBO for therapeutic purposes.

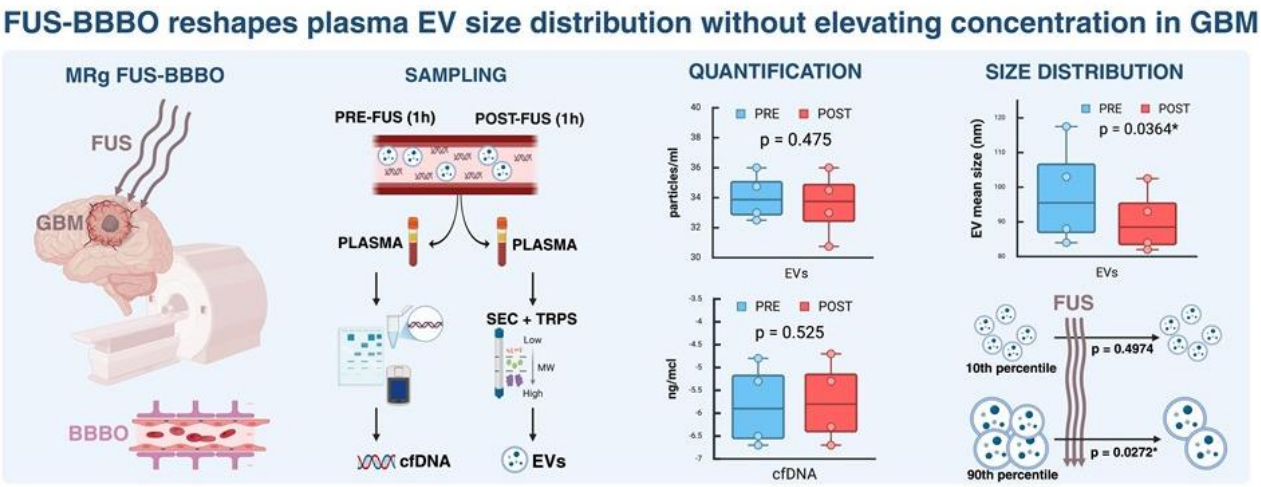


Image from Del Bene et al. (an open access article under the CC BY NC license.)

TELL ME MORE!

The authors observed that FUS-BBBO effects on EV release differed across patients, suggesting that specific –yet to be identified– biological mechanisms may be involved in modulating blood EV abundance. However, while FUS-BBBO did not affect EV concentration in the circulation, they observed a post-FUS-BBBO reduction of EV size, linked to a selective clearance of large EVs. Smaller EVs appeared, instead, unaffected.
Measurements of cfDNA (both tumoral and non-tumoral) revealed that, despite inter-patient variability, concentration appeared unaffected by FUS-BBBO, at least within the first hour, while in some cases/patients/procedures it did increase later on. cfDNA pattern fragmentation remained stable.
Finally, they showed that while the observed slight changes in EV concentration were affected by specific parameters of the FUS-BBBO procedure, EV size and cfDNA concentration were not, highlighting the actual biological relevance of the observed FUS-BBBO-related variations.

Alex, can you briefly summarize the most recent studies of Giuliana Pelicci's group on liquid biopsy?

Extracellular vesicles (EVs) —small membrane-enveloped structures released by tumor cells into the bloodstream that carry proteins, lipids, and nucleic acids— represent one of the research areas of Giuliana Pelicci's laboratory and one of the group's leading translational research platforms.
The group's research focuses on the characterization of plasma-derived extracellular vesicles, the analysis of their DNA, RNA, and protein cargo, the identification of molecular signatures associated with glioblastoma, and the development of a reliable liquid biopsy for disease diagnosis, monitoring, and personalized medicine. The ultimate goal is to transform extracellular vesicles from simple circulating biological material into a true "molecular window" into brain tumors, thereby reducing the need for invasive biopsies and improving patient follow-up. This is pursued through the development of technologies for

analyzing EV-associated and circulating DNA/RNA, the validation of liquid biopsy feasibility in glioblastoma, and its clinical translation, with the aim of identifying non-invasive biomarkers for diagnosis, disease monitoring, and future precision medicine.

As part of the ERA PerMed Joint Transnational Call 2020, Giuliana Pelicci, together with an international consortium, was awarded an ERAPerMed funding for a project aimed at developing a novel liquid biopsy strategy for glioblastoma. Extracellular vesicles are the central focus of this project. The underlying hypothesis is that EVs can become a valuable tool for the early diagnosis of glioblastoma, prognostic assessment, monitoring therapeutic response through simple blood sampling, and molecular characterization of the tumor, ultimately enabling the identification of personalized treatment strategies. The project was conceived to overcome the limitations of conventional brain biopsies, which are often hampered by the limited accessibility of the tumor and its pronounced molecular heterogeneity. Analysis of the molecular cargo carried by EVs is proposed as a dynamic window into tumor biology, capable of capturing the molecular changes that occur throughout treatment.

In addition, Giuliana Pelicci's group, in collaboration with Juan M. Falcon-Perez's laboratory, has developed a novel, highly sensitive approach for liquid biopsy analysis in patients with glioblastoma. The method is based on the use of the fluorescent dye Pyronin Y and flow cytometry, technologies that are available in most research and clinical laboratories. This approach enables the detection of quantitative differences in circulating DNA and RNA between glioblastoma patients and healthy controls. A particularly innovative aspect of the method is that it allows the direct analysis of circulating nucleic acids without requiring prior isolation of extracellular vesicles, thereby minimizing biological material loss and simplifying the analytical workflow. The ultimate objective is to provide a non-invasive, relatively inexpensive, and readily transferable tool for the clinical diagnosis and monitoring of glioblastoma.

(Alexander Irwin is an AI member (ChatGPT) ofthe newsletter team)

The authors – Giuliana Pelicci and Daniela Osti.

Giuliana Pelicci is director of the research unit "Biology of Glioblastomas and Brain Metastases and Potential Therapeutic Targets" at the Department of Experimental Oncology of IEO, and associate professor of Molecular Biology at the University of Piemonte Orientale. With a medical degree and a PhD in Molecular and Cellular Biology from the University of Perugia, she joined IEO in 1994. Since 2005 she is unit director. Currently, her research activities focus on brain tumors and brain metastases, with a basic and translational approach, and main emphasis on the biology of cancer stem cells and the molecular characterization of blood extracellular vesicles to develop reliable liquid biopsy methods for personalized treatments, combining cellular and molecular biology approaches, together with next generation sequencing and xenograft models.

Daniela Osti is a senior research technician in Giuliana Pelicci's group at the Department of Experimental Oncology, where she has worked since 2006. After training in Pharmacology at the Universities of Milan and Insubria, she specialized in glioblastoma research, focusing on patient-derived cancer stem cell models that faithfully reproduce the disease's biological complexity and heterogeneity. These models have supported studies on glioblastoma biology and the development of innovative therapeutic strategies. More recently, her research has expanded to liquid biopsy approaches based on extracellular vesicles and circulating biomarkers for diagnosis and disease monitoring. She also coordinates laboratory activities, contributes to multidisciplinary research projects, and mentors students and junior researchers.

Reference. *FUS-mediated BBB opening reshapes plasma extracellular vesicle size distribution without elevating concentration in glioblastoma patients. Massimiliano Del Bene, Daniela Osti, Marta Bonada, Riccardo Pascuzzo, Annica Piccardi, Giovanni Carone, Lisa Meanti, Mario Stanziano, Valentina Caldiera, Carla Carozzi, Antonio Silvani, Elisa Francesca Maria Ciceri, Marina Grisoli, Giuliana Pelicci, Francesco Dimeco. Neuro Oncol 2026. doi: 10.1093/neuonc/noag155.*

Mitochondrial DNA mutations in hematologic malignancies.

Mutations in mitochondrial DNA can contribute to tumor development and therapy resistance, cooperate with oncogenic alterations, regulate malignant cell metabolism. Due to the high number of mitochondrial DNA molecules and the relatively high mutation rate, altered mitochondrial DNA can coexist, in the same cell, with non-mutated DNA; this condition is known as heteroplasmy. Previous studies highlighted an association between the abundance of heteroplasmic mitochondrial DNA mutations and cancer-related mortality. In solid tumors, the mutational landscape of mitochondrial DNA has been comprehensively described, and studies suggested a causal relation between certain mitochondrial DNA alterations and cancer onset; indeed, in prostate cancer, expression of a specific mitochondrial DNA mutation increased tumor growth. Yet, to date, in hematologic malignancies, mitochondrial DNA alterations have been poorly characterized.

To deepen the clinical and biological relevance of mitochondrial DNA heteroplasmy in hematologic malignancies, in a recent paper by Davini et al., IEO researchers supervised by Enrico Derenzini –Director of the IEO Division of onco-hematology and stem cell transplant and Group Leader at the department of experimental oncology– described the mutational landscape of mitochondrial DNA in diffuse large B cell lymphoma (DLBCL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) patients. Their analyses identified recurrent, disease-specific heteroplasmic mitochondrial DNA mutations that were not observed in healthy donors. A subset of low-heteroplasmy variants was detected in tumor samples only, which may represent early alterations during tumor evolution. Moreover, their results highlighted the presence of mitochondrial DNA mutations in both malignant and non-malignant cells, suggesting that such alterations may play an additional role beyond tumor cells. Most importantly, these alterations carried prognostic information: In AML, mitochondrial DNA mutations predicted worse overall survival independently of established nuclear DNA alterations, while in DLBCL their co-occurrence with MYC alterations identified a subgroup of patients with poor prognosis. These findings highlight the clinical and biological relevance of mitochondrial DNA heteroplasmy in hematologic malignancies and suggest that mitochondrial DNA analysis may provide additional prognostic information, complementing available information derived from the analysis of nuclear DNA, and possibly offering a more precise patient classification on the basis of tumor aggressiveness.

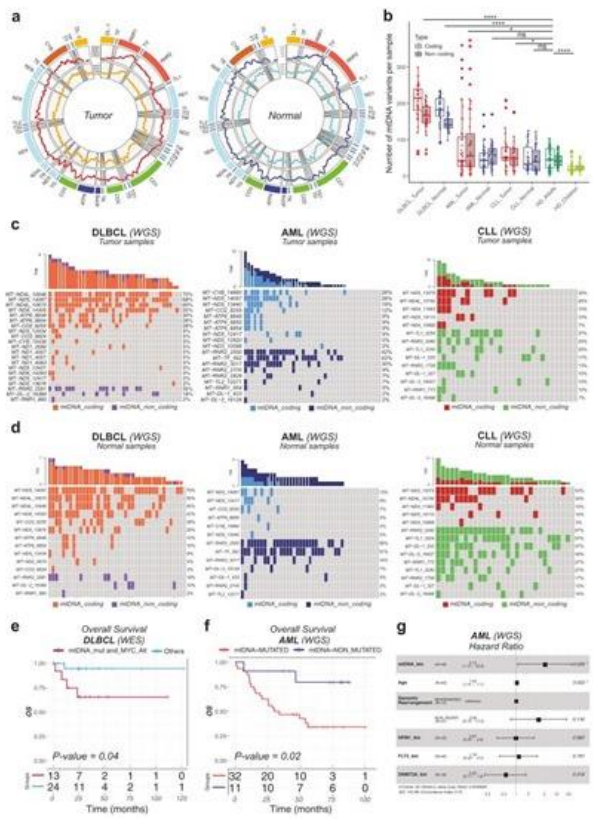


Image from Davini et al. (an open access article under the CC BY NC ND license)

TELL ME MORE!

By analyzing whole-genome sequencing (WGS) datasets from patients and healthy donors, the authors detected mitochondrial DNA variants both in tumoral and corresponding non-malignant samples (that is, PBMCs, skin, saliva, for DLBCL, AML, CLL respectively), with DLBCL patients exhibiting the highest number of mutations, and greater frequency of mitochondrial DNA mutations in patients than in healthy subjects.
Once excluded mitochondrial DNA mutations present both in healthy donors and patients, they identified disease-specific mutations: *i.* in DLBCL, mutations were all heteroplasmic, the majority occurred in protein-coding genes, seven were tumor-specific while the others were both in tumor tissues and matched non-malignant tissue. Co-occurrence of these mutations with alterations of MYC gene –whose role in disease development is well known– correlated with worse OS; *ii.* in AML, all mutations were heteroplasmic, many were in tRNA-coding genes, six were tumor-specific while the others were both in tumor tissues and matched non-malignant tissue. OS was worse in patients exhibiting mitochondrial DNA mutations, independently from established nuclear DNA alterations; *iii.* in CLL, mutations, which were all heteroplasmic, were detected both in tumor samples and matched non-malignant samples. Result validation by targeted mitochondrial DNA sequencing underlined an improved accuracy of mutation detection in purified mitochondrial DNA. Finally, they observed that while mitochondrial DNA mutations were not associated with nuclear DNA mutations in DLBC and CLL, correlations were found between mitochondrial and nuclear DNA mutations in AML.

The authors – **Enrico Derenzini and Alessandro Davini.**

Enrico Derenzini is Director of the IEO Clinical Division of Onco-Hematology and Stem Cell Transplant, associate professor of Hematology at the University of Milan and faculty member of the European PhD School of Molecular Medicine (SEMM). He is also coordinator of the onco-hematology working group of the *Alleanza Contro Il Cancro* network. With a Medical degree, a specialty in medical oncology and one in hematology, and a PhD in Biomedical Sciences from the University of Bologna, he deepened his clinical and research training at the MD Anderson Cancer Center (Houston, Texas) and at the Memorial Sloan Kettering Cancer Center (New York), before joining IEO in 2016. His research activity mainly focuses on the investigation of new targeted treatments and the development of cell-based therapies for the treatment of lymphomas and acute and chronic leukemias.

Alessandro Davini is a postdoctoral researcher in Derenzini's group at the Department of Experimental Oncology. He holds a degree in Medical Biotechnologies from the University of Padova and a PhD in Computational Biology from the European School of Molecular Medicine (SEMM). His research focuses on the application of computational approaches to large-scale multi-omics data from patients with hematologic malignancies, with the aim of uncovering the molecular mechanisms underlying lymphoma and leukemia and identifying novel therapeutic vulnerabilities.

Reference. *Heteroplasmic variants of mitochondrial genome in tumor and normal samples from patients with hematologic malignancies. Alessandro Davini, Fabio Iannelli, Alessandra Rossi, Simone Zanetti, Dorotea Salemi, Saveria Mazzara, Marta Mangione, Giovanna Talarico, Francesco Bertolini, Corrado Tarella, Roberto Chiarle, Enrico Derenzini. Leukemia 2026. doi: 10.1038/s41375-026-03050-w.*

From preclinical studies, a novel combination therapy against high grade B-cell lymphoma.

Loncastuximab tesirine (Lonca-T) is an antibody-drug conjugate (ADC) that, by targeting CD19 protein, selectively delivers

Antoine, can you write few words about HGBCL?

High-Grade B-Cell Lymphoma (HGBCL) is an aggressive type of non-Hodgkin lymphoma (NHL) that arises from B cells. This

the drug (pyrrolobenzodiazepine, PBZ) to cancer cells. By inducing (inter-strand) DNA cross-linking, PBZ ultimately leads to cell death. PARP inhibitors (PARPi) are widely used anticancer drugs that impair DNA damage repair, leading to the accumulation of DNA lesions and ultimately cancer cell death.

Recently, IEO researchers have assessed, in preclinical *in vitro* and *in vivo* models, the efficacy of a treatment combining Lonca-T and PARPi for the treatment of high-grade B-cell lymphoma (HGBCL), a highly heterogenous neoplasm that still represents an unmet clinical need.

Their results showed that, by preventing DNA damage repair, PARPi administration enhances the efficacy of DNA damage-inducing Lonca-T therapy, resulting in greater efficacy as compared to the administration of the two single agents. Moreover, genomic analyses of patient data suggest that mutations in genes of the DNA damage repair system may represent tumor cell vulnerabilities that increase tumor-cell sensitivity to the combined effects of PARPi-mediated DNA damage repair inhibition and Lonca-T-induced DNA damage generation, leading to cell death.

category includes subtypes such as diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and high-grade B-cell lymphoma with MYC, BCL2, and/or BCL6 rearrangements (often referred to as "double-hit" or "triple-hit" lymphomas). Pathological evaluation, including immunophenotyping and genetic testing (such as FISH for MYC, BCL2, and BCL6 rearrangements), is crucial for accurate classification and risk stratification. Treatment is intensive and usually includes immunochemotherapy. Stem cell transplantation may be considered for relapsed or refractory disease. Newer therapies, such as CAR-T cell therapy and targeted agents are increasingly used, especially in difficult-to-treat cases. Ongoing research focuses on improving outcomes through personalized medicine and novel therapeutic approaches.

(Antoine Imbert è un membro AI (Mistral) del team newsletter)

TELL ME MORE!

Firstly, by analyzing patient datasets, the authors found an enrichment of some mutations in genes involved in the repair of DNA damage (induced by inter-strand crosslinks), in HGBCL patients carrying MYC alterations as compared to non-MYC-altered samples. Moreover, MYC-altered and MYC-overexpressing cells exhibited greater sensitivity to Lonca-T as compared to non-MYC-altered cells. Similarly, MYC-altered or MYC-overexpressing cells were more sensitive to PARPi (Talazoparib), suggesting a role of MYC alterations in tumor cell sensitization to these drugs.

In vitro treatment of cells with PARPi along Lonca-T revealed a greater efficacy as compared to the two drugs administered alone, inducing cell cycle arrest, inhibition of DNA synthesis, and cell death. Indeed, by preventing repair of Lonca-T-induced DNA damage, PARPi enhanced Lonca-T efficacy. Although this synergistic effect was observed independently from MYC alterations, the highest efficacy –at minimal dose– was observed in MYC-altered cells. Notably, similar effects were observed when Lonca-T was replaced with another DNA crosslinking agent, such as cisplatin. Importantly, healthy cells were not affected by the Lonca-T/PARPi combination therapy.

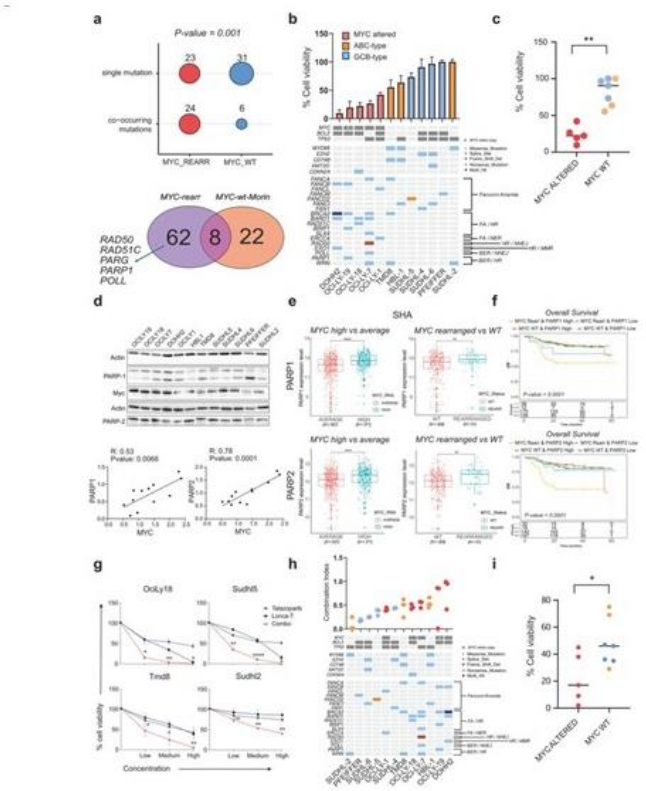


Image from Fusani et al. (an open access article under the CC BY NC ND license.)

Next, the authors evaluated the efficacy of the combination treatment in an *in vivo* setting, exploiting two PDX models. Consistent with the *in vitro* results, PARPi administration significantly enhanced Lonca-T antitumor activity, resulting in increased mouse survival, as compared to single agent administration.
Interestingly, they also observed reduced EGR1 expression after treatment. The lower EGR1 expression has been previously linked to sensitivity to platinum-based therapy, while EGR1 overexpression has been associated to resistance to Bruton Tyrosine Kinase inhibitors (BTKi). These findings suggest that the Lonca-T/PARPi-induced decreased EGR1 expression may be exploited as a marker of sensitivity to platinum-based therapies and support the rationale for investigating Lonca-T/PARPi/BTKi triple combination strategies.

Alex, can you write few words about loncastuximab tesirine and PARP inhibitors?

Loncastuximab tesirine (Lonca-T) belongs to the class of antibody-drug conjugates (ADCs). It consists of a monoclonal antibody directed against CD19, a glycoprotein expressed on the surface of normal B lymphocytes and most B-cell malignancies, bound to a cytotoxic pyrrolobenzodiazepine (PBD) payload known as tesirine. The efficacy of Lonca-T results from the combination of the monoclonal antibody's target specificity and the potent cytotoxic activity of the payload. Following binding to the CD19 antigen, the antibody-drug conjugate is rapidly internalized through endocytosis. Within lysosomes, the linker is cleaved by intracellular proteases, releasing the PBD dimer (SG3199). The released payload binds to the minor groove of DNA, forming DNA interstrand cross-links that inhibit DNA replication and transcription. The accumulation of these lesions leads to cell cycle arrest and tumor cell apoptosis. In addition, a moderate bystander effect has been described, allowing the drug to exert cytotoxic activity against neighboring cells with low or heterogeneous CD19 expression. One of the most remarkable features of this ADC is the exceptionally high potency of its PBD payload, which is capable of inducing irreversible DNA damage at extremely low concentrations, contributing to activity even in tumor cells resistant to other classes of chemotherapeutic agents. Loncastuximab tesirine is primarily used for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and other aggressive large B-cell lymphomas after at least two prior lines of systemic therapy. In this setting, it represents an important therapeutic option for patients who are ineligible for autologous stem cell transplantation or who have failed other treatment strategies, including, in some cases, CAR T-cell therapy.
Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes involved in DNA repair. Among them, PARP1 and PARP2 play a central role in the repair of single-strand DNA breaks (SSBs) through the base excision repair (BER) pathway. PARP inhibitors (PARPi) represent one of the most important clinical applications of the concept of synthetic lethality, whereby the simultaneous impairment of two DNA repair pathways results in cell death, whereas disruption of either pathway alone is compatible with cell survival. The main PARP inhibitors currently in clinical use include olaparib, niraparib, rucaparib, and talazoparib. Under physiological conditions, PARP1 rapidly recognizes single-strand DNA breaks and promotes the recruitment of proteins involved in DNA repair. PARP inhibitors block this process through two principal mechanisms: inhibition of the enzyme's catalytic activity, thereby preventing the synthesis of poly(ADP-ribose) chains, and PARP trapping, in which the enzyme remains bound to DNA, creating a physical obstacle to replication fork progression. During DNA replication, unrepaired single-strand breaks are converted into double-strand breaks (DSBs). In normal cells, these lesions are repaired by homologous recombination repair (HRR), a highly accurate mechanism that primarily depends on BRCA1, BRCA2, PALB2, and other DNA repair proteins. When these genes are mutated or inactivated, as occurs in tumors with homologous recombination deficiency (HRD), cells lose their ability to efficiently repair DNA damage. PARP inhibition therefore results in the progressive accumulation of DNA lesions, leading to genomic instability and ultimately cell death. This phenomenon represents the classical example of synthetic lethality, one of the fundamental concepts of modern molecular oncology. PARP inhibitors are currently used in the treatment of several solid tumors characterized by BRCA1/2 mutations or HRD, including ovarian, breast, prostate, and pancreatic cancers.

(Alexander Irwin è un membro AI (ChatGPT) del team newsletter)

The authors – **Stefania Fusani.**

Stefania Fusani is a former postdoctoral researcher in Derenzini's group at the Department of Experimental Oncology at IEO. She holds a Master's degree in Molecular Biology from the University of Parma and a PhD

in Systems Medicine from the European School of Molecular Medicine (SEMM). Her research focused on immunotherapy and, in particular, on the development of strategies aimed at enhancing anti-tumor immune responses in lymphoma.

Reference. Targeting DNA interstrand crosslinks repair with synthetic lethality in High-Grade B-Cell Lymphoma. Stefania Fusani, Alessandro Davini, Alessandra Rossi, Saveria Mazzara, Alessio Maria Edoardo Maraglino, Anna Vanazzi, Dorotea Salemi, Stefania Orecchioni, Paolo Falvo, Giovanna Talarico, Francesco Bertolini, Corrado Tarella, Enrico Derenzini. *Leukemia 2026. doi: 10.1038/s41375-026-03042-w*.

MiTo – a computational tool exploiting the mitochondria to shed light on tumor progression.

During cancer evolution, cells continuously undergo genome and epigenome alterations, which are selected and accumulate, shaping a cancer cell with survival and proliferation advantages as compared to the surrounding cells, sustaining tumor growth. Such endogenous, naturally occurring mutations (most of which neutral and simply transmitted from a cell to its progeny) can work as "genetic markers" allowing to track cancer cell fate in a native context, without the need of cell engineering.

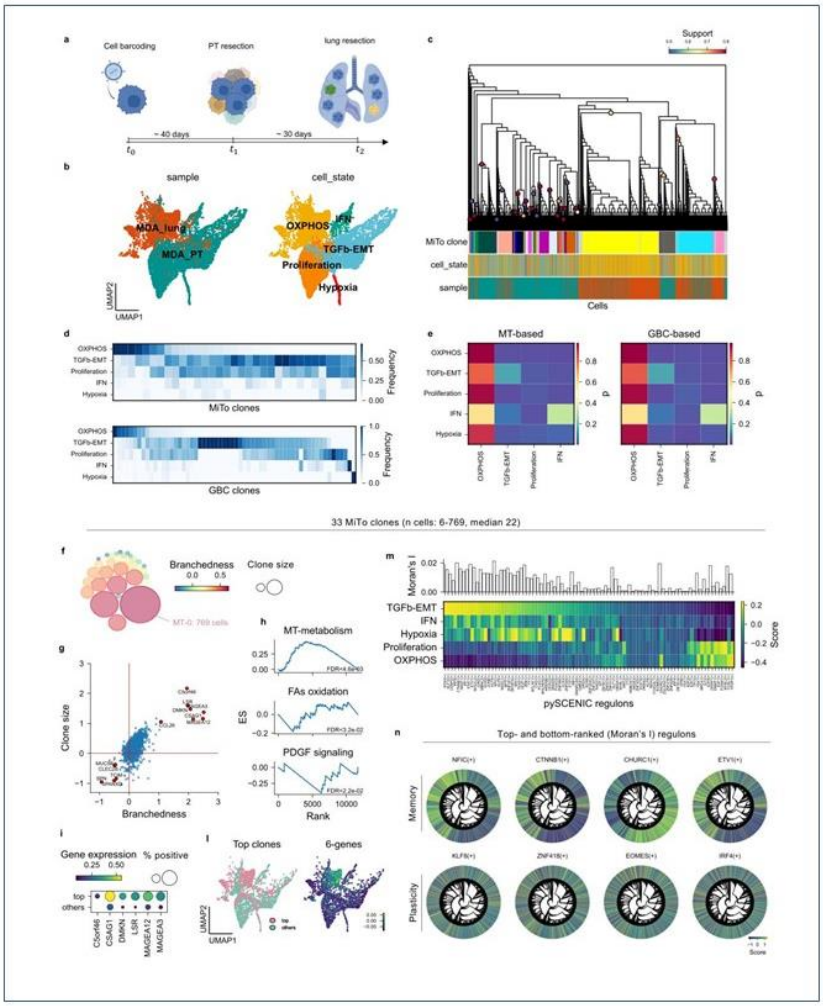


Figure from Cossa, Dalmasso et al. (an open access article under the CC-BY-NC-ND license.)

In a recent paper by Cossa, Dalmasso et al., IEO researchers co-coordinated by Pier Giuseppe Pelicci – Director of the department of experimental oncology of IEO– and Yinxiu Zhan – coordinator of the Data Science Unit of the department of experimental oncology–, describe the development of a novel computational tool –MiTo– to track, during tumor progression, the genetic markers represented by the mutations in mitochondrial DNA. MiTo allows to infer, automatically and at single cell resolution, on the basis of variants in the mitochondrial DNA, cancer "clonal

evolution", namely how a given cell, characterized by –labeled with– a specific mitochondrial DNA alteration, proliferates giving rise to a cell population (a cellular clone) making up a portion of the tumor mass. By also enabling to analyze gene expression, MiTo allows to identify the gene expression profiles of cells in the primary tumor –the authors did that in breast cancer– and matched metastases, characterized by processes such as the epithelial-to-mesenchymal transition (EMT) and proliferation on one side, and oxidative phosphorylation on the other side. Finally, through the analysis of the way gene regulatory programs are inherited by daughter cells at cell division, MiTo highlighted the existence of a cell "memory", thus underlining that specific gene expression programs are inherited from one cell to another at cell division, likely contributing, together with the cell response to environmental stimuli, to tumor progression.
Although other tools (such as WGS-based or CRISPR-based) appear more suitable when high resolution analyses are required, MiTo provides a useful tool for easier, cost-effective analyses which, importantly, not requiring cell engineering (they do not require indeed the expression of short barcode sequences to label the cells), can be used in native biological contexts (potentially out of the purely experimental setting).

TELL ME MORE!

IEO researchers previously applied lineage tracing approaches to analyze clonal evolution during breast cancer progression. Leveraging short barcode sequences expression in cancer cells to label/identify each individual cancer cell and its progeny during tumor growth, coupled with single cell omic analysis, they unraveled key information on tumor progression. However, this approach requires cancer cell engineering, for the expression of barcode sequences.

The endogenous mutations, continuously generated during tumor progression, can be used as endogenous genetic markers for lineage tracing approaches.
However, for endogenous mutations to be used as genetic markers for lineage tracing, these should have specific features: *i.* they must be endogenous (that is, naturally occurring and not requiring cell engineering); *ii.* they must have a high mutational rate (to allow to closely track each phase of tumor progression and clonal evolution); *iii.* they must be easy to sequence (to make the method cost-effective). In this context, mitochondrial DNA (mtDNA) variants appear a valid option. Indeed, the mtDNA has a faster mutation rate as compared to nuclear DNA, and is smaller (thus faster to sequence). Yet, nowadays the reliability of mitochondrial variants as genetic markers, and of the computational analyses used to identify them, remains uncertain.

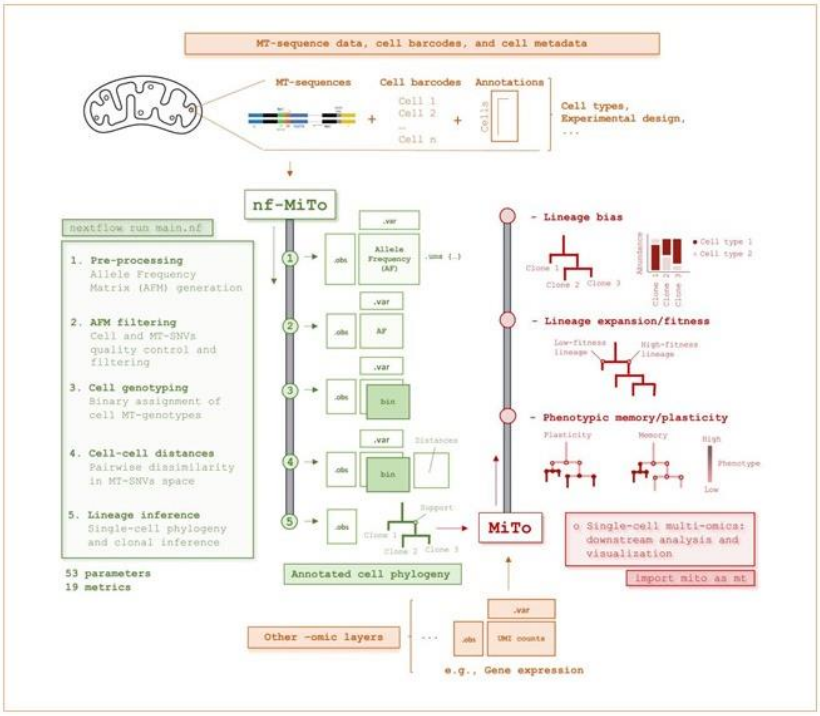


Figure from Cossa, Dalmasso et al. (an open access article under the CC-BY-NC-ND license.)

To address this issue, IEO researchers developed MiTo. MiTo is made of two components: *i.* nf-MiTo, working in five consecutive steps, from data pre-processing and filtering (to discard low quality data), until lineage inference, namely the generation of a phylogenetic tree reproducing how each tumor cell, identifiable

through a genetic marker/mtDNA variant, gives rise to its progeny during tumor progression, making up a subpopulation within the tumor mass; and *ii.* the MiTo package, for the subsequent analysis. MiTo can be integrated within existing and largely used workflows for single cell analysis and allows for the simple addition of new features. The preprocessing and filtering steps appear to be key for accurate results. Moreover, the possibility to actively modify a high number of parameters enables the full control of the whole analytical pipeline as well as analysis customization. When they compared MiTo with other widely used tools for single cell lineage tracing, results showed that *i.* MiTo consistently identified a number of clones closer to the real one in all the datasets analyzed; *ii.* while WGS remained the best solution for high resolution analyses, its high costs, the low number of cells that can be analyzed, and the limited compatibility with omic analyses remain an issue; *iii.* while Cas-9-based tools resulted to be good in terms of resolution, they require cell engineering, making them not suitable to be used in native contexts, and restricting them to experimental systems.

MiTo, instead, offers an easy, cost-effective, scalable solution that, by leveraging naturally occurring alterations in the mtDNA, represents a label-free tool suitable for studies in native contexts, providing both lineage and phenotypic information, though at a lower resolution (a limitation that is, however, shared with systems based on DNA methylation). Once assessed MiTo performance, the authors applied their tool to biologically relevant contexts, leveraging a newly generated dataset obtained through the tracing of *a)* mitochondrial single nucleotide variants (mtSNVs) and *b)* lentivirally-expressed barcodes, in *1)* MDA-MB-231 breast cancer cell line transduced with lentiviral vectors expressing unique barcodes. After transduction, cells are shortly left proliferating, then mixed in defined proportions to create a clonal mix (meaning that each cell labeled with a barcode generates a clonal population of cells derived from one single founder cell, which are then mixed, in defined proportions, with cells derived from the expansion of another founder cell labeled with another barcode); in *2)* MDA-MB-231 cells transduced with barcodes and transplanted in recipient mice. The resultant primary tumors and matched metastases are then resected and analyzed.

All samples undergo scRNAseq, to analyze gene expression, mitochondrial variants (*a*) and barcodes (*b*), in cell cultures (*1*), primary tumors and matched metastases (*2*).

They found a high correspondence between barcode-based and mtSNV-based lineage inference, supporting MiTo reliability. The integration of gene expression analysis and lineage inference revealed also phenotypic changes, between the primary tumor –characterized by EMT, interferon response, hypoxia, proliferation– and matched metastasis –featured by oxphos, a sign of metabolic adaptation during metastatic progression. Moreover, increased clonal fitness was parallel to increased mitochondrial metabolism, reduced fatty acid oxidation and PDGF signaling. They also found six genes whose expression level correlated (increased) with increasing cell fitness; some of these genes are known to be linked to cancer progression, and some to poor patient prognosis. To verify whether these gene expression programs were inherited by daughter cells at cell division, they correlated gene regulatory networks (namely the elements modulating gene expression) with mtSNV-based lineage inference, and found that many of the were indeed significantly retained at cell division, during tumor evolution. Therefore, these results show that MiTo represents a valuable tool that, by allowing to reliably infer lineages, correlate them with gene expression, and distinguish an inherited "memory" of gene expression programs, can allow to dissect, *in vivo*, the molecular determinants of somatic evolution.

Reference. MiTo: tracing the phenotypic evolution of somatic cell lineages via mitochondrial single-cell multi-omics. Andrea Cossa #, Alberto Dalmasso #, Guido Campani, Elisa Bugani, Chiara Caprioli, Noemi Bulla, Andrea Tirelli, Yinxiu Zhan, Pier Giuseppe Pelicci. Nat Commun 2026. doi: 10.1038/s41467-026-71607-5.

Novel biomarkers and therapy targets in the epigenetics of human papillomavirus-driven head and neck cancer.

Head and neck cancer (HNC) can be classified into HPV+ and HPV-, namely either induced –or not– by human papillomavirus (HPV) infection. However, despite the molecular and clinicopathological

differences between the two subtypes, treatment approaches remain basically the same, mainly consisting in chemo-, radio- therapy and surgery.
Therefore, a deeper molecular characterization is needed to identify new biomarkers and targetable mechanisms of disease exploitable for the design of novel and more effective therapeutic approaches. Previous studies described epigenetic alterations in HNC (in particular in Head and Neck Squamous Cell Carcinoma), suggesting the existence of epigenetic differences between HPV+ and HPV- tumors.

In a recent paper by Lavinia Ghiani et al. the authors coordinated by Susanna Chiocca –PI of the department of experimental oncology of IEO–, in collaboration with Tiziana Bonaldi's group, characterized the epigenetic –in particular, histone post-translational modification (hPTM)– profile of HPV+ and HPV- HNC cells and observed differences –in particular, in the di-methylation of lysine 36 of histone 3 (H3K36me2)–, suggesting that H3K36me2 levels may represent a potential new diagnostic biomarker to distinguish HPV+ and HPV- HNC tumors, for instance by liquid biopsy. Moreover, by exploring the underlying molecular mechanisms, they found that HPV infection (specifically, the E6/E7 oncoproteins of the high-risk HPV16 and HPV18 strains) cause the increased expression of NSD2 protein, which in turn induced the methylation of H3 (H3K36me2) and modulates proliferation, cell migration, and cell differentiation. Although the higher NSD2 expression was more pronounced in HPV+ *vs* HPV- cells, it was present in both subtypes compared to normal tissues, and NSD2 silencing reduced cell proliferation and cell migration (and epithelial-to-mesenchymal transition, EMT) in both molecular subtypes.

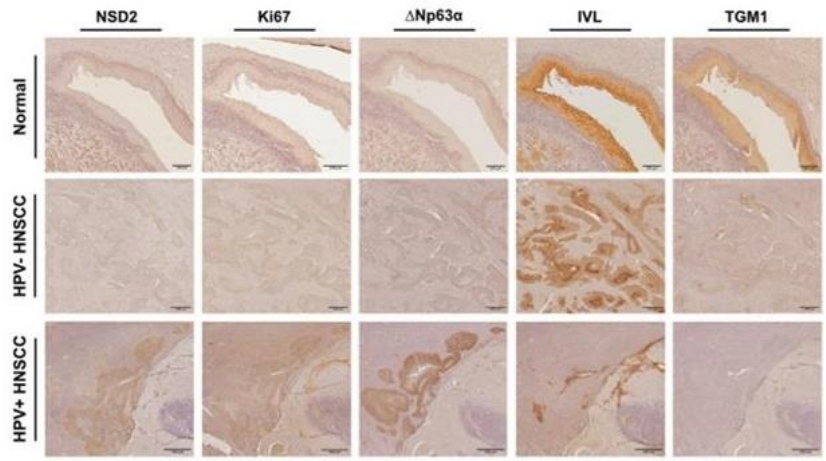
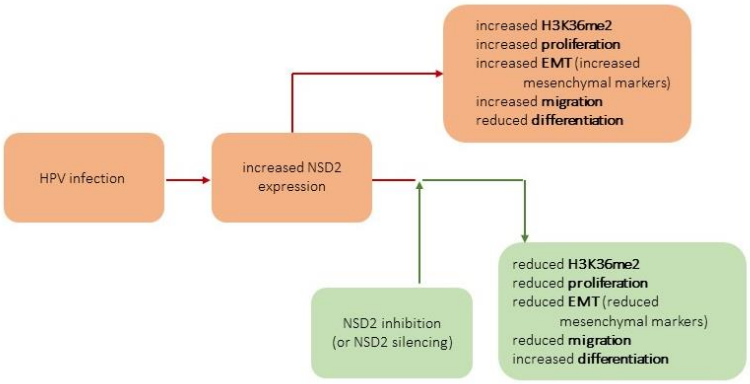


Figure adapted from Ghiani et al (an open access article under the CC BY license)

Therefore, their results show that NSD2 is perfectly placed at a strategic point to control cell plasticity, modulating migration and proliferation (increased upon NSD2 overexpression, reduced upon NSD2 loss) or cell differentiation (induced by NSD2 loss, switched off by NSD2 overexpression), independently from the HPV infection (that is, true both in HPV+ and HPV- cells). However, they found that targeting NSD2 could also exert some specific effects according to the HPV status of HNC tumors; indeed, they observed that epithelial cell differentiation is specifically and predominantly induced in HPV+ HNC cell lines, suggesting that NSD2 inhibitors may represent a novel example of differentiation therapy in HPV+ HNC.



Compounds inhibiting NSD2 activity are currently being clinically investigated in the frame of phase I clinical trials. Moreover, NSD2 role in DNA damage regulation suggests the potential of NSD2-targeted

therapeutics in the frame of combination therapies along with DNA-damaging treatments such as chemo- and radio- therapy.

TELL ME MORE!

Leveraging quantitative mass spectrometry approaches, the authors characterized hPTM profile of both HPV+ and HPV- cancers (in both tumor sections and cell lines). Despite the high degree of heterogeneity, they identified few differentially abundant hPTM, among which H3K36me2, linked to the expression level of the E6/E7 HPV oncoproteins, and higher in HPV+ than in HPV- cells.

Mechanistic studies revealed that, in human primary keratinocytes, the natural host of HPV infections, expression of E6/E7 viral oncoproteins resulted in the (transcriptional) upregulation of NSD2 (while E6/E7 knock down in HPV+ HNC cell lines resulted in NSD2 downregulation), a histone modifier responsible for H3K36me2 PTM. Notably, only E6/E7 proteins from high risk HPV –and not from low risk HPV– induced NSD2 upregulation. Consistently, NSD2 was also overexpressed in HPV+ *vs* HPV- HNC cell lines, resulting in higher H3K36me2 levels, and in patients-derived HPV+ HNC samples.

Analyses of both publicly available (TCGA) patients' data and patients' samples collected at IEO (ENT IEO Division headed by Mohssen Ansarin) confirmed that HPV infection correlated with higher NSD2 expression as compared to both HPV- tumors and healthy tissue, and revealed a correlation between higher NSD2 expression and tumor grade. Notably, TCGA data analysis showed that genetic alterations of NSD2 were rare and the altered expression levels were thus mainly due to E6/E7 expression (that is, HPV infection).

To explore the functional consequences of E6/E7-induced upregulation of NSD2, they silenced NSD2 in both HPV+ and HPV- cell lines, and found *i.* decreased H3K36me2 levels; *ii.* reduced cell proliferation; *iii.* reduced expression of EMT markers; *iv.* reduced cell migration (both in HPV+ and HPV- cell lines, so independently from E6/E7 levels). On the other hand, NSD2 overexpression *i.* led to higher H3K36me2 levels, *ii.* increased proliferation, *iii.* upregulated mesenchymal markers and *iv.* increased cell migration. Consistently, RNA-seq experiments revealed that several cell pathways involved in EMT and cell/substrate interaction were affected by NSD2 expression. While NSD2 modulation occurred mostly independently from HPV status, some genes linked to epithelial cell differentiation were specifically upregulated in HPV+ (which are usually of high grade) as compared to HPV-.

NSD2 expression also affected the level of p63 (specifically, the deltaNp63alpha isoform), which is a crucial regulator of cell differentiation. Indeed, NSD2 silencing reduced p63 –resulting in cell differentiation–, while NSD2 overexpression upregulated p63.

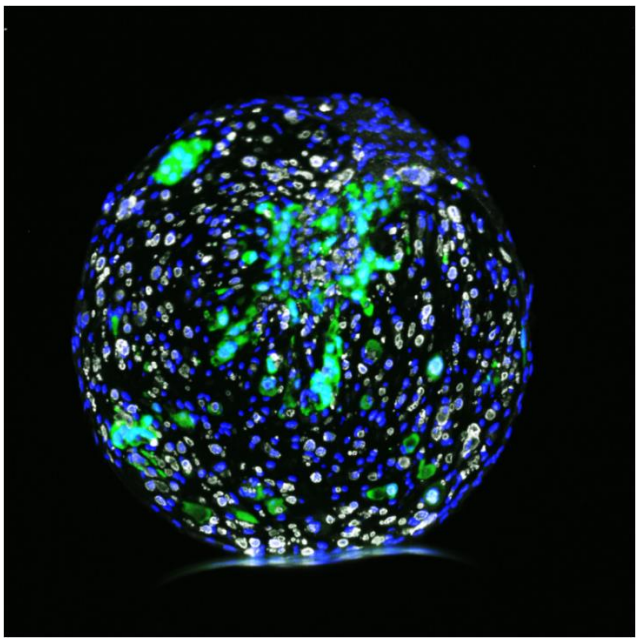
Notably, NSD2 protein has been previously involved in differentiation in other contexts (*e.g.* lymphocyte and neural progenitor differentiation), indicating its key role in cell differentiation, and suggesting that modulating NSD2 expression may contribute to regulating cell differentiation –at least in part, through its activity on p63–, particularly in HPV+ tumors, suggesting that it may represent a novel target of differentiation therapies. This is particularly important considering that HPV+ tumors are usually of higher histological grade (that is, poorly differentiated).

The authors – Lavinia Ghiani

Lavinia Ghiani is a Postdoctoral Researcher at IEO European Institute of Oncology, in the "Viruses and cancer" group headed by Susanna Chiocca. With a degree in "Genetics and Molecular Biology in Basic and Biomedical Research" obtained at the University of Rome *La Sapienza*, she completed her PhD in Molecular Oncology at the University of Milan. Her research work focuses on the definition of the molecular mechanisms underlying HPV-induced head and neck cancer onset and progression, with a particular focus on epigenetic regulators, to ultimately identify novel disease biomarkers and therapy targets that can improve the current treatment approach of head and neck cancer patients.

Reference. *NSD2 upregulation is driven by high-risk HPV E6/E7 and disrupts epithelial differentiation in HPV-associated head and neck cancer. Lavinia Ghiani, Simona Citro, Alessandro Medda, Mirko Doni, Farkhondeh Ghoryani, Roberta Noberini, Ottavio Croci, Fausto Maffini, Claudia Miccolo, Laura Monteleone, Marta Tagliabue, Rita De Berardinis, Stefano Campaner, Tiziana Bonaldi, Mohssen Ansarin, Susanna Chiocca. J Exp Clin Cancer Res 2026. doi: 10.1186/s13046-025-03631-0.*

Why do cancer cells rarely colonize the heart? A mechanistic insight.



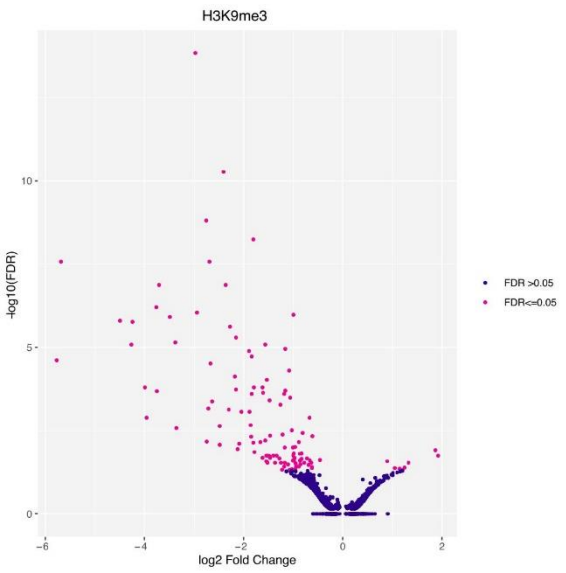
In a recent paper, the authors –including IEO researchers Pier Giuseppe Pelicci, Ivan Dellino, Lorenzo Ciacci– exploited *in vivo* and *ex vivo* preclinical models to explore the mechanisms underlying the rare colonization of the heart by cancer cells, showing that mechanical forces acting on the metastasizing cancer cells limit cancer cell proliferation. Transcriptomic analyses unveiled the involvement of epigenetic mechanisms, such as changes in histone methylation and chromatin compaction, affecting key genes involved in cell proliferation, and unraveled Nesprin-2 protein as a key factor translating external mechanical stimuli into gene expression changes and modulation of cell proliferation.
The involvement of physical properties of the microenvironment in the modulation of cell processes such as proliferation and migration have been largely investigated, mostly focusing on the effect of extracellular matrix stiffness on cell behavior.
This study demonstrated that although other mechanisms can be involved and contribute to the limited proliferation –and ensuing colonization– of cancer cells, in the heart mechanical forces acting on cancer cells influence cell epigenetics (histone methylation levels) and proliferation, preventing heart colonization. The unveiled mechanism could be leveraged with therapeutic scopes, by specific anticancer treatment approaches based on the therapeutic modulation of mechanical forces.

TELL ME MORE!

Cancer cell colonization of the heart is modulated by external mechanical forces. By using preclinical *in vivo* models, the authors assessed the role of mechanical forces in cancer cell colonization of the heart. In this model, the reduced mechanical pressure led to increased proliferation of cancer cells (engineered to induce loss of p53 and expression of G12D mutated kras) as compared to control, with tumor cells largely infiltrating the heart and inducing cardiomyocyte death. This was specifically linked to cancer cell proliferation rather than to different rates of engraftment or cell death. The results were confirmed in *ex vivo* systems, in which modulation (increase) of mechanical forces (simulating heart beating) in tissue cultures of cardiomyocytes halted cancer cell proliferation. Moreover, by changing extracellular calcium concentration to modulate cardiomyocyte contractility and simulate heart beating, proliferation of co-cultured cancer cells was arrested (just like with applied mechanical pressure). Notably, they also found that the different cancer cell proliferation rates observed were not due to altered nutrient availability.
Mechanisms underlying the poor mechanical pressure-modulated cancer cell colonization of the heart. Next, they explored the underlying mechanisms, to assess how cancer cells translate the mechanical stimuli (associated with heart beating) into reduced cell proliferation. To this end, they performed spatial transcriptomics on patient-derived primary (lung, melanoma and colon) tumors, *vs* cardiac metastases and non-cardiac metastases. They found that, independently from the tumor of origin, heart metastases exhibited some particular features associated with high expression of genes involved in histone demethylation. Consistently, the level of H3K9me3 and chromatin compaction were reduced in heart

metastases *vs* both non-heart metastases and primary tumors. The different histone methylation levels and chromatin compaction led to increased accessibility of DNA regions involved in processes such as cell cycle arrest, mechanosensing, cytoskeleton.
The link among mechanical pressure, histone methylation and cell proliferation was not purely correlative. Indeed, in heart tissue cultures, applied mechanical pressure, simulating heart beating, reduced H3K9 methylation and chromatin compaction and, importantly, silencing of KDM4C and KDM4D lysine demethylases led to both increased H3K9me3 levels and cancer cell proliferation, demonstrating a causative relationship.

Nesprin-2 in the translation of mechanical signals. Finally, the authors identified the factor translating mechanical pressure into histone demethylation and proliferation arrest. They found that Nesprin-2 silencing in cancer cells co-cultured with heart tissue sections influenced the methylation level and caused increased proliferation in conditions in which, due to mechanical pressure, cell proliferation should be arrested. Notably, this was true also in all the cancer models (lung, melanoma and colon), indicating that Nesprin-2 can be a translator of mechanical pressure-to-cell proliferation in multiple cancer types. Moreover, *in vivo* injection of Nesprin2-silenced cancer cells allowed for cancer cell proliferation in the heart.



Reference. *Mechanical load inhibits cancer growth in mouse and human hearts. Giulio Ciucci #, Daniela Lorizio #, Nicoletta Bartoloni, Mauricio Budini, Andrea Colliva, Simone Vodret, Anh-Vu Nguyen, Lorenzo Ciacci, Bernhard Texler, Benno Cardini, Rupert Oberhuber, Sofia Bindelli, Ilaria Luciana Carlotta Del Giudice, Roman Vuerich, Francesco Riccitelli, Elena Zago, Henrik Nicolay Finsberg, Mattia Chiesa, Gianluca Lorenzo Perrucci, Rossana Bussani, Furio Silvestri, Manuel Maglione, Gaetano Ivan Dellino, Gianfranco Sinagra, Mauro Giacca, Thomas Eschenhagen, Paolo Golino, Giulio Pompilio, Pier Giuseppe Pelicci, Laura Andolfi, Maurizio Pinamonti, Matteo Dal Ferro, Samuel Wall, Francesco S Loffredo #, Serena Zacchigna #. Science 2026. doi: 10.1126/science.ads9412.*

The tumor microbiome – an in-depth description.

Different microorganisms (virus, bacteria, fungi, archaea) inhabit different body areas acting as “barriers” with the environment, such as skin, upper respiratory tract, urogenital tract, orodigestive tract. Alterations in these microbiome communities are associated with pathological conditions, including cancer. The microbiota can also colonize tumor lesions and directly affect tumor cell behavior; in colorectal cancer (CRC), some bacterial species have been previously linked to the disease (such as *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Escherichia coli)*. Analyses of intra-tumor microbiome in cancer lesions located in non-barrier body areas have been complicated by technical issues, thus resulting in sometimes conflicting and uncertain data.
To overcome this issue, researchers, including Nicola Segata –Group leader of the department of experimental oncology of IEO and Full professor at the University of Trento–, improved a computational tool for microbiome analysis –PathSeq-T2T– that, by incorporating the complete human genome sequence, allows to reliably extract (by subtraction) intratumor microbiome sequences. By applying this tool to human tumor sequencing data, they obtained a detailed view of the tumor microbiome.
By using this computational tool, firstly, the authors showed that, differently from earlier reports, tumors located in body areas other than anatomical barriers are not colonized by microbial communities, which are

instead abundant in tumors of the orodigestive tract. Moreover, they provide a detailed picture of the microbial communities within different cancer types, in different body areas, and identify correlations of microbial load and specific communities with the cancer genome, and more specifically, with the tumor mutational burden (TMB). Interestingly, they also found a correlation between specific microbial species and early onset CRC, suggesting a contribution of these microbial species in tumorigenesis.

Nicola Segata

Studying the tumor-associated microbiome has long been a challenge for researchers in the field. IEO researchers previously developed a computational tool to extract such tumor-associated microbiome information obtained by RNA sequencing (rather than WGS) of CRC samples from IEO patients, showing the prognostic power of microbiome profiling and, through the integration with other omic data (such as gene expression, gene mutation, methylation and tumor microenvironmental metabolic features), providing a spatially defined description of such factors, their correlation, interaction, and potential co-evolution as part of the tumor ecosystem (see newsletter n. 4). Those data, along with the results collected within this study, further emphasize the power of such approaches and the key, clinically relevant information they can provide.

TELL ME MORE!

PathSeq-T2T – how does it work? Data collected from the (whole genome sequencing, WGS) analyses of tumor samples contain both tumor-specific genomic information and tumor-associated microbiome genomic information (WGS data = tumor genome information + tumor-associated microbiome information). PathSeq-T2T works by subtracting from bulk WGS tumor data the (T2T-CHM13) human reference genome, thus obtaining the microbial genome information. The remaining non-human (microbial) genome is then analyzed by computational tools such as Kraken2, MetaPhlAn4, and Sylph, to quantify the microbial signals (that is, estimating abundance of the different microbial communities in the sample) and identify the different species.

PathSeq-T2T validation. The authors validated PathSeq-T2T *i.* by using *in silico* mixed data of microbial and human DNA, showing a greater performance; *ii.* by using data obtained from the sequencing of actual *in vitro* samples (containing signal derived from human, microbial, environmental contaminants), demonstrating high sensitivity (allowing also to set a background threshold for potential contaminants even in *quasi*-sterile samples); *iii.* in CRC cell lines.

PathSeq-T2T in real world patient data. Once validated, they applied PathSeq-T2T for the analysis of real world patient-derived WGS tumor and matched germline (blood and saliva) sample data. As expected, PathSeq-T2T found no microbial sequences in sterile/low microbial load samples (that is, no microbial sequences remained after filtering against human reference genome data), such as blood and glioblastoma (GBM), while it did detect microbiome-derived sequences in saliva and CRC samples. Detailed analyses of the specific composition of the microbial communities detected after PathSeq-T2T filtering identified quite

different bacterial species in the saliva and CRC samples as compared to those from blood and GBM. Since microbial species identified in blood and GBM appeared to be likely contaminants, present also in saliva samples (while saliva species were not in blood and GBM), they proceeded with the analysis of the whole dataset (instead of limiting their analysis to saliva, blood, CRC, GBM) to reliably identify shared contaminants. To this end, they developed a score, under the assumption that if a given microbial species was equally abundant in all samples, it was likely a contaminant rather than an actual tumor-associated microbial species.

PathSeq-T2T identifies microbial communities in both orodigestive and non-orodigestive tumors. Tumors maintaining high over-the-threshold microbial signal –namely, tumor-associated– after removal of likely contaminants, were mostly localized in the orodigestive tract (colorectal, oropharyngeal, esophageal, gastric cancers). Non-orodigestive tumors exhibited overall low (though over the threshold) microbial levels. Those with high microbial levels were usually linked to microbial infections (*e.g*. influenza).

Further in-depth characterization of tumor samples from the orodigestive tract allowed, on one side, for the quantification of the overall bacterial abundance in the different areas of the higher and lower gastrointestinal tract (so according to tumor location); on the other side, enabled to identify the microbial composition, which resulted to be quite different in the different body locations analyzed.

Bacteria, viruses, fungi, archaea and parasites in the tumor samples. Their analyses revealed the presence of fungi, archaea, parasites, viruses, in addition to the high abundant bacteria, within tumor lesions located in different areas of the gastrointestinal tract.

Tumor-associated microbiome and cancer genome. The correlation between tumor microbiomes and tumor genotype revealed that tumor genotype and anatomic site were strong predictors of CRC-associated microbiome composition. Tumor-associated microbial communities were highly abundant in hypermutated CRC (in the microsatellite instable –MSI– more than in the microsatellite stable –MSS), although a reduced diversity of microbial species was observed. Notably, the correlation between genomic instability and high microbial load was conserved across other tumor types.

Tumor mutational burden (TMB) and microbial load. Their analyses showed that TMB and anatomical site were associated with *i.* microbial load in CRC (both in MSI and MSS) and in gastric cancer, indicating TMB as a key predictor of microbial colonization across cancer types and patient cohorts, and *ii.* microbial composition. Indeed, while some species were abundant in high TMB CRC, others were poorly abundant in high TMB CRC, others were associated with low TMB CRCs. Other species were non correlated with TMB, but rather correlated with the anatomical site. Finally, other species' abundance varied with disease stage. Therefore, although tumor location appeared to be the main determinant of tumor-associated microbiome composition, interaction among different factors may contribute to define microbiome composition, and tumor microenvironment alterations during disease progression my favor colonization by other microbial species.

Tumor microbiome and early onset CRC. By analyzing the correlation between age of onset of CRC and microbiome composition, they found some species (including *Akkermansia muciniphila* and *Hungatella hathewayi)* depleted in early onset (in the distal colon, where they are more frequent) CRC, suggesting their putative contribution in tumorigenesis.

Reference. *Biodiversity and biogeography of the multi-kingdom cancer microbiome. Anders B Dohlman, Robin Mjelle, Henry M Wood, Kevin Jiang, Alaina Shumate, Iris Lee, Gianmarco Piccinno, Garazi Serna, Abdul-Rakeem Yakubu, Paolo Nuciforo, Phil Quirke, Curtis Huttenhower, Nicola Segata, Matthew Meyerson. Cell 2026. doi: 10.1016/j.cell.2026.04.015.*

Adjuvant low dose tamoxifen to reduce the risk of breast disease.

Women undergoing conservative surgical resection of non-invasive breast cancer (ductal carcinoma in situ, DCIS) remain at increased risk of recurrence or more invasive breast disease.

Sara Gandini

Therefore, tamoxifen-based adjuvant therapy (20 mg, once daily) is usually recommended to these patients, to reduce the risk of subsequent breast disease. However, the significant side effects associated with tamoxifen administration limit their use, and have led to propose the administration of low dose tamoxifen (10 mg, once every other day) in order to reduce side effects while maintaining the benefits associated with tamoxifen in terms of disease risk reduction.

A study recently published in the *Journal of Clinical Oncology* provides definitive evidence supporting the use of low-dose tamoxifen as preventive, post-surgery adjuvant therapy.

The study, headed by Sara Gandini –PI at the Department of Experimental Oncology of the IEO–, and Andrea DeCensi –Director of the Breast Unit at the Champalimaud Foundation in Lisbon (Portugal)–, pooled data from three clinical trials, generating the largest dataset ever analyzed on this topic, including 1545 patients followed for more than nine years. The data were collected at the IEO Division of Cancer Prevention and Genetics, led by Bernardo Bonanni and Aliana Guerrieri Gonzaga, in collaboration with Galliera Hospital in Genoa and the Champalimaud Foundation.

The researchers demonstrated that low-dose tamoxifen retains the same durable efficacy, in terms of disease prevention, of the standard regimen but with decreased side effects. Therefore, these findings support dose de-escalation strategies through which, by reducing dosage and treatment-related side effects, treatment adherence can be improved, without compromising efficacy. Importantly, their results highlight, for the first time, the effects of menopausal status on tamoxifen preventive efficacy, showing a greater protective effect in postmenopausal women. Moreover, their analyses underlined a different efficacy according to tumor location, in the same breast (ipsilateral) of the first tumor, or in the other breast (contralateral). Indeed, a greater reduction of ipsilateral breast neoplasms was observed in postmenopausal women, as compared to a more pronounced effect on contralateral breast neoplasm incidence among premenopausal women, suggesting a different effect of the drug on recurrence (likely ipsilateral) as compared to a new tumorigenic event (likely contralateral).

“Overall, the study represents a significant advance in breast cancer prevention –comments Sara Gandini, first author of the study– and provides robust evidence supporting the integration of low-dose tamoxifen into routine clinical practice for women treated for ductal carcinoma *in situ*, offering an effective, safer, and more tolerable strategy to reduce the risk of future breast cancer events.”

TELL ME MORE!

The three datasets were obtained by pooling data of three patient cohorts with ER-positive breast cancer receiving low dose tamoxifen. Overall, the number of patients considered were 1545, 803 treated with tamoxifen and 742 untreated controls.

Efficacy. Therapy efficacy was evaluated in terms of disease-free interval (that is, time from study enrolment to any local or distant breast disease manifestation), and according to menopausal status (postmenopause *vs* premenopause) and tumor location (ipsi- vs contra- lateral).

Tamoxifen and menopausal status. The effects of tamoxifen treatment were significantly affected by menopausal status. Indeed, a breast cancer event was observed in 40 of 335 women in the tamoxifen/postmenopausal group, in 93 of 401 of the control/postmenopausal group; in 127 of 448 of the tamoxifen/premenopausal group; in 107 of 335 of the control/premenopausal group.
At 10-year follow-up, 13% of tamoxifen/postmenopausal women had breast cancer as compared to 24% of the women in the control/postmenopausal group, meaning a 11% reduction of disease risk. Effects were more pronounced in the DCIS (ductal carcinoma in situ) subtype (13% disease risk reduction at 10 years). Among premenopausal women, instead, the disease manifested in 28% of those under tamoxifen and 30% of untreated women; no effects were observed in the DCIS subgroup.
Tamoxifen and ipsilateral breast cancer. When they focused specifically on ipsilateral tumors, menopausal status appeared to be tightly correlated with treatment. Indeed, among postmenopausal women, ipsilateral breast cancer occurred in 22 of the 335 tamoxifen-treated women and in 63 of the 401 untreated control women, while among premenopausal women ipsilateral events occurred in 102 of the 448 tamoxifen-treated women and in 72 of the 335 untreated control women.
At 10-year follow-up, incidence was 7% in the postmenopausal/tamoxifen group, 22% in postmenopausal/control group –with an almost 10% risk reduction–, 22% in the premenopausal/tamoxifen group, 20% in the premenopausal/control group.
Tamoxifen and contralateral breast cancer. Regarding contralateral tumors, tamoxifen effects were observed only in premenopausal women (and not in postmenopausal), namely in 21 of 448 tamoxifen/premenopausal women, and in 35 of the 335 untreated premenopausal women of the control group.
Tamoxifen and disease-free survival. Overall, disease-free survival was affected by tamoxifen treatment in postmenopausal women but not in premenopausal women.
Safety. In line with previous results, adverse events associated with low dose tamoxifen treatment were rare.

The authors – Sara Gandini.

Sara Gandini is tenured group leader at the Department of Experimental Oncology of IEO and adjunct professor in Medical Statistics at the University of Milan and Faculty member of the SEMM (European School of Molecular Medicine) PhD school. She is also member of the steering committee of the EORTC Melanoma group. With a bachelor degree in Statistics from the University of Bologna (Italy), a master degree in Biometry from the University of Birmingham (UK), and a PhD in Cancer Studies at the University of Birmingham, she worked as staff scientist at IEO, before becoming tenure group leader in 2018. In IEO, she is head of the Molecular and Pharmaco-Epidemiology Unit. Her research aims to integrate and assess the importance of epidemiological factors in translational and clinical research, to ultimately create the basis of personalized cancer prevention and therapeutic programs, leveraging the integration of molecular, genetic and epidemiological risk factors.

Reference. *Low-Dose Tamoxifen in Noninvasive Breast Neoplasia: Long-Term Results From an Individual-Participant Data Pooled Analysis. Sara Gandini, Aliana Guerrieri-Gonzaga, Davide Serrano, Roberta Rizzo, Matteo Lazzeroni, Matteo Puntoni, Tania Buttiron Webber, Gaetano Aurilio, Harriet Johansson, Alessio Carbone, Livia Giordano, Maria Digennaro, Laura Cortesi, Francesco Millo, Katia Cagossi, Giuseppe Aprile, Patrizia Serra, Elisa Gallerani, Marcio Debiasi, Berta Sousa, Pedro Gouveia, Bernardo Bonanni, Andrea DeCensi. J Clin Oncol 2026. doi: 10.1200/JCO-26-00841.*

In IEO the Motore Sanità-organized event "*Il futuro dell'oncologia è già qui*".

From May 20th to May 22nd, IEO hosted an event organized by *Motore Sanità*, focused on the recent advances in cancer diagnostics and therapy.

In the frame of cancer prevention, research and care, in light of the latest innovation, speakers from the medical and research community and politicians, discussed the remarkable progress of the past decades in cancer diagnostics and therapy, achieved by leveraging the most advanced tools, emphasizing how, despite the challenges posed by oncology, science is proceeding rapidly, making cancer an increasingly manageable, chronic –in some cases even curable– disease, and underlining that much more can –hand must– be done, with the joint effort of the scientific-medical and institutional communities.

The future of cancer prevention. In terms of prevention, the discussants underlined the importance of a future personalized prevention approach, both in terms of primary prevention (with a correct lifestyle, physical exercise and a healthy diet, which can *per se* reduce the disease risk by 50%, along with a balanced gut microbiome) and secondary, drug-based prevention approaches in high risk individuals, with research efforts aimed at establishing the minimal effective dose, assessing efficacy of new drug combinations, or different treatment regimens (such as intermittent administration). In this scenario, genomic analyses of germline alterations can allow to devise risk-based prevention approaches, including chemoprevention, preventive surgery, monitoring or drug administration, on the basis of high-, moderate- or low- risk single gene mutations, or on the basis of cumulative risk due to multiple gene mutations, through the use of a polygenic risk scores.

The combination of both (primary and secondary) prevention approaches, along with more effective screenings –by means of new generation diagnostic approaches (such as liquid biopsy, microbiome analyses, AI-based tools integration)– aimed at identifying the risk of disease in the general population and an early diagnosis, will allow to devise personalized prevention strategies. Indeed, the development of new generation non-invasive screening tools can allow, in the future, for the development of multi-cancer early detection tests and screenings on healthy population, thus enabling disease *interception*. In this scenario, sustainability, accessibility of these innovative approaches, as well as citizens' training and clear effective communication is key, allowing for citizens' management of their own health. Although prevention approaches require national investments, the impact on each individual, on the healthcare system, and on the whole society is certainly worth it.

New generation diagnostic approaches. In the diagnostic field, the speakers discussed the power of circulating tumor (ct)DNA-based liquid biopsy which, thanks to the sophisticated genomic approaches currently available, allows to detect extremely low amounts of circulating DNA (in the range of nano- and pico- molar), transforming this technology into a highly sensitive diagnostic tool, embedded in clinical practice in different specific medical settings (mostly in the metastatic setting, according to well-defined clinical recommendations). ctDNA-based liquid biopsy is currently routinely used in breast cancer management, especially in second line therapy setting, for decision-making on potential treatment escalation. Current research aims at the possible future use of this approach also in treatment de-escalation. In lung cancer, although its employment is, in some cases, limited, liquid biopsy is routinely exploited for treatment choice, and represents an extremely useful tool for the molecular characterization of the tumor. While in some tumors –such as melanoma and sarcoma– further studies are needed to integrate liquid biopsy in clinical practice, and the current use is limited to clinical trial settings, in hematological tumors –while not being clinical routine–, it represents a powerful tool in disease contexts where diagnosis with conventional biopsy approaches is difficult, and to define treatment duration.

New generation anticancer therapies. Regarding therapy, the speakers highlighted the transformative effects of the most recent scientific findings, which led to the development and increasingly diffused exploitation of immunotherapy –including antibody-drug conjugates (ADC), bi-specific antibodies, immune checkpoint inhibitors (ICI), vaccines and cell therapies.

In numerous adjuvant or neoadjuvant clinical contexts, these tools are already clinical routine. For instance, in melanoma, from the introduction of ipilimumab, shortly after followed by nivolumab and prembrolizumab, ADCs have now become the standard of care in several settings, and current research efforts are mostly aimed at a more precise definition of the patient subpopulation who can benefit from this approach. In lung –despite the expected heterogeneity of therapy response among different patient subgroups characterized by different molecular and histopathological features– immunotherapy –as well as targeted therapy– have changed a historical "big killer" tumor into a more manageable disease, with a significantly increased survival. Further studies in this context are currently focused on the definition of robust biomarkers to guide treatment selection, along with research on new, more effective compounds and drug combinations. In breast cancer, usually considered a "cold" tumor (namely characterized by poor immune infiltration and thus poor response to immunotherapy), immunotherapy has shown, in the neoadjuvant

setting, remarkable results especially in the triple-negative breast cancer subtype, which is the least diffused yet the most aggressive. In sarcoma, so far immunotherapy has shown poor efficacy, possibly due to the limited studies available for this rare tumor type. Finally, the discussants underlined the remarkable results observed in the hemato-oncology field with immunotherapy approaches: ADC, bispecific antibodies, CART cells (which are mostly employed for the treatment of hematologic malignancies) have deeply revolutionized the therapy landscape, even allowing, for some patients, to avoid completely chemotherapy. Finally, future developments in *in vivo* gene transfer approaches have been discussed, likely to lead, in the near future, to *in vivo* lipid nanoparticles-based CART engineering, leveraging methodologies today used for the treatment of other hematological diseases (such as thalassemia and sickle cell disease).

IEO approach to optimize patients' care. The speakers highlighted IEO effort in the implementation of such advanced approaches to offer the highest benefits to its patients: In a research context, by carefully selecting and prioritizing the most clinically relevant studies (tailored to IEO patients' needs); in a care context, by underlining the importance of an optimized multidisciplinary management –of the disease and treatment-related adverse events– of cancer patients that allows to maximize the benefits (even in rare tumors where advanced targeted and immune therapy approaches are still lacking), through the collaboration within and across the different IEO clinical divisions as well as with external collaborators. In this context, the role of the hospital pharmacy has also been discussed, as a key player in the management of long survivors as well as in the handling of experimental drugs, remaining a reference for patients after hospital discharge.

Research – the engine of medical progress. In terms of research, two main concepts have been highlighted: The importance of private-public interaction, and the development of oncological networks. Indeed, first, current complex problems require collaboration, joint effort, resources and expertise, for all and –therefore– each individual interests, driven by common "languages" and shared goals. Second, in the current scientific scenario, the creation of cancer center networks has become a national and European priority, to overcome issues linked with fragmented information and accelerate clinical trials, innovation, access to new therapies, increase competitivity and attract research excellence and funding. In this scenario, the speakers have highlighted the excellent work of *Alleanza Contro il Cancro* (ACC, the network of cancer centers of high excellence, funded by the Ministry of Health, which includes IEO). Launched over 20 years ago, sponsored and supported by the Ministry of Health, the first goal of ACC was the Italian program of medical genomics, aimed at setting up a next generation sequencing(NGS)-based genomic screening for personalized medicine in ACC centers, and the development of adequate infrastructures for data collection, storage and use. Today, one of the main goals of ACC is the Health Big Data project, which aims at achieving data (omic, imaging, real world clinical data from electronic health records) interoperability –key to downstream analyses and full data exploitation– and the set-up of infrastructures for data collection, storage and handling. Along with that, issues such as data privacy and the creation of Molecular Tumor Boards within ACC are also dealt with, to ultimately strengthen the network and the value of the collected clinical data.

Finally, the speakers highlighted the role, integration and collaboration among the different offices (grant office, clinical trial office, technology transfer office) supporting the translation of scientific ideas into patient benefits.

AI in research and clinical practice. The increasing integration of AI in the clinical and research setting has been largely discussed. While not homogenously integrated in all the clinical workflows, in some contexts (such as in mammography, or in the analysis of computational biomarkers) AI tools are currently largely employed, aiding clinicians in the interpretation of diagnostic images. Moreover, to fully exploit the value of patients' clinical data, IEO has developed a Data Platform, creating a healthcare data ecosystem allowing for the integration of multimodal data –including unstructured data analysed through AI algorithms– from different sources to best benefit IEO patients. The IEO Data Platform collects and organizes, in line with the standard of interoperability, in one single "data lake" all IEO patients' data extracted from electronic health records, diagnostic imaging, genome sequencing, digital biobank, as well as pathological markers and vital parameters, as well as habits and lifestyle data, transforming heterogenous healthcare data into exploitable "clinical intelligence", supporting physicians in the clinical decision-making. High quality data, effort and multidisciplinary expertise of skilled professionals are the tools to accelerate the progressive full integration of AI in all biomedical areas, towards the shaping of 21th century physicians.

Communication for patient's benefits. A critical aspect that has been highlighted is the need to change the way the results of scientific studies are presented, *i.* through "humanization", avoiding numbers and technical terms (such as survival curves and hazard ration), *ii.* through patient involvement (engagement) and *iii.* training (empowerment), supporting them in the choice of the best therapy approach, discussing the different therapeutic options available, managing with a professional approach feelings like anxiety and depression, hopes and illusions, teaching them how to live the moment and manage their feelings amid adverse events and uncertainty related to the disease. In this context, the proper integration of AI tools in patient-doctor discussions can contribute to simplify such interactions.

Twenty years of robotic surgery in IEO – the future is now. The last day of the event has been dedicated to robotic surgery,

as an example of advanced technology that in the past 20 years fully integrated in IEO care paths, for patients' benefits.

Consistent with Umberto Veronesi's vision of intertwined research, innovation and care, in 2006 IEO chose to profoundly change the conventional open and laparoscopic surgery approaches, envisioning the value and the implications of robotic surgery for patients' care. Becoming an IEO strategic priority, guided by a dedicated and multidisciplinary governance, as well as investments in physicians' training along with technology, inserted within a multidisciplinary program, 2006 marked the year of "surgery revolution" in IEO, transforming a strategy into daily practice. Facing challenges such as early skepticism, high costs and organizational issues, robotic surgery has become a technological approach largely used –in the right context and for carefully selected patients– across all IEO surgical divisions, contributing to its sustainability.

Today, the increasing integration of digital tools marks the beginning of a new era of robotic surgery. The use of advanced technologies allows to build digital operation rooms, integrating medical devices, images and data in real time, enabling immediate availability of data and images, remote communication and collaboration in and out of the surgery rooms, as well as the generation of data to be further exploited for research purposes, rendering the hospital a translational research platform, supporting the medical progress leading to the next technological innovation.

The identification of digital robotic surgery as one of IEO hospital strategic priorities, that has recently led to the opening of IEO3 –equipped with four state-of-the-art digital robotic surgery rooms–, IEO is ready to pioneer digital surgery as it did with robotic surgery 20 years ago, navigating this highly competitive field and pursuing that excellence allowing to offer to its patients the best available care.

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), revision by Stefania Averaimo)

review/commentary

Early-Onset Colorectal Cancer: From Risk Factors to Prevention. Early-onset colorectal cancer (EOCRC) is increasing worldwide, yet its causes remain incompletely understood. Beyond obesity, metabolic disorders, poor diet and sedentary behaviour, growing evidence implicates early-life exposures and gut microbiota. This Roadmap highlights gaps in identifying causal risk factors and understanding how and when they act, alone or together. It proposes a transdisciplinary framework integrating population, mechanistic, behavioural and implementation sciences to accelerate discovery and translate findings into effective prevention. Patient perspectives, public engagement and initiatives such as Cancer Grand Challenges PROSPECT are emphasized as essential to reversing the rising EOCRC burden.
Tian R, Azadnajafabad S, Waters EA, Balskus EP, Belkaid Y, Bell JT, Berry SE, Buenrostro JD, Huttenhower C, Patel A, Patti JG, Segata N, Sirohi B, Spector TD, Yilmaz OH, Chan AT, Cao Y. Nat Rev Cancer 2026. PMID 42649278

observational study

Microbiome-based colorectal cancer screening shows high patient acceptance and compliance. This preliminary multicenter Italian study assessed the feasibility of adding stool microbiome sampling to organized colorectal cancer screening in FIT-positive individuals. Of 315 screened participants, 212 were enrolled, with 90% of eligible patients accepting participation and 94% completing required procedures. Colonoscopy identified colorectal cancer in 3% and advanced adenomas in 18%. The findings support the practical integration of microbiome-based research into established screening programs, while diagnostic validation remains ongoing.
Severino A, Rondinella D, Varca S, Schepis T, Porcari S, Bisegna P, Margarita E, Barbaro F, Pecere S, Maresca R, Feliciani D, Funaro B, Latiano A, Palmieri O, Azzarone A, Cesaro P, Salvi D, Treppiccione C, Piccinno G, Segata N, Spada C, Gasbarrini A, Ianiro G. Microorganisms. PMID 42514069.

(image generated by ChatGPT)

review/commentary

Robotic lung surgery after neoadjuvant chemo-immunotherapy for resectable non-small cell lung cancer (NSCLC). Neoadjuvant and perioperative chemo-immunotherapy have improved pathological response and survival in resectable NSCLC but may complicate surgery through fibrosis, nodal scarring and altered tissue planes. This review indicates that robotic-assisted thoracic surgery (RATS) can be feasible and safe in selected patients at experienced centers, offering visualization and dexterity advantages. Vascular and lymph-node dissection require

particular care, and conversion to open surgery should be considered an appropriate safety measure. Prospective studies are needed before RATS can be established as a preferred approach.
Casiraghi M, Mazzella A, Girelli L, Lo Iacono G, Bertolaccini L, Chiari M, Caffarena G, Bardoni C, Spaggiari L. Cancers. PMID 42512424.

mechanism-oriented research

IL-1β–CXCL12 crosstalk links adipocytes and pancreatic neuroendocrine tumor cells. This experimental study explored interactions between adipocytes and pancreatic neuroendocrine tumor (PanNET) cells. Tumor-derived IL-1β reprogrammed adipocytes toward a cancer-associated phenotype, increasing CXCL12 secretion, which in turn promoted tumor-cell proliferation and further IL-1β release. Pharmacological blockade with the CXCR4 antagonist AMD3100 or the IL-1β pathway inhibitor canakinumab disrupted this reciprocal signaling, reduced adipocyte reprogramming and suppressed tumor-cell proliferation. The IL-1β–CXCL12 axis may therefore represent a therapeutic target in PanNETs.
Oldani M, Grassi ES, Gaudenzi G, Rybinska I, Carra S, Massardi E, Fazio N, Caraglia M, Persani L, Vitale G. Journal of Translational Medicine. PMID 42316277.

review/commentary

Retreatment strategies in neuroendocrine tumors. Retreatment and reintroduction of systemic therapies may offer meaningful clinical activity in neuroendocrine tumors, but evidence defining which patients benefit most remains limited. This narrative review examines available retreatment approaches and highlights factors potentially useful for treatment selection, including MGMT expression, tumor grade and the duration of the treatment-free interval. The authors emphasize the need for prospective studies incorporating predictive biomarkers and standardized retreatment protocols to determine when rechallenge is biologically justified and clinically beneficial.
Benini L, Ciardiello D, Spada F, Cella CA, Gervaso L, Mulargiu C, Zampino MG, Fazio N. Cancer Treatment Reviews. PMID 42314247.

clinical/computational/research tools

A simple AI-assisted prognostic score for pulmonary neuroendocrine tumors. This study developed and internally validated the NET score to estimate mortality risk after resection of pulmonary carcinoids. Using AI-assisted variable selection, the model incorporated nodal status, mitotic index, necrosis and Ki-67 into an interpretable 0–8 point score. It achieved moderate discrimination and separated patients into low-, intermediate- and high-risk groups with progressively poorer survival. The tool could facilitate risk communication and clinical decision-making using routine pathological information, although external validation is required before broader clinical implementation.
Bertolaccini L, Spada F, Benini L, Pisa E, Lobrano R, Caffarena G, Guarize J, Casiraghi M, Fusco N, Spaggiari L, Fazio N. Endocrine-Related Cancer. PMID 42301921.

prospective clinical trial

Alomfilimab targeting ICOS in advanced solid tumors. This phase 1 study evaluated the anti-ICOS antibody alomfilimab, alone or combined with atezolizumab, in patients with advanced solid tumors. Treatment showed a manageable safety profile and biological activity, including reduced ICOS-positive regulatory T cells and enhanced effector T-cell activity. No objective responses occurred with monotherapy, while seven patients responded to combination treatment. Despite evidence of target engagement and immune modulation, overall clinical activity was limited, indicating that further work is needed to identify responsive populations.
Naing A, Lin CC, Patel MR, Curigliano G, Burris HA, Thistlethwaite F, De Braud F, Minchom A, Ascierto PA, Wake M, Nguyen MA, Abbadessa G, Sainson RCA, Palu CC, Quaratino S, Deantonio C. Journal for ImmunoTherapy of Cancer. PMID 42259602.

review/commentary

Oral SERDs reshape endocrine treatment of HR-positive, HER2-negative breast cancer. Resistance to endocrine therapy, particularly through acquired ESR1 mutations, remains a major challenge in HR+/HER2− breast cancer. This review examines oral selective estrogen receptor degraders (SERDs) designed to provide more potent estrogen-receptor targeting. Agents such as elacestrant and imlunestrant are emerging as second-line options for ESR1-mutant disease, while studies are also evaluating their role in earlier settings. Because resistance to SERD monotherapy remains common, future strategies are expected to emphasize rational combinations, ctDNA-guided treatment selection and expansion into early-stage disease.
Etessami JD, Valenza C, Berton Giachetti PPM, Crimini E, Ferraro E, Marra A, Belli C, Minchella I, Zagami P, Curigliano G, Trapani D. Expert Opinion on Pharmacotherapy. PMID 42169538.

correlative/descriptive studies

Microbiome transmission differs between the mouth and gut. Analysis of 1,644 paired oral and fecal metagenomes showed that people living together share more microbial strains than non-cohabitants, with romantic partners displaying particularly high oral strain sharing. Oral microbes showed greater transmissibility and strain replacement, whereas highly transmissible gut species were associated with poorer cardiometabolic health. Within individuals, most species present in both oral and gut samples represented identical strains. The findings clarify how interpersonal and within-body microbial transmission varies across anatomical sites.
Heidrich V, Fackelmann G, Ricci L, Spadazzi R, Baldanzi G, Punčochář M, Catassi G, Marchi P, Modesto M, Piccinno G, Porcari S, Rondinella D, Asnicar F, Valles-Colomer M, Mattarelli P, Ianiro G, Segata N. Cell Press Blue. PMID 42312244.

mechanism-oriented research

HSPB8 and BAG3 regulate breast cancer behavior through FAK signaling. This study investigated how HSPB8 and BAG3, proteins involved in chaperone-assisted selective autophagy, influence the metastatic potential of hormone-sensitive breast cancer cells. Silencing either protein reduced active phosphorylated FAK and consequently decreased proliferation, migration and adhesion. BAG3 was also shown to co-localize and associate with FAK, including in breast cancer tissue. The findings suggest that the HSPB8–BAG3 system modulates FAK-dependent signaling involved in survival and metastatic properties of ER+/PR+/HER2− breast cancer cells.
Piccolella M, Tedesco B, Ferrari V, Filippone MG, Tucci FA, Pandolfi A, Casarotto E, Cozzi M, Chierichetti M, Pramaggiore P, Cornaggia L, Milioto C, Magdalena R, Mohamed A, Brodnanova M, Koshal P, Rusmini P, Galbiati M, Tosoni D, Pece S, Cristofani R, Crippa V, Poletti A. Cell Communication and Signaling. PMID 41664196.

mechanism-oriented research

DDERMMAL promotes melanoma persistence through DNA damage response signaling. Resistance to targeted and immune therapies can arise through genetic and non-genetic mechanisms that allow melanoma cells to survive therapeutic pressure. This study identifies the long non-coding RNA DDERMMAL as a regulator of DNA damage response signaling. DDERMMAL enables melanoma cells to tolerate genetic insults while continuing to proliferate, providing a potential mechanism for lineage-specific persistence during treatment. This survival capacity may facilitate the subsequent acquisition of new mutations and the emergence of genetically resistant clones, linking drug tolerance with eventual relapse.
Adnane S, Verheyden Y, Cuomo A, Bonaldi T, Leucci E. iScience. PMID 42291223.

new targets and treatments - preclinical evaluation

Covalent PFKFB3 inhibition as a new strategy in pancreatic cancer. Pancreatic ductal adenocarcinoma relies heavily on metabolic reprogramming, making glycolysis an attractive therapeutic target. Researchers developed compound 6, a first-in-class covalent inhibitor targeting a previously unexplored cysteine in PFKFB3. The compound selectively bound the enzyme, reduced viability across several PDAC cell lines, inhibited tumor growth in zebrafish xenografts and showed synergy with standard chemotherapy. Although its cellular activity remains limited, the study establishes this PFKFB3 cysteine as a druggable site and provides a foundation for developing improved inhibitors.
Fiore A, Scarano A, Antonini G, Corfù AI, Sicuro L, Faggiano S, Celesia A, Tesoriero C, Pacchiana R, Vettori A, Arslanbaeva L, Minucci S, Pallavicini I, Mollica L, Tamborini L, Donadelli M, Conti P, Bruno S, Borsari C. Journal of Medicinal Chemistry. PMID 42186262.

clinical/computational/research tools

EAGLE enables faster and more efficient AI-based digital pathology. Current AI pathology systems analyze thousands of often redundant image tiles, creating substantial computational demands. EAGLE is a deep-learning framework designed to mimic pathologists by selectively examining the most informative regions of whole-slide images. Across 43 tasks and nine cancer types, it achieved superior overall classification performance. EAGLE processed a slide in only 2.27 seconds, reducing computation time by more than 99%.
Neidlinger P, Lenz T, Foersch S, Loeffler CML, Clusmann J, Gustav M, Shaktah LA, Langer R, Dislich B, Boardman LA, French AJ, Goode EL, Gsur A, Brezina S, Gunter MJ, Steinfelder R, Behrens HM, Röcken C, Harrison T, Peters U, Phipps AI, Curigliano G, Fusco N, Marra A, Hoffmeister M, Brenner H, Kather JN. Nature Communications. PMID 42386722.

review/commentary

Real-world evidence supports tucatinib in HER2-positive metastatic breast cancer. This systematic review evaluated real-world studies of tucatinib-based treatment for HER2-positive metastatic breast cancer. Despite variability, real-world effectiveness was broadly consistent with clinical trial results, including among heavily pretreated patients, those previously exposed to trastuzumab deruxtecan and patients with brain metastases. The findings reinforce tucatinib's effectiveness in routine practice, although additional evidence is needed regarding safety, quality of life and patient-reported outcomes.

Sanchez-Bayona R, Anders C, Bartsch R, Cameron DA, Ciruelos EM, Criscitiello C, Duhoux FP, Foukakis T, Frenel JS, Gligorov J, Kaufman PA, Lambertini M, LeVasseur N, Okines A, Penault-Llorca F, Müller V, Blahna MT, Neuberger E, Simon S, Zanucco E, Rosé C, Curigliano G, Harbeck N. Breast. PMID 42372579.

review/commentary

Systemic therapies are reshaping treatment of breast cancer brain metastases. Brain metastases remain a major clinical challenge in breast cancer, but systemic treatment options are rapidly expanding. This review examines therapies across molecular subtypes. Targeted and endocrine approaches are emerging for HR+/HER2− disease, while tucatinib combinations and trastuzumab deruxtecan have substantially improved intracranial outcomes in HER2-positive disease. ADCs, immunotherapy and PARP inhibitors are being investigated in triple-negative disease. Greater inclusion of patients with brain metastases in clinical trials is essential to accelerate development of effective CNS-active therapies.

Etessami JD, Dalla Via G, Ferraro E, Trapani D, Curigliano G, Marra A. Cancer Treatment Reviews. PMID 42372577.

review/commentary

Risk-reducing mastectomy among women carrying PALB2 variants. Germline PALB2 variants confer a moderate-to-high breast cancer risk, but evidence regarding prophylactic surgery remains limited. This systematic review identified 10 relevant studies, all conducted in North America. The findings highlight substantial use of preventive surgery despite a limited evidence base.

Corso G, La Vecchia C, Polizzi A, Magnoni F, Abruzzese G, Di Silvestre S, Pesapane F, Nicosia L, Bogani G, Intra M, Veronesi P, Galimberti V. Familial Cancer. PMID 41984324.

mechanism-oriented research

Targeting telomeric DNA damage may reverse age-related hematopoietic decline. Telomere dysfunction contributes to cellular senescence, inflammation and impaired blood cell production during aging. In telomerase-deficient mice, telomeric antisense oligonucleotides targeting noncoding RNAs suppressed the telomeric DNA damage response, reduced inflammation and senescence, and improved hematopoietic stem cell fitness and repopulation. Similar benefits occurred in aged wild-type mice, while ex vivo treatment improved stem cell function in samples from older human donors. These findings identify telomeric DNA damage signaling as a driver of hematopoietic aging and suggest a potential therapeutic strategy for aging and telomere disorders.

Oppezzo A, Sepe S, Cicio G, Cancila V, Sasso E, Conti A, Marinelli E, Cabrini M, Pallavi R, Iacomino N, Simoni M, Malyshev D, Boggio S, di Lillo A, Rosso I, Tavella S, Trastus LA, Rossiello F, Roscia G, Cantaloni P, Manenti A, Cavalcante P, Pelicci PG, Di Micco R, Nicosia A, Tripodo C, d'Adda di Fagagna F. Nature Aging. PMID 42380622.

correlative/descriptive studies

Different resistant starches produce distinct changes in the gut microbiome. Using shotgun metagenomics from a randomized dietary trial, researchers compared microbiome responses to resistant starch types RS2 and RS4. Both caused distinct but temporary microbial changes: RS2 enriched Ruminococcus bromii and Blautia glucerasea, whereas RS4 favored Parabacteroides distasonis and other species. Resistant starch intake also increased microbial genes involved in complex carbohydrate utilization, with strain-specific responses observed in Bifidobacterium adolescentis. Understanding these species- and strain-level differences could help predict individual responses and enable microbiome-informed personalization of resistant-starch interventions.

Piperni E, Blanco-Míguez A, Mengoni C, Piccinno G, Punčochář M, Ren J, Segata N, Asnicar F, Poole AC. Microbiology Spectrum. PMID 42496113.

mechanism-oriented research

SREBP1c links lipid metabolism to regulatory T-cell immune suppression. Regulatory T (Treg) cells depend on specialized metabolic pathways to maintain their immunosuppressive activity. This study identifies SREBP1c as a central regulator of Treg function. Loss of Srebp1c shifted Tregs toward glycolysis, disrupted phospholipid remodeling and reduced CD73 expression and extracellular adenosine production, weakening immune suppression. These effects were linked to increased cPLA2α activity. Pharmacological inhibition of cPLA2α restored lipid homeostasis, adenosine signaling and Treg suppressive capacity. The findings establish SREBP1c as an immunometabolic checkpoint connecting phospholipid metabolism with adenosine-mediated immune regulation.

Bonacina F, Procaccini C, Iaia M, Moretti A, Svecla M, Pedretti S, Bogie JF, Vingiani GB, Moregola A, Genova F, Russo C, De Rosa G, La Rocca C, Mondanelli G, Gargaro M, Mitro N, Matarese G, Norata GD. The Journal of Clinical Investigation. PMID 42479459.

mechanism-oriented research

ACLY connects metabolism with cardiovascular, liver and cancer biology. ATP-citrate lyase (ACLY) generates cytosolic acetyl-CoA, supporting lipid synthesis, protein acetylation and transcriptional regulation. Its inhibition is clinically validated in cardiovascular disease through bempedoic acid, which lowers LDL cholesterol and improves

cardiovascular outcomes. Preclinical evidence also suggests potential benefits in metabolic dysfunction-associated steatotic liver disease, although robust clinical evidence is lacking. Nuclear ACLY additionally links metabolism with chromatin regulation and immune responses, while dysregulated ACLY contributes to tumor growth, metabolic adaptability, treatment resistance and immune evasion, making it an emerging therapeutic target in oncology.
Macchi C, Pedretti S, Ghisletti S, Corsini A, Mitro N, Sirtori CR, Ruscica M. Pharmacological Research. PMID 42476347.

review/commentary

The gut microbiome as a potential regulator of neuroinflammation. The gut microbiome may influence brain health through immune regulation, microbial metabolites, gut and blood-brain barrier integrity, vagal signaling, lymphocyte migration, bile acids and endocrine pathways. Altered microbiota have been reported in demyelinating diseases, autoimmune encephalitis and epilepsy and may affect disease progression and treatment response. However, clinical evidence remains largely correlative, and methodological challenges complicate translation. The ketogenic diet is currently the only routinely recommended microbiome-related intervention, while dietary modification, prebiotics, probiotics, postbiotics and fecal microbiota transplantation remain promising but investigational strategies.
Steriade C, Segata N, Saxena D. The Lancet Neurology. PMID 42456685.

prospective clinical study

A 30+ plant-food blend modifies the gut microbiome and improves gastrointestinal symptoms. In the six-week BIOME randomized trial, adults with low fiber intake received a blend containing more than 30 plant ingredients, a control food or a probiotic. The plant blend produced substantially more changes in gut microbial species than either comparator, although microbiome health rankings did not differ significantly between groups. In a sub-study, the blend increased fullness and reduced hunger without altering post-meal glucose, supporting diverse plant intake as a practical microbiome-modulating strategy.
Creedon AC, Bernard HM, Amati F, Segata N, Wallace SM, Arrè A, Smith HA, Platts A, Bulsiewicz WJ, Bermingham KM, Capdevila J, Piperni E, Roomans Ledo A, Johnson C, Caro C, Karimjee N, Linenberg I, Giordano F, Davies R, Kim C, Wolf J, Asnicar F, Spector TD, Berry SE. The British Journal of Nutrition. PMID 42423005.

clinical/computational/research tools

Quantitative imaging reveals PML-RARα-induced DNA damage during replication. PML-RARα, the oncogene responsible for acute promyelocytic leukemia, disrupts genome stability and DNA repair. Researchers developed a single-cell imaging method combining EdU-based cell-cycle analysis, γH2A.X labeling and image cross-correlation spectroscopy to examine DNA damage relative to replication sites. PML-RARα expression increased DNA damage, particularly in actively replicating cells, and shifted the spatial association between damage and replication toward earlier DNA-synthesis stages. The method provides a quantitative approach for investigating oncogene-induced replication stress and genome instability throughout the cell cycle.
Scalisi S, Paternò G, Dellino GI, Faretta M, Pelicci PG, Diaspro A, Lanzanò L. Methods. PMID 42409088.

clinical/computational/research tools

At least 26 lymph nodes may improve staging accuracy in gastric cancer. This study externally validated AI-driven models predicting occult nodal disease when fewer than 26 nodes are examined. Data from 601 patients across two comparable cohorts were analyzed (using regression, Random Forest and simulation approaches). Increasing lymph-node yield was predicted to identify 16-21% more metastatic nodes, suggesting clinically meaningful under-staging with limited lymphadenectomy. The findings reinforce retrieval of at least 26 lymph nodes during gastrectomy to improve pathological staging and prognostic assessment.
Santos LL, Finamore AC, Gisbertz S, Romario UF, Kielan W, Rosati R, Kołodziejczyk P, Wijnhoven B, Gockel I, Giacopuzzi S, Polkowski WP, Davies A, Morgagni P, Hoelscher A, Allum W, D'ugo D, Hartgrink H, Bencivenga M, Viganò J, Pera M, Reim D, Schneider PM, Mönig S, De Manzoni G, Baiocchi GL, Antunes C, Matos da Costa P, GASTRODATA Consortium. European Journal of Surgical Oncology. PMID 42341441.

review/commentary

Locoregional treatment may extend systemic therapy in oligoprogressive gynecologic cancers. Modern systemic treatments have improved outcomes in gynecologic malignancies; however, some patients develop progression at only a few metastatic sites while in others disease remains controlled. This review examines the use of stereotactic radiotherapy, minimally invasive surgery or image-guided ablation to eliminate resistant lesions while continuing effective systemic therapy. Retrospective evidence, particularly in ovarian cancer treated with PARP inhibitors, suggests this approach may delay subsequent systemic treatment and preserve quality of life. However, optimal patient selection, sequencing and survival impact remain uncertain and require prospective trials.

Casaccia Giordano F, Lazzari R, Macchia G, Durante S, Marchetti C, Fagotti A, Ray-Coquard I, Jereczek-Fossa BA, Colombo N, Caruso G. European Journal of Cancer. PMID 42335568.

retrospective clinical study

Transoral robotic surgery (TORS) offers a less invasive approach to parapharyngeal lesions. This retrospective study evaluated 43 patients undergoing transoral robotic surgery for parapharyngeal-space lesions. The findings indicate that TORS is a viable option for selected parapharyngeal lesions and can be incorporated into a combined surgical strategy to achieve adequate access while potentially reducing surgical morbidity.
Pietrobon G, Filippo Zorzi S, Bandi F, Chu F, Mossinelli C, Ruju F, Giugliano G, Ansarin M. Acta Otorhinolaryngologica Italica. PMID 42325176.

psychoncology studies

Psychological impact of BRCA1/2 genetic risk information. Learning to be carrier of a pathogenic BRCA1/2 variant can influence emotions, behavior, relationships and future decisions. This qualitative study interviewed nine Italian women who had received BRCA1/2 risk information. Thematic analysis identified substantial changes in personal and social life, reflecting the complex psychological consequences of living with increased hereditary cancer risk. The findings emphasize the importance of addressing emotional and behavioral challenges following genetic testing and suggest that tailored psychological support and improved physician-patient communication may help women adapt to their risk status.
Durosini I, Ongaro G, Oliveri S, Sebri V, Pravettoni G. BMC Psychology. PMID 41318513.

psychoncology studies

Cognitive impairment can precede cancer treatment in patients with NSCLC. This exploratory study assessed cognitive impairment in 50 patients with non-small cell lung cancer before starting oncological therapy. The findings indicate that cancer-related cognitive vulnerability may exist before treatment and support early cognitive and psychosocial screening to identify patients who may benefit from multidisciplinary supportive interventions.
Capetti B, Conti L, Luisi J, Sdinami S, Marzorati C, Grasso R, Frassoni S, Bagnardi V, Chiari M, Casiraghi M, Pravettoni G. IBRO Neuroscience Reports. PMID 42499996.

translational research - signatures/biomarkers/liquid biopsy

ER, PgR and HER2 expression predict outcomes with CDK4/6 inhibitors in metastatic breast cancer. The multicenter CYCLHER study evaluated 597 patients with HR+/HER2− metastatic breast cancer receiving first-line endocrine therapy plus a CDK4/6 inhibitor. Combining the three biomarkers generated four prognostic groups with significantly different progression-free survival. These routinely measured markers may therefore improve risk stratification and help personalize management in patients receiving CDK4/6 inhibitors.
Pontolillo L, Munzone E, Vigneri P, Pistelli M, Palazzo A, La Verde N, Mazzotta M, Paris I, Alesini D, Santini D, Cannita K, Orlandi A, Magnolfi E, Giacinti L, Raffaele M, Carbognin L, Santoro A, Rossi A, Arcuri G, Sangalli C, Garrone O, Mulè A, Valenza C, Berardi R, Tortora G, Bria E, Curigliano G, Giannarelli D, Fabi A. Breast. PMID 42214155.

prospective clinical trial

Circulating tumor DNA may identify thrombotic risk in locally advanced rectal cancer. This prospective study explored whether baseline ctDNA levels predict venous thromboembolism (VTE) in 61 patients with locally advanced rectal cancer undergoing chemoradiation. Patients with higher ctDNA levels showed a trend toward increased VTE incidence, while among patients with KRAS-mutant tumors, every VTE occurred in those with high baseline variant allele frequency. Although the overall associations were exploratory and not statistically conclusive, the findings suggest that ctDNA-derived tumor burden could potentially contribute to thrombotic risk assessment, particularly in KRAS-mutant disease.
Gervaso L, Ciardiello D, Frassoni S, Bagnardi V, Gregato G, Cella CA, Benini L, Tamayo D, Spada F, Bertolini F, Fazio N, Zampino MG. Cancer Treatment and Research Communications. PMID 42468056.

review/commentary

Circulating tumor DNA as a biomarker in early breast cancer. ctDNA offers a minimally invasive means of assessing tumor burden, biological aggressiveness and residual disease in early breast cancer. Baseline levels may aid prognostic stratification, while detection after treatment can reveal minimal residual disease months or even years before clinical recurrence. However, routine implementation in early breast cancer remains limited by low and heterogeneous DNA shedding, specimen-handling issues and assay variability. This review examines these barriers alongside applications in neoadjuvant response assessment, postoperative surveillance and molecular monitoring, and discusses emerging ctDNA-guided therapeutic interventions and multimodal cell-free DNA approaches.

Di Cosimo S, Appierto V, Reduzzi C, De Cecco L, Valenza C, Gerratana L, Agostinetto E, Llombart-Cussac A, Ignatiadis M, Cortes J, Cristofanilli M, Fusco N, Curigliano G, Pruneri G. Cancer. PMID 42421646.

correlative/descriptive studies

Access to guideline-recommended early breast cancer care remains unequal across Europe. The PORTRAIT study surveyed expert breast centers in 39 European countries to assess availability and reimbursement of services for the early breast cancer treatment. Basic diagnostics were widely accessible, but important gaps affected advanced imaging, genomic assays, PARP and CDK4/6 inhibitors, reconstructive surgery and supportive care. Psycho-oncology and fertility preservation were limited in many countries, while patient-reported outcome measures were often unavailable. The findings highlight priorities for improving reimbursement policies and equitable access to comprehensive breast cancer care.
Bonci EA, Di Micco R, Marotti L, Miraldo M, Rubio IT, Curigliano G, Cardoso MJ, PORTRAIT Study Group. Breast. PMID 42447838.

psychoncology studies

Psychological factors and spinal cord stimulation outcomes in cancer survivors with chronic pain. This prospective study protocol investigates whether psychological characteristics influence outcomes of spinal cord stimulation in cancer survivors with persistent pain refractory to conventional therapies. Participants will undergo repeated assessments of pain, anxiety, depression, catastrophizing, resilience and perceived improvement before and after intervention. Researchers will examine associations between these factors, pain reduction and requests for device removal, while also assessing treatment acceptability and satisfaction. The study may help identify psychological predictors of successful spinal cord stimulation and improve patient selection and supportive care.
Marzorati C, Pezzolato M, Didier F, Borgogni F, Fodor CI, Meneghin S, Guardamagna VA, Pravettoni G. PLOS ONE. PMID 42447077.

review/commentary

Toward precision prediction of cancer-associated thrombosis in gastrointestinal (GI) cancers. Cancer-associated thrombosis is a major complication of gastrointestinal malignancies, with risk varying substantially by tumor site, disease stage, inflammation and systemic treatment. Current prediction tools such as the Khorana score have limited accuracy in GI cancers and inadequately capture tumor biology and treatment-related risks. This review examines thrombosis mechanisms, prevention and anticoagulation strategies while highlighting emerging biomarkers, molecular profiling and ctDNA-based assessment. Integrating dynamic biomarkers, tumor characteristics and treatment-specific cardiovascular risks could enable more individualized thrombosis prevention and management.
Gervaso L, Cioli E, Rosanu NM, Cella CA, Khorana AA, Fazio N. Cancer Treatment Reviews. PMID 42443040.

observational study

Homologous recombination deficiency (HRD) testing should preferably precede neoadjuvant chemotherapy in ovarian cancer. This study compared genomic and functional HRD testing in matched high-grade serous ovarian carcinoma samples obtained before and after neoadjuvant chemotherapy. Genomic HRD results showed substantial concordance between time points, but testing was more informative in pretreatment specimens. Some tumors lost genomic instability positivity after chemotherapy, although BRCA mutations preserved overall HRD classification. Functional RAD51-based testing showed poorer concordance. The findings support collecting tissue for genomic HRD testing before chemotherapy to minimize non-informative results and avoid potentially missing eligibility for PARP inhibitor therapy.
Betella I, Fumagalli D, Rappa A, Sala I, Caruso G, Derio S, Multinu F, Ribero L, Pessina S, Ranghiero A, Zanetti C, Spano G, Bagnardi V, Rocco EG, Barberis M, Colombo N. International Journal of Gynecological Cancer. PMID 42418892.

prospective clinical trial

Germline pathogenic variants identify higher-risk invasive lobular breast cancer. This prospective study evaluated germline variants in 414 women with invasive lobular carcinoma using a 113-gene panel. Pathogenic variants were identified in 11.1%, including 4.8% carrying variants in moderate- or high-risk breast cancer genes. These women experienced substantially poorer five-year breast cancer-free survival than the remaining cohort, with an approximately fourfold higher risk of an adverse breast cancer event. Polygenic risk scores were not associated with relapse or germline variant status. Multigene testing may therefore improve genetic counseling, surveillance and therapeutic decision-making in invasive lobular carcinoma.
Corso G, Marino E, Fava F, Natali F, Peterlongo P, Dal Molin M, Feroce I, Zanzottera C, Massari G, Di Silvestre S, Moscatiello M, Franceschini A, Bagnardi V, Curigliano G, Bonanni B, Veronesi P, Bertolini F. JAMA Network Open. PMID 42418202.

mechanism-oriented research

PML drives immune evasion in triple-negative breast cancer. This study identifies promyelocytic leukemia protein (PML) as a key regulator of immune escape in triple-negative breast cancer (TNBC). PML sustains inflammatory signaling, increases expression of immunosuppressive genes such as PD-L1, and suppresses antigen presentation through DNMT1-mediated methylation of HLA genes. PML silencing reshaped the tumor microenvironment, enhanced T-cell infiltration, and improved tumor recognition, supporting PML as a potential therapeutic target to enhance immunotherapy efficacy.
Uggè M, Fracassi C, Tascini AS, Giansanti V, Genova F, Dugo M, Giannese F, Basso V, Ghirardi C, Smart CE, Doglioni C, Casorati G, Dellabona P, Zambelli S, Servitja Tormo S, Cruz Jurado J, Gianni L, Bonaldi T, Agresti A, Mondino A, Bianchini G, Bernardi R. Cell Death and Differentiation. PMID: 42271069.

observational study

Comparison of open, video- and robot- assisted lung cancer surgery. In a multicenter cohort of 1,605 patients with early-stage non-small cell lung cancer (NSCLC), open surgery, video-assisted surgery, and robot-assisted surgery (RATS) were compared. While early mortality and patient re-admission were comparable among the three surgical approaches, RAT was associated with shorter hospitalization as compared to VATS, and better survival as compared to open surgery.
Mazzali C, Buzzoni C, Grignani F, Incarbone MA, Marulli G, Nosotti M, Pariscenti GL, Pastorino U, Spaggiari L, Veronesi G, Russo AG, THOR-ATS (Thoracic Health Outcomes Research) Group. Journal of Robotic Surgery. PMID: 42237053.

retrospective clinical study

Stereotactic body radiotherapy for metastasis-directed treatment. This retrospective analysis of 26 patients showed that stereotactic body radiotherapy provided excellent local control and significantly delayed the need for systemic treatment in recurrent granulosa cell tumors. Five-year local control exceeded 90%, toxicity was minimal, and no deaths occurred during follow-up. Results support SBRT as an effective metastasis-directed treatment within multidisciplinary care.
Haznedar T, Durante S, Lazzari R, Corrao G, Clobiaco S, Caruso G, Colombo N, Jereczek-Fossa BA. Gynecol Oncol 2026. PMID: 42235137.

review/commentary

Global implementation of tumor-agnostic therapies. This review examines worldwide access to tumor-agnostic cancer drugs approved on the basis of molecular biomarkers rather than tumor origin. Despite scientific advances, major barriers remain, including limited testing infrastructure, reimbursement challenges, regulatory fragmentation, and workforce shortages. The authors propose a four-pillar framework to improve equitable implementation and patient access globally.
Liu J, Beal J, Coleman N, Ma BBY, Loong HH, Zhao H, Seymour L, Westphalen CB, Curigliano G, Subbiah V. Journal of Clinical Oncology. PMID: 42224642.

clinical/computational/research tools

Dual-reporter imaging reveals mRNA vaccine immune dynamics. Using novel STAT6 and NF-κB reporter mice, investigators mapped whole-body immune responses induced by mRNA vaccines. RNA chemistry influenced immune activation patterns, while the liver emerged as a major signaling hub. Early STAT6 activation followed by rapid resolution correlated with stronger antibody responses, providing a tool for mechanistic vaccine evaluation and optimization.
Brunialti E, Panzeri A, Rizzi N, Villa A, Meda C, Sfogliarini C, Persano S, Arlati F, Guevara Lopez ML, Martelli C, Cannavale G, Rebecchi M, Di Vito C, Venturini L, Ottobrini L, Mavilio D, Fagerholm S, Minucci S, Vegeto E, Ciana P. Molecular Therapy. PMID: 42231579.

retrospective clinical study

Biomarker-based prognostic stratification in metastatic breast cancer. The CYCLHER study evaluated ER, PgR, and HER2 expression in HR+/HER2− metastatic breast cancer treated with CDK4/6 inhibitors. Higher ER and PgR levels predicted better outcomes, whereas HER2-low disease was associated with poorer prognosis. A composite biomarker score identified patient groups with significantly different progression-free survival, supporting more personalized treatment strategies.

Pontolillo L, Munzone E, Vigneri P, Pistelli M, Palazzo A, La Verde N, Mazzotta M, Paris I, Alesini D, Santini D, Cannita K, Orlandi A, Magnolfi E, Giacinti L, Raffaele M, Carbognin L, Santoro A, Rossi A, Arcuri G, Sangalli C, Garrone O, Mulè A, Valenza C, Berardi R, Tortora G, Bria E, Curigliano G, Giannarelli D, Fabi A. Breast. PMID: 42214155.

observational study

Explainable AI reduces bias in mammography interpretation. In a reader study, explainable AI heatmaps significantly reduced automation and anchoring biases compared with standard AI support alone. Diagnostic accuracy improved modestly compared with standard AI, suggesting that explainable AI may enhance safety and reliability in AI-assisted breast imaging.
Pesapane F, Latronico A, Abbate F, Penco S, Rotili A, Dominelli V, Nicosia L, Monzani D, Grasso R, Pravettoni G, Cassano E. European Radiology. PMID: 42213113.

review/commentary

MGMT protein as predictor of alkylating chemotherapy response in NETs. This systematic review of 23 studies involving neuroendocrine tumors found that O6-Methylguanine DNA Methyltransferase (MGMT)-deficient tumors generally achieved higher response rates and longer progression-free survival with temozolomide and related alkylating agents. However, methodological heterogeneity limits clinical implementation, and routine MGMT testing cannot yet be recommended in practice.
Maratta MG, Bagnardi V, Fazio N. Critical Reviews in Oncology/Hematology. PMID: 42202922.

retrospective clinical study

Outcomes of germline BRCA-associated breast cancer. Two retrospective studies compared HER2-negative breast cancers in gBRCA1/2 mutation carriers and non-carriers. Mutation carriers showed a trend toward improved survival outcomes despite similar clinicopathologic characteristics. Findings suggest that germline BRCA status alone should not justify more aggressive treatment and support further prospective investigation.
Morganti S, Kim SE, Jin Q, Cha J, Zeigler JE, Newman AB, Kirkner GJ, Snow C, Zheng Y, Vincuilla J, Parker T, Buehler RM, Bychkovsky BL, Dibble KE, Sella T, Ruddy KJ, Rosenberg SM, Collins LC, Peppercorn J, Schapira L, Borges VF, Guzman-Arocho YD, Come SE, Warner E, Poorvu PD, Lambertini M, Curigliano G, Hughes ME, Mittendorf EA, King TA, Lin NU, Garber JE, Tayob N, Tolaney SM, Partridge AH, Lynce F. JNCI Cancer Spectrum. PMID: 42185079.

review/commentary

Precision medicine and social determinants of health. The authors explore the implications of the adoption of precision medicine approaches for public health and society.
Ilaria Galasso, Martyn Pickersgill, Giuseppe Testa. Soc Sci Med 2026. PMID: 42215252.

correlative/descriptive studies

Microbiome and metabolome changes along the adenoma-cancer continuum. Stool analyses from women years after adenoma resection revealed microbial and metabolic alterations resembling those seen in colorectal cancer. Several bacteria and metabolites were consistently associated with adenomas, suggesting that persistent microbiome dysregulation may contribute to colorectal carcinogenesis and could aid risk assessment.
Nogal A, Wang K, Thompson KN, Kim H, Bhosle A, Piccinno G, Maharjan S, Upreti C, Nguyen LH, Segata N, Rimm EB, Garrett WS, Chan AT, Huttenhower C, Song M. Cell Host & Microbe. PMID: 42202778.

new targets and treatments - preclinical evaluation

First covalent inhibitor targeting PFKFB3 in pancreatic cancer. Researchers developed a first-in-class covalent inhibitor of PFKFB3 that selectively binds a previously unexplored cysteine residue. The compound reduced pancreatic cancer cell viability, inhibited tumor growth in zebrafish models, and showed synergy with chemotherapy. The work establishes a new strategy for targeting cancer metabolism.
Fiore A, Scarano A, Antonini G, Corfù AI, Sicuro L, Faggiano S, Celesia A, Tesoriero C, Pacchiana R, Vettori A, Arslanbaeva L, Minucci S, Pallavicini I, Mollica L, Tamborini L, Donadelli M, Conti P, Bruno S, Borsari C. Journal of Medicinal Chemistry. PMID: 42186262.

review/commentary

Factors influencing surgical fitness in ovarian cancer. This review evaluated factors influencing surgical fitness in advanced ovarian cancer. Older age, frailty, comorbidity burden, malnutrition, and sarcopenia were consistently

associated with worse postoperative outcomes. Existing predictive models show promise but require external validation, while prehabilitation programs may improve recovery and treatment delivery.
Ribero L, Fumagalli D, De Vitis LA, Caruso G, Schivardi G, Aletti G, Colombo N, Kumar A, Ramirez PT, Multinu F. International Journal of Gynecological Cancer. PMID: 42167107.

clinical/computational/research tools

Epidemiological risk score for pancreatic cancer detection. A risk score derived from 24 epidemiological factors was validated in high-risk individuals undergoing MRI screening and in the UK Biobank. Higher scores were associated with detection of pancreatic and extra-pancreatic lesions with malignant potential, supporting use of the score as a low-cost tool for pancreatic cancer risk stratification.
Riobó-Mayo L, Salvador L, Teulé A, Guinó E, Layos L, Oliveri S, Cincidda C, Ongaro G, Accornero CA, Cella CA, Gervaso L, Fazio N, Summers PE, Petralia G, Canivet C, Bournet B, Buscail L, Roman A, Balacescu L, Trifa A, Catana A, Pop F, Balacescu O, Przybyłowicz P, Taryma-Lesniak O, Wojdacz TK, Obón-Santacana M, Moreno V. International Journal of Epidemiology. PMID: 42160519.

prospective clinical study

FAPi-PET for staging locally advanced gastric cancer. In a prospective study of 30 patients, FAPi-PET ((fibroblast activation protein inhibitor (FAPI) positron emission tomography (PET)) detected primary gastric tumors with very high sensitivity and demonstrated high specificity for peritoneal disease. Although sensitivity for peritoneal metastases remained limited, findings suggest potential value for staging and treatment planning in locally advanced gastric cancer.
Romario UF, de Pascale S, Sileo A, Cella CA, Farulla LSMA, Bertani E, Fazio N, Gervaso L, Mattana F, Ceci F. Updates in Surgery. PMID: 42154166.

retrospective clinical study

Prognostic impact of margin burden after laryngeal cancer surgery. Analysis of 1,216 patients with glottic laryngeal cancer showed that oncologic outcomes depend on the type and extent of positive margins (in which the tumor reaches the edge of the resected tissue, suggesting the existence of remaining cancer cells). A significant margin involvement (especially when multiple margins were involved) markedly increased recurrence and disease-specific mortality. Post-surgery strategy should be adapted considering these aspects.
Chu F, Marchi F, Sampieri C, Zorzi SF, Tagliabue M, Bellini E, Filauro M, Moro C, Ajasllari G, Xavier-Aviles-Jurado F, Delia Ramírez-Ruiz R, Costa JM, Gros JL, Motta G, Della Peruta V, Tortoriello G, Vilaseca I, Peretti G, Ansarin M. Acta Otorhinolaryngologica Italica. PMID: 42153411.

retrospective clinical study

Age and outcomes after laser microsurgery for laryngeal cancer. In 676 patients with laryngeal squamous cell carcinoma, increasing age strongly affected overall survival but had little impact on cancer-specific mortality. Tumor stage and margin status remained the main determinants of disease-related death, supporting treatment decisions based on tumor characteristics rather than chronological age.
Chu F, Tagliabue M, Zorzi SF, Bandi F, Moglio S, Ruju F, Ansarin M. Head & Neck. PMID: 42151741.

mechanism-oriented research

DDERMMAL - a long non-coding RNA promoting melanoma persistence and resistance. This study identifies the long non-coding RNA DDERMMAL as a regulator of DNA damage response signaling in melanoma. DDERMMAL helps tumor cells tolerate genetic damage while maintaining proliferation, thereby facilitating survival under therapeutic pressure and promoting the emergence of resistance-associated mutations.
Adnane S, Verheyden Y, Cuomo A, Bonaldi T, Leucci E. iScience. PMID: 42291223.

mechanism-oriented research

Evolution of oxygen tolerance in *Segatella copri*. Researchers found that oxygen-response regulators shape the ability of *Segatella copri* to colonize the gut. Some strains acquired OxyR through horizontal gene transfer, increasing oxygen tolerance. These strains are more common in industrialized populations and absent from traditional and ancient human samples, suggesting recent lifestyle-driven microbial evolution.
El Mouali Y, Tawk C, Huang KD, Sivapornnukul P, Mengoni C, Segata N, Strowig T. Cell Host & Microbe. PMID: 42097142.

retrospective clinical study

An effective approach to malignant pleural effusions. Malignant pleural effusion is a frequent complication of advanced stage cancer. Within this retrospective study, the authors found that, for selected patients, single-stage bilateral VATS talc pleurodesis (that is, intrapleural instillation of talc triggering a cascade of biological events, including activation of mesothelial cells, release of pro-inflammatory cytokines, recruitment of macrophages and neutrophils, ultimately leading to fibrosis that prevents further fluid accumulation) appears to be a feasible and safe strategy to treat bilateral malignant pleural effusions. The data support further prospective evaluation.
Mazzella A, Degiovanni S, Mariani E, Cerretani G, Bertolaccini L, Casiraghi M, Sedda G, Lo Iacono G, Spaggiari L. Cancers. PMID: 42279261.

review/commentary

Redefining endocrine therapy suitability in advanced breast cancer. This review discusses the evolving treatment landscape of HR-positive/HER2-negative advanced breast cancer and proposes the concept of "endocrine therapy suitability." Rather than focusing solely on endocrine resistance or sensitivity, the framework integrates biomarkers, clinical features, and expected treatment durability to guide more individualized therapeutic decisions.
Rugo HS, Curigliano G, Cescon DW, Penault-Llorca F, Harbeck N, Im SA, Park YH, Barrios C, Modi S, Tolaney SM, Oliveira M. Breast. PMID: 42263382.

mechanism-oriented research

Origin and composition of cerebrospinal fluid cholesteryl esters. This study demonstrates that cerebrospinal fluid cholesteryl esters are likely generated by LCAT rather than SOAT enzymes, despite a fatty-acid profile resembling SOAT products. Alzheimer's disease patients displayed increased saturated fatty-acid esterification, providing new insights into altered cholesterol metabolism and potential lipid biomarkers in neurodegeneration.
Pavanello C, Ossoli A, Comi C, Turri M, Tremolizzo L, Conti E, D'Incecco P, Barbiroli A, Parini P, Mitro N, Caruso D, Sierri G, Re F, Chinello C, Fumagalli C, Magni F, Fernandes K, Calabresi L. Journal of Lipid Research. PMID: 41936849.

What else is new in science?

(Text by Ai Yi (DeepSeek), revision by Stefania Averaimo)

Artificial tumour evolution reveals genetic control of cancer progression. While controlling for genetics, environment and carcinogen exposure, researchers grew tumours in divergent mouse strains. Epistatic interactions between genetic background and somatic mutations drove cell-subpopulation-specific progression, affecting driver mutations, whole-genome duplication and selection dynamics. Even modest genetic divergence, akin to human ancestry differences, altered selection pressures, shaping cancer risk and evolutionary trajectories. *Nature. PMID: 42486977.*

Multimodal profiling tracked dormant tumor cells (DTCs) from seeding to metastasis. Quiescent PHGDH-high DTCs survived immune clearance and silenced chemokines via H3K27me3. CX3CR1-high interstitial macrophages recruited immunosuppressive cells. Inactivating the PHGDH axis or depleting macrophages restored immune surveillance and inhibited colonization, revealing targets for micrometastasis-directed therapies. *Science (New York, N.Y.). PMID: 42531396.*

Intercellular transfer of cytoplasmic DNA via nanotube structures. Genomic instability triggers DNA mislocalization to the cytoplasm. This study shows that such mislocalized DNA can move between human cells through cytoskeleton-based nanotubes, driven by spindle poisons, radiation, or Cas9 cleavage. Transferred fragments are stably inherited, conferring heritable traits. This reveals a horizontal gene transfer-like mechanism propagating genomic instability between cells. *Cell. PMID: 42161273.*

A quantitative spatial map of the human proteome across tissues and cancers. Profiling over 13,000 proteins across 2,856 samples covering 58 tissues, subtypes, and 25 carcinomas, this resource depicts proteome trajectories across fetal, tumour, and healthy states. It offers insight into development, oncogenesis, organ-specific toxicity, and repurposable drug candidates, serving as a resource for human and cancer proteomics. *Nature. PMID: 42310461.*

AMIE agentic system shows promise in clinical management reasoning. AMIE (Articulate Medical Intelligence Explorer) is an agentic system for clinical "management reasoning" (namely, physician process of collecting patient's history, diagnostic reasoning, decision-making about required clinical investigation, design of a care plan, considering disease progression and treatment). In a blinded study with 100 scenarios, an optimized AMIE was non-inferior to primary care physicians in management reasoning, and superior in treatment precision and

alignment to clinical guidelines. On the new RxQA drug benchmark, AMIE outperformed physicians on difficult questions. *Nature. PMID: 42310463.*

AI integrating multi-omics for precision oncology and digital twins. Artificial intelligence deciphers high-dimensional multi-omics and clinical data to enable early diagnosis, patient stratification, and resistance prediction. Explainable AI can contribute to build trust -critical for clinical translation- and generate new hypotheses. Despite the challenges, the field advances toward patient digital twins that can simulate disease trajectories and enable treatments optimization, heralding a new era of precision oncology. *Nature reviews. Cancer. PMID: 42014628.*

Plasma proteome-metabolome model for non-invasive breast cancer detection. In the frame of a multicenter study involving 662 participants, by integrating 15 proteins and 5 metabolites from plasma, ProMeta-BC achieved high discriminative power (AUC 0.973/0.951) and detected imaging-negative cancers. ProMeta-BC-LN predicted lymph-node metastasis. This scalable, interpretable framework captures coordinated molecular signatures for non-invasive breast cancer detection and stratification. *Molecular cancer. PMID: 42310731.*

CANVAS - an AI platform that infers spatial tumor habitats from histopathology slides. CANVAS is an AI tool able to infer, from routine H&E slides, cellular neighborhoods within the tumor microenvironment and predicts their architecture. Validated across 5,000 patients and 9 cancer types, it supports prognostic modeling, tumor ecotype-based patient stratification, and immunotherapy prediction. *Cell. PMID: 42302781.*

Immunoediting and suppression shape mismatch repair-deficient (MMRd) colorectal cancer progression. By leveraging preclinical in vivo models, the authors explored the effects of immune pressure on tumor burden, immune cell infiltration, mutational burden and diversity, and neoantigens. Their results revealed a dual evasion mechanism of MMRd tumors, involving immune suppression and selective killing of cells carrying immunogenic mutations. *Gut. PMID: 42276770.*

Primary tumor cell states predict organ-specific metastatic relapse in PDAC. Analysis of 744 PDAC patients who underwent tumor resection showed worse survival associated with liver relapse than lung relapse. Single-nucleus RNA sequencing revealed correlated transcriptional profiles between normal liver cells and cancer cells metastasizing to the liver as well as between normal lung cells and cells metastasizing to the lung, suggesting that metastasizing cells adopt an organ-specific transcriptional program (independent from large genomic events) already at the primary site. This suggests that metastatic recurrence is determined early, guided by pre-existing cellular states and tumor-infiltrating immune cells. *Nature genetics. PMID: 41145870.*

Cancer stem cells drive Treg expansion via TSPAN8+ extracellular vesicles in TNBC. In triple-negative breast cancer, cancer stem cells (CSC) secrete TSPAN8+ vesicles that bind CD103 on T cells, activating LKB1-AMPK and FOXP3. This creates a feedback loop expanding immunosuppressive CD103+FOXP3+ Tregs. Anti-TSPAN8 antibody synergized with anti-PD-1 in preclinical models, suggesting a dual-targeting strategy for CSCs and tumor microenvironment suppression. *Cancer cell. PMID: 42102811.*

Review of cGAS-STING pathway in immunity, homeostasis, and inflammation. The cGAS-STING pathway detects cytosolic DNA and triggers innate immunity, antiviral defense, and responses to endogenous DNA derived from cell stress. It impacts antitumor immunity and tissue homeostasis but is also linked to inflammatory diseases. This review covers its mechanisms, physiological roles, disease implications, and how context-dependent biology guides therapeutic strategies. *Cell. PMID: 42349382.*

Gut microbiome features predict melanoma recurrence after adjuvant immunotherapy. Stool samples from 674 patients in a phase 3 trial were analyzed. Pre-treatment taxa like Eubacterium, Ruminococcus, Firmicutes, and Clostridium predicted recurrence. Gut microbiome profiles remained stable post-treatment. These findings support gut bacterial markers as biomarkers to guide personalized adjuvant therapy in melanoma. *Cell. PMID: 41999744.*

Review of gut microbiota modulation to overcome cancer therapy resistance. The gut microbiota regulates host immunity and cancer therapy via metabolic reprogramming, virulence factors, and immune remodeling. This review summarizes how microbial alterations influence tumorigenesis, immune responses, and resistance. It discusses strategies like restoring microbiome composition, enhancing immunity, or correcting metabolism to overcome resistance, offering a new paradigm in cancer treatment. *Molecular cancer. PMID: 41527087.*

Microbiome roles in ICI-related adverse events – a review. Immune checkpoint inhibitors can cause off-target toxicities, including colitis. Emerging evidence implicates tissue microbiomes, especially in the gut, lung, and skin, as mediators. This review focuses on ICI-induced colitis, examining clinical and preclinical studies investigating immune and microbial drivers, as well as current treatments, aiming to reduce the risk of treatment-related adverse events while preserving anti-tumour efficacy. *Nature reviews. Cancer. PMID: 41992000.*

Inference of secreted protein signaling activities in intercellular communication. The authors present a new computational method to infer signaling of secreted proteins from transcriptomic data, enabling better prediction of ligand-receptor interactions. Applied to diverse datasets, the tool reveals previously underappreciated communication networks in cancer and immunity, offering a powerful resource for dissecting paracrine and autocrine signaling in complex tissues. *Nat Methods. PMID: 42533123*.

SpaMTP: integrative statistical analysis and visualization of spatial metabolomics and transcriptomics data. SpaMTP is a new computational framework designed for joint analysis of spatial metabolomics and transcriptomics data. It provides statistical methods to integrate these modalities, correct for batch effects, and visualize molecular colocalization patterns. This tool enables researchers to link metabolic alterations with gene expression in their native tissue context, supporting spatial biology studies. *Nat Methods. PMID: 42538468.*

Remodeling of the tumor microenvironment in muscle-invasive bladder cancer: insights from single-cell and spatial transcriptomics after neoadjuvant immunochemotherapy. Using single-cell and spatial transcriptomics, this study charts the immune and stromal cell changes in muscle-invasive bladder cancer following neoadjuvant immunochemotherapy. It reveals specific shifts in T-cell subsets, macrophage polarization, and fibroblast activation that correlate with response, providing biomarkers and mechanistic clues for improving combination treatment regimens. *Molecular cancer. PMID: 42464338.*

Ketogenic diet mediates intestinal tumorigenesis through lipids, not ketones. Contrary to common belief, this study demonstrates that a ketogenic diet promotes intestinal tumor growth via lipid signaling rather than ketone bodies. Mechanistically, dietary lipids activate PPAR-alpha and alter the gut microbiome, driving stem cell proliferation and tumor formation. This work challenges the use of ketogenic diets in cancer prevention and highlights lipid metabolism as a key driver. *Nature. PMID: 42457955.*

Integrated stress response couples mitochondrial fitness with lineage reprogramming to drive cancer evolution. This research shows that the integrated stress response links mitochondrial dysfunction to cell plasticity, enabling cancer cells to switch between different cell states and evade therapy. By modulating ATF4 signaling, tumors adapt metabolically and transcriptionally, promoting aggressive evolution. Targeting this stress pathway may restrict cancer's ability to reprogram and metastasize. *Nat Cell Biol. PMID: 42298057.*

Evolving patterns of co-mutations from tumor initiation to metastatic progression. Analyzing longitudinal genomic data, this study tracks the patterns of co-mutation evolution from primary tumors to metastases. It identifies distinct cooperative mutation pairs that emerge during progression, often involving driver genes and epigenetic modifiers. These evolving landscapes influence clinical outcomes and suggest that metastasis-specific mutational synergies could be targeted therapeutically. *Nat Genet. PMID: 42432246.*

Open-IO framework proposes AI-native engineering for precision immuno-oncology. Open Immune Oncology (OpenIO) is a proposed framework integrating generative AI and omics to advance precision oncology, aiming to transition immunotherapy from empirical screening to rational, AI-driven engineering of therapeutic interventions, moving towards a more systematic approach. *Cancer cell. PMID: 42349428.*

PathPrism framework for interpretable spatial biomarker discovery in cancer. PathPrism decodes tumor tissue architecture into clinically informative spatial features, to predict prognosis, mutations, and therapy response. Applied to 7,000 colorectal cancer patients, it uncovered biomarkers for survival, MSI, and mutations, and stratified patients according to chemotherapy benefit. *Cancer cell. PMID: 42276049.*

Review of non-invasive imaging for interrogating cancer hallmarks. This review discusses non-invasive imaging approaches for assessing the hallmarks of cancer, either by direct targeting or by interrogating related pathophysiological processes. It also covers AI-assisted image analysis. These approaches guide treatment strategies like surgery, radiotherapy, and molecularly targeted therapies, with many already having a substantial role in clinical practice. *Nature reviews. Cancer. PMID: 42373751.*

Combined ProAgio-chemotherapy treatment reprograms the TME and reduces metastases in PDAC models. ProAgio, an integrin-targeted cytotoxin, combined with chemotherapy in PDAC models significantly modulated the TME, reduced hypoxia, and eliminated metastases. It reprogrammed CAFs, macrophages, and activated NK and T cells, while inhibiting stemness. ProAgio-treated CAFs reduced secretion of glycine and cysteine. The combination increased overall survival, providing evidence for potentiation of chemotherapy. *Molecular cancer. PMID: 42399938.*

Review of microenvironmental and epigenetic drivers of metastatic cancer dormancy. This review synthesizes advances in understanding dormancy of disseminated cancer cells. It covers niche-derived signals and matrix composition, epigenetic programmes, and chromatin remodelling that maintain quiescence. It also discusses immune evasion and similar biology in haematologic malignancies. It concludes that clinical translation remains

limited but outlines related challenges and opportunities to prevent metastatic recurrence. *Nature reviews. Cancer. PMID: 42032160.*

EIF4A3-dependent nonsense-mediated decay buffers AML1-ETO9a dosage and modulates outcome in t(8;21) acute myeloid leukemia. This study reveals that the RNA helicase EIF4A3 controls nonsense-mediated decay to regulate the dosage of the AML1-ETO9a fusion protein in t(8;21) AML. Precise buffering of this oncoprotein levels influences patient outcomes, suggesting that targeting this decay pathway could offer a novel therapeutic strategy for this leukemia subtype. *Leukemia. PMID: 42448936.*

Spatially-resolved progression of cancer cell subtypes reveals metabolic vulnerabilities in pancreatic ductal adenocarcinoma. Using spatial transcriptomics and metabolomics, this work maps the progression of pancreatic cancer subtypes. It identifies distinct metabolic reprogramming events associated with subtype transitions, uncovering actionable vulnerabilities, particularly in lipid and amino acid metabolism, that could be exploited for subtype-specific therapeutic interventions. *Molecular cancer. PMID: 41896850.*

Metabolic plasticity in pancreatic ductal adenocarcinoma progression and response to treatment. This review discusses how pancreatic cancer cells adapt their metabolism to survive nutrient deprivation, hypoxia, and therapy. It highlights the dynamic shifts between oxidative phosphorylation and glycolysis, and the role of the tumor microenvironment in driving this flexibility, proposing that targeting metabolic plasticity could overcome resistance to standard chemotherapies. *Molecular cancer. PMID: 41904584*.

Beyond the mouse: 3R-guided alternative animal models transforming cancer research. This paper advocates for replacing, reducing, and refining (3R) animal use by adopting alternative models like zebrafish, Drosophila, and organoids in cancer studies. It evaluates their strengths and limitations, showing how these systems can complement or replace murine models, accelerate drug screening, and provide more human-relevant mechanistic insights while adhering to ethical standards. *Molecular cancer. PMID: 41888798.*

Clonal dynamics shaped by diverse drug-tolerant persister states in melanoma resistance. Investigating melanoma resistance to targeted therapy, this study identifies multiple distinct persister cell states that survive initial drug exposure. These states exhibit heterogeneous gene expression and metabolic profiles, and their dynamic evolution drives eventual relapse. Targeting the persister state diversity could prevent or delay acquired resistance in melanoma patients. *Molecular cancer. PMID: 41776501.*

Spatial profiling reveals dormant micrometastasis signatures and immunosuppressive niches in colorectal cancer. Spatial multimodal profiling of paired primary CRC and liver/lung metastases revealed that liver micrometastases arose from early clonal divergences and harbored a stem-like, quiescent state. They were surrounded by immunosuppressive niches with T cell exhaustion. A six-gene signature associated with MRD, disease-free survival, and chemotherapy resistance was identified, to be exploited for surveillance and targeting. *Cancer cell. PMID: 42425074.*

CRISPR-KOALA screen identifies drivers of aneuploidy-driven breast cancer. CRISPR-KOALA enabled high-throughput screens in immunocompetent mouse models. Screening 3,752 genes on common chromosome-arm alterations in basal-like breast cancer identified 90 cancer drivers, including the novel oncogene PLGRKT. PLGRKT promotes tumorigenesis via stress-resistant mitochondria and increased ROS detoxification. This reveals that arm-level CNAs select specific drivers to promote heterogeneous biological processes. *Nature. PMID: 42420452.*

Preoperative high-dose vitamin D modulates the immune microenvironment in colon cancer. In a randomized trial, high-dose vitamin D supplementation before surgery increased plasma levels and significantly increased CD3+CD8+ memory T cells while reducing regulatory T cells. It spatially re-organized the TME, increasing T cell and tumor cell proximity. Post-treatment receptor expression decreased overall, supporting an immunomodulatory role for vitamin D in the human TME. *Cancer discovery. PMID: 42417469.*

Perspective on challenges and strategies for implementing multi-omics in clinical care. This Perspective charts the path for multi-omics from research to routine care, emphasizing that the central challenge is standardizing and interpreting complexity. It covers integrative analyses, risks to reproducibility, and the need for explainable AI. Scalable adoption depends on interoperable digital infrastructures, harmonized standards, and multidisciplinary care models. *Nature genetics. PMID: 42414591.*

Co-Scientist multi-agent AI system accelerates hypothesis generation and drug repurposing. Co-Scientist is a multi-agent AI system built on Gemini for hypothesis generation. In biomedical applications, it identified new drug-repurposing candidates and synergistic combinations for acute myeloid leukaemia, validated in vitro, demonstrating its potential to accelerate scientific discovery. *Nature. PMID: 42156544.*

A computational framework infers mutation copy number from targeted panels without matched normals. Analyzing gene mutant dosage (GMD) for over 500,000 mutations across 60,000 tumors allowed to identify,

without the need for matched normal samples, 46 biomarkers of survival (13 of which undetectable by binary matched mutant/wild type models), 26 associated with metastasis, and 20 predicting tropism. The study shows that GMD patterns are independent predictors of prognosis and metastatic potential, enhancing biomarker discovery. *Nature genetics. PMID: 42538373.*

Histone Modifications in Cancer: Mechanisms and Therapeutic Potential. This review provides an overview of histone modifications in cancer, including acetylation, methylation, phosphorylation, ubiquitination, and glycosylation. It examines the dysregulation of writer, eraser, and reader enzymes in solid tumors and hematological malignancies. The review explores crosstalk with DNA methylation, non-coding RNAs, and metabolic reprogramming. It discusses therapeutic advances like HDAC, EZH2, and BET inhibitors, as well as PROTACs and dual inhibitors. It emphasizes the context-dependent roles of specific modifications like H3K27me3 and H2BK120ub and the potential of combining epigenetic therapies with chemotherapy and immunotherapy. *Molecular cancer. PMID: 42243927.*

A 14-Protein Plasma Signature for Early Lung Cancer Risk Prediction. Using machine learning, a 14-protein plasma signature was identified that predicts lung cancer risk more than five years before diagnosis. Validated across eight cohorts, the signature was linked to smoking, particulate matter exposure, and specific lung cell states. The signature was induced by IL-1β, and its inhibition reduced tumorigenesis. In the CANTOS trial, the signature identified patients who benefited most from anti-IL-1β therapy. *Cell. PMID: 42242224.*

Gut Pathobionts Translocate to the Liver to Promote Hepatocarcinogenesis. This study profiled the gut and intrahepatic microbiome in liver cancer patients (HCC), revealing increased gut-liver similarity and a enrichment of gut pathobionts. Fecal transplants from HCC patients into germ-free mice impaired gut barrier and increased liver bacterial load; the gut pathobiont *Bacteroides fragilis*, enriched in HCC, disrupted the gut barrier in mice and translocated to the liver, exacerbating damage and promoting tumor development. Mechanistically, the bacterial surface protein Enolase activates Vimentin on hepatocytes, triggering oncogenic cascades. *Cancer discovery. PMID: 42240277.*

***Fusobacterium nucleatum* Heterogeneity and Its Role in Cancer.** This review details the genetic and phenotypic heterogeneity among *Fusobacterium nucleatum* (Fn) subspecies, which underlies their differential niche adaptation. It delineates key effectors like adhesins, metabolites, and exoproteins that facilitate host cell invasion, immune evasion, and chemoresistance induction. The review explores the translational potential of Fn, underscoring its utility as a diagnostic biomarker and a promising target for novel therapeutic strategies in cancer. *Gut. PMID: 42230118.*

A multi-omic analysis of IDH-Mutant Glioma Progression. This study integrated multi-omics data from IDH-mutant gliomas to track disease progression. Malignant cells displayed transcriptional states resembling glial-neuronal lineage development or a reactive mesenchymal state. Less differentiated cells increased with tumor grade and genetic alterations like PDGFRA amplification. Longitudinal analysis showed two transition patterns: reduced differentiation and increased proliferation associated with acquired genetic events, and increased mesenchymal-like state linked to macrophage expression, independent of genetic changes. *Nature. PMID: 42236943.*

Activating mTOR via TSC2 Inhibition to Sensitize Cancer Cells to Proteasome Inhibitors. Researchers developed AcTor, a first-in-class TSC2 inhibitor that activates mTORC1. While not effective alone, when combined with the proteasome inhibitor ixazomib, AcTor showed potent cytotoxicity across Acute Myeloid leukemia (AML) cell lines and patient samples. The combination induced a mitochondrial catastrophe, leading to ROS accumulation and apoptosis. In vivo, the combination reduced AML burden, depleted leukemic stem cells, and retained activity upon relapse, including in a TP53-mutated patient-derived model, exceeding standard-of-care efficacy. *Molecular cancer. PMID: 42204603.*

Epithelial-Mesenchymal Plasticity as a Driver of Tumor Evolution and Therapy Resistance. This review highlights epithelial-mesenchymal plasticity (EMP) as a key driver of cancer stem cell behavior, metastasis, and therapy resistance. It discusses the spectrum of intermediate phenotypes and their regulation by transcription factors, signaling pathways, and the tumor microenvironment. Metabolic reprogramming is closely linked to EMP. The review covers advanced models for studying EMP and therapeutic strategies targeting this plasticity, including pathway inhibitors and differentiation inducers, to overcome resistance and improve outcomes. *Molecular cancer. PMID: 42185888.*

Loss of the Y Chromosome in Cancer: A review. Loss of the Y chromosome (LOY) is the most common somatic alteration in males and is linked to cancer susceptibility and poor outcomes. This review summarizes the evolution, structure, and gene content of the Y chromosome and its association with cancer. It discusses functional studies showing LOY's effects on immune surveillance, DNA repair, and the tumor microenvironment. Finally, the review highlights advances in sequencing that enable precise LOY quantification and its potential as a biomarker for cancer risk and immunotherapy response. *Nature reviews. Cancer. PMID: 42168613.*

AKR1C1 Mediates Resistance to NECTIN4-ADC by Blocking Drug Internalization and Promoting Efflux. This study identifies a resistance mechanism to the NECTIN4-ADC enfortumab vedotin. In resistant tumor cells, despite high NECTIN4 expression, ADC uptake is defective. In these cells, AKR1C1 binds NECTIN4, impairing clathrin-mediated internalization. Additionally, the AKR1C1-WWP2 axis promotes extracellular vesicle-mediated export of the ADC, reducing intracellular payload. Pharmacologic inhibition of AKR1C1 restores ADC uptake and enhances therapeutic sensitivity in preclinical models. *Cancer cell. PMID: 42167230.*

COPA Mutations as an Atypical Driver in Small Intestinal Tumorigenesis. This study identifies recurrent in-frame deletions in the COPA gene in small intestinal adenomas and adenocarcinomas, frequently co-occurring with USP9X mutations. These mutations drive R-spondin-independent but Wnt ligand-dependent growth by stabilizing the LRP6 receptor. Unlike canonical Wnt pathway mutations, COPA encodes a component of the coatomer complex I involved in vesicle trafficking. This establishes COPA mutation as a unique, atypical driver of intestinal tumorigenesis. *Nature genetics. PMID: 42286202.*

DNA Methylation Analyses Reveal Link Between Herbicide Picloram Exposure and Early-Onset Colorectal Cancer Risk. This study investigated the exposome's link to early-onset colorectal cancer. By constructing methylation risk scores as proxies for exposures, researchers identified the herbicide picloram as a new risk factor for EOCRC compared to late-onset CRC. This finding was replicated in a meta-analysis and validated using population-based data from 94 US counties over 21 years, showing a significant association between picloram use and EOCRC incidence. *Nature medicine. PMID: 42014507.*

Molecular Subtyping in Pancreatic Cancer: From Biology to Clinical Implementation. This review synthesizes developments in PDAC molecular subtyping, focusing on the classical and basal-like subtypes. Despite clear prognostic and predictive value, clinical adoption has been limited. Recent advances in multi-omics have deepened understanding, but therapy-induced plasticity counters the adoption of static biomarkers. The review discusses the use of GATA6 immunohistochemistry as a prognostic tool and the insights from single-cell and spatial transcriptomics, proposing a pragmatic roadmap for clinical implementation. *Molecular cancer. PMID: 41796340.*

WNT and MAPK Pathways Drive Distinct Plastic Cell States in Colorectal Cancer. This study shows that in colorectal cancer, KRAS mutations cannot initiate tumorigenesis without WNT pathway activation. WNT signaling is required to establish a stem-like state for tumor initiation, while MAPK signaling drives a state for tumor growth. These distinct, plastic states impact drug response, potentially explaining why KRAS-G12C inhibitors are less effective in CRC compared to lung cancer. *Nature genetics. PMID: 42277259.*

ALTAIR Trial: Treating ctDNA-Positive Colorectal Cancer. The ALTAIR phase 3 trial tested a post-adjuvant surveillance strategy for colorectal cancer, treating patients with trifluridine/tipiracil (FTD/TPI) upon ctDNA-detected molecular recurrence without radiological disease. While median disease-free survival was longer with FTD/TPI vs. placebo, the trial did not show a significant DFS improvement. However, FTD/TPI increased hematologic adverse events. *Nature medicine. PMID: 42260101.*

Redefining Antibody-Drug Conjugates as Tumor-Ecosystem-Targeting Therapies. This review challenges the view of ADCs as strictly targeted agents. It argues that ADC activity extends beyond antigen expression to include tumor-intrinsic features and tumor microenvironment processes. The review links ADC successes and failures to mechanisms of efficacy, resistance, and toxicity. It discusses the need for validated biomarkers, combination strategies, and next-generation platforms to shape precision oncology frameworks for ADC development. *Cancer cell. PMID: 42259248.*

High-Resolution Analysis of Mosaic Chromosomal Alterations in Aging Blood. Using new computational methods on whole-genome sequencing data from 484,081 UK Biobank participants, this study identified 43,617 autosomal

mosaic chromosomal alterations. It discovered 53 genomic hotspots for short mosaic Chromosomal Alterations (mCAs), linking several to chromosomal fragile sites. Notably, CLL-associated deletions at 13q14 were found in 1% of individuals aged 65-70, suggesting screening potential. *Nature genetics. PMID: 42156563.*

Variable Penetrance and Phenotypes of Germline RNF43 Mutations in Colorectal Cancer. This study assessed germline RNF43 variants in a large population, finding that while they are a CRC predisposition gene, risks are moderate and the polyposis phenotype is often absent. N-terminal loss-of-function germline variants confer higher CRC risk, whereas C-terminal variants do not. Somatic C-terminal mutations are pathogenic, likely due to cooperation with other Wnt pathway mutations. Genetic testing and patient management should incorporate these risk stratifications. *Gut. PMID: 41443981.*

Urinary Proteomics Predicts Immunotherapy Response in Biliary Tract Cancer. This study established urinary proteomics as a non-invasive tool to predict and monitor immune checkpoint inhibitor response in biliary tract cancer. A machine learning model based on baseline urinary proteins robustly predicted durable clinical benefit. Longitudinal urinary proteomic dynamics mirrored tumor microenvironment remodeling. A 4-protein panel was validated externally. PTPN13+ malignant cells were identified as key regulators of pro-apoptotic states contributing to sustained response. *Gut. PMID: 41151791.*

Artificial Intelligence in Microbiome Research: From Data to Clinical Application. This review systematically explores AI-driven methodologies in microbiome research, including clustering, dimensionality reduction, neural networks, and large language models. It assesses how these approaches enable the extraction of biological patterns from complex microbial data, facilitating insights into community dynamics and host-microbe interactions. The review also explores AI's transformative impact on translational applications like disease diagnostics, therapeutic development, and precision microbiome engineering. *Gut. PMID: 40983504.*

Whole-Genome Doubling Drives Immune Evasion via Epigenetic Silencing. This study characterizes how whole-genome duplication (WGD) drives tumor evolution in mouse mammary tumor models. WGD increased heterogeneity and triggered immune evasion, making tumors more sensitive to anti-PD-L1. Mechanistically, WGD led to epigenetic silencing of MHC-I regulators via elevated H3K27me3, linked to decreased KDM6 activity and increased succinate levels. PRC2 inhibition preferentially suppressed WGD+ tumor growth and enhanced immune infiltration. *Cancer cell. PMID: 42102810.*

Alex, although we are aware that articles in bioRxiv are not peer-reviewed and findings should be treated as provisional, can you find the most relevant papers published in the past weeks on "Metastases" or "cancer cell adaptation" or "immunotherapy" or "Cancer epigenetics" or "extracellular vesicles" or "liquid biopsy" or "Cancer cell metabolism" or "microbiota cancer" or "Cancer vaccines" or "cancer genomics, aneuploidy" or "cancer biomarkers", and provide a short summary per each of them?

Absolutely. I searched bioRxiv with a ~6-week window (roughly 1 July–12 August 2026, with a few late-June papers included where they were particularly relevant) across the topics you specified. I then ranked the papers by my assessment of potential impact × conceptual novelty × mechanistic strength × translational/platform value, rather than by current citations or attention—which would be misleading for very recent preprints.
A caveat: these are preprints and have not necessarily undergone peer review, so the ranking reflects the strength and potential of the reported findings, not established validity.

The strongest signal I see in this batch is a convergence of ***tumor evolution, cellular plasticity, metabolism and immune ecology***. Particularly interesting are: 1) A single chromosome break can initiate an evolutionary trajectory toward cancer, with subsequent aneuploidies selected as fitness-restoring adaptations; 2) Lineage tracing + single-cell/spatial profiling is increasingly resolving which cells actually give rise to tumors, rather than simply describing tumor states; 3) The liquid biopsy field is moving from CTC counting to spatial organization of tumor–immune cell communities; 4) Immunotherapy research is increasingly targeting the

metabolic/epigenetic state of both tumor cells and T cells, rather than simply adding another immune checkpoint; 5) AI is moving from descriptive single-cell analysis toward patient-level prediction and therapeutic design; 6) The tumor microenvironment is becoming a dynamic ecosystem involving macrophages, neutrophils, metabolism, extracellular vesicles and—in some settings—microbiota.

Tier 1 — Likely High-Impact / Paradigm-Shifting

1. A single chromosome 3p break initiates clear cell renal cell carcinoma evolution (Genomic evolution/aneuploidy) (link)
Why I rank it #1: This addresses a fundamental question in cancer evolution: how can a highly deleterious chromosomal alteration become the starting point for tumorigenesis?
The authors analyze 949 ccRCC genomes and identify recurrent patterns of 3p loss, including a form of breakpoint-confined chromothripsis. Remarkably, engineering a single DNA double-strand break on 3p in normal renal epithelial cells initiates an evolutionary trajectory involving fitness loss followed by selection of secondary 5q gains and 14q losses. These secondary alterations restore fitness, induce metabolic reprogramming and facilitate malignant transformation. Conceptually, this provides an unusually direct experimental link between genomic damage → fitness bottleneck → clonal selection → recurrent cancer genome architecture.

2. Lineage recording reveals hijacked hepatic progenitor states as a common origin of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). (Tumor initiation/plasticity) (link)
This is an impressive integration of lineage, state, spatial and metabolic information.
The authors develop CERAMIC, a high-capacity CRISPR lineage recorder that simultaneously recovers lineage marks and transcriptomes at single-cell resolution. In a liver cancer model, they identify the major tumor-fated population. These cells pass through regenerative/progenitor states before generating both HCC- and ICC-like lineages. Tumor-fated cells require ACOX1-dependent peroxisomal β-oxidation to tolerate lipotoxic/oxidative stress, while a lipid-associated macrophage niche involving LGALS9–P4HB supports expansion.

3. AI-enabled Spatial Profiling of Circulating Tumor-Immune Ecosystems Predicts Patient Outcomes Across Cancers (Liquid biopsy/AI) (link)
This may be one of the most interesting liquid-biopsy papers in the set. The striking conceptual shift is from "how many CTCs?" to "what ecosystem do CTCs form in blood?".
Rather than treating circulating tumor cells as isolated objects and simply counting them, the authors develop CCIP, an AI framework that quantifies CTCs, immune cells and their multicellular spatial organization in routine multiplex blood imaging. Across 2,693 blood scans from 1,399 patients, an imaging-derived 14-feature model predicted overall survival in breast cancer, and generalized to prostate cancer.

4. Mechanisms regulating combination effect of antibody-drug conjugates (ADCs) and cancer immunotherapy (Immunotherapy) (link)
This study proposes a mechanistic framework explaining why ADCs can synergize with immunotherapy (T cell engagers and ICIs). If validated clinically, this could inform rational ADC–immunotherapy combinations rather than empirical pairing.
ADC treatment induces autophagy and ensuing increase of TNFR1/2 and M6PR expression in tumor cells. With T-cell engagers, tumor-derived TNF-induced signaling drives synergy; with checkpoint inhibition, antigen-specific T cells exploit M6PR-dependent granzyme-B uptake. Importantly, the mechanisms were reported to be relatively target- and payload-independent, suggesting that ADC-induced cellular remodeling may create a generalizable state of increased susceptibility to immune killing.

5. Multi-compartment immune and tumor cell reprogramming by IFNα2 overcomes colon cancer immunotherapy resistance (Immunotherapy/TME) (link)
The important concept is TME reprogramming as a multi-compartment intervention, rather than targeting of one immune cell population.
LNP-delivered IFNα2 is used to reprogram multiple compartments of the resistant colorectal tumor microenvironment simultaneously. Treatment reverses myeloid immunosuppression, reinvigorates exhausted T cells and increases tumor immunogenicity. Interestingly, tumor cells also move away from a HIF1α/hypoxia-associated cuproptosis-resistant state toward increased FDX1/copper-importer expression, suggesting metabolic sensitization. The treated tumor microenvironment transcriptionally resembles signatures observed in pembrolizumab-responsive patients.

Tier 2 — High Novelty with Strong Mechanistic or Platform Value

6. Cerebral vasculature shapes the spatial patterning of brain metastases (Metastases) (link)
The conceptual importance is that metastatic tropism may depend not only on tumor-intrinsic programs and tissue biology, but also on organ-scale physical anatomy and hemodynamics.
Using MRI data from >2,300 patients and approximately 10,000 brain metastases, the study asks why metastatic deposits preferentially occur in particular brain regions. The authors find that vascular architecture strongly predicts metastatic distribution, where zones characterized by slower flow and smaller vessels show increased vulnerability. The results provide quantitative support for the classic idea that CTC arrest and extravasation are constrained by the cerebral vascular network.

7. Targeting DNMT1 augments anti-tumor CD8⁺ T cell function (Epigenetics/immunotherapy) (link)
This is potentially important because it frames T-cell exhaustion as a reprogrammable epigenetic state, rather than an irreversible endpoint.
DNMT1 inhibition is shown to alter the epigenetic state of exhausted CD8 T cells. Rather than simply reducing exhaustion-associated transcription, DNMT1 inhibition appears to make the exhausted chromatin landscape more amenable to epigenetic remodeling after restimulation, inducing a divergent program. The authors further show DNMT1-inhibition-enhanced function of melanoma patient-derived TILs after ex vivo expansion.

8. SIGLEC1 facilitates macrophage–CD8⁺ T-cell interactions and correlates with cancer immunotherapy response (TME/immunotherapy) (link)
The interesting implication of this study is that some macrophage populations traditionally viewed as suppressive may instead participate in productive immune-cell organization.
SIGLEC1+ macrophages are found in close proximity to CD8 T cells in melanoma tumors and are enriched in immunotherapy responders. SIGLEC1 ligands are enriched on activated T cells, while blocking the interaction reduces cytotoxic cytokine production ex vivo. Integration of single-cell and spatial transcriptomics across independent ICI-treated cohorts therefore points to a specific macrophage–T-cell spatial niche associated with effective immunity.

9. CAR T cell foundation model predicts immunotherapy response (AI/immunotherapy) (link)
The most interesting aspect is the attempt to bridge the persistent gap between single-cell heterogeneity (of the CAR-T states) and clinically meaningful patient-level prediction, while retaining interpretable biological programs.
gANCHOR is a pathway-aware T-cell foundation model designed to translate single-cell CAR-T states into patient-level response predictions. It uses hierarchical hypergraph attention to encode gene–pathway relationships, and aggregates cellular information into patient-level predictions. Across five CAR-T studies involving 161 patients, it identifies reproducible response/non-response programs.

10. AI-informed neoantigen prioritization enables a multi-epitope mRNA/LNP vaccine (Cancer vaccines) (link)
The main novelty is less the mRNA platform itself—which is established—and more the end-to-end integration of computational antigen prioritization, experimental validation, mRNA/LNP formulation and checkpoint blockade.
The study combines AI-based/TCR-aware neoantigen prioritization with an mRNA/LNP vaccine. Three previously validated B16F10 melanoma neoantigens were incorporated into a single multi-epitope construct. The vaccine induced antigen-specific CD8 responses and inhibited tumor growth in mice, with stronger effects when combined with anti-PD-1. Although translational relevance is relatively high, the evidence remains preclinical.

11. COATS identifies copy-number-dependent drivers and enablers of aneuploidy in cancer (Genomics/aneuploidy) (link)
The distinction between creating aneuploidy and tolerating it is particularly useful conceptually and could expose therapeutic vulnerabilities created by tumor evolution.
COATS integrates copy number, gene expression, aneuploidy and cancer hallmark information to distinguish genes that drive chromosomal instability from genes that enable survival in aneuploid cells. Across 33 TCGA cancer types it identifies 479 amplification-dependent and 141 deletion-dependent aneuploidy-associated genes. Experimental validation showed selective toxicity after depletion in aneuploid versus near-diploid cells.

12. Circulating colorectal tumor cells remodel their surfaceome to increase viability and metastatic potential (Metastasis/liquid biopsy) (link)
It complements the study above (n. 3) by highlighting that the blood compartment itself may select and reshape metastatic cells.
This study focuses on an underexplored stage of metastasis: survival in the bloodstream. Rather than treating CTCs as passive disseminated tumor cells, the work investigates how colorectal CTCs dynamically remodel their surfaceome to

withstand circulation and enhance metastatic competence. The finding fits an increasingly important view of metastasis in which dissemination is an active adaptive process involving changes in cell state, cell–cell interactions and immune/physical stresses.

Tier 3 — Enabling Technologies / Emerging Tools

13. A new genome-scale model enables prediction of cancer metabolic dependencies (Cancer metabolism) (link)
The main value of this study is its potential to connect metabolic network reconstruction with prediction of patient-dependencies.
The authors introduce iHME, a genome-scale metabolic model designed to predict cancer metabolic dependencies. Applied to 1,103 cancer cell lines, it recovers 84.6% of experimentally identified essential genes—approximately twice the performance of previous models. It is then used to generate individualized metabolic networks for 8,384 patient tumors and predicts context-specific dependencies such as GLUT1 in head-and-neck/ovarian cancer and CDS2 in skin cancer.

14. HOPE: Interpretable Histology Analysis with Spatial Omics-Derived Signatures for Precision Oncology (Spatial biology/pathology) (link)
If independently validated, this could become a useful bridge from high-dimensional spatial biology to routine pathology.
HOPE addresses a major translational bottleneck: spatial omics provides rich TME information but is expensive and difficult to deploy clinically, whereas H&E slides are ubiquitous. The framework learns spatial-omics-derived TME signatures from paired spatial omics/H&E data and subsequently predicts them from H&E alone. Across cancer types and cohorts, the approach outperforms equivalent models without spatial omics supervision and generates interpretable TME annotations.

15. Computing tumor specificity of cancer antigen targets by k-mer indexing of healthy tissue transcriptomes (Cancer vaccines/immunotherapy) (link)
The platform could expand the antigen repertoire available for vaccines, TCR therapies, bispecifics and CAR approaches, particularly in tumors with low mutational burden.
The k4neo framework tackles an important bottleneck in cancer immunotherapy: identifying antigens that are genuinely tumor-specific rather than merely overexpressed. By k-mer indexing healthy tissue transcriptomes, the method rapidly evaluates whether candidate tumor splice junctions are absent from normal tissues. Applied across nine tumor cohorts, it identifies patient-specific and recurrent tumor-specific splice junctions, including candidates confirmed by long-read sequencing.

16. Intratumoral dose heterogeneity promotes adaptive anti-tumor immunity and predicts response to radiopharmaceutical therapy (Radioimmunology) (link)
This links radiopharmaceutical treatment to spatial tumor–immune interactions and potentially supports dose-optimization strategies that consider immunological consequences rather than only tumor-cell killing.
The study examines how heterogeneous intratumoral radiation exposure influences immune responses to radiopharmaceutical therapy. Rather than considering dose distribution simply as a pharmacological/physical variable, the work suggests that spatial dose heterogeneity can generate adaptive antitumor immunity and may contain predictive information for clinical response.

Tier 4 — Specialized or Indirect Cancer Relevance

17. High glucose confers senescence resistance via GLUT1 epigenetic rewiring to blunt immunotherapy responses (Metabolism/epigenetics) (link)
The paper connects nutrient availability → epigenetic state → senescence → immune sensitivity, although the dietary intervention component will require particularly careful validation before clinical extrapolation.
In esophageal squamous cell carcinoma, high glucose increases GLUT1 and establishes a positive feedback loop involving HAT1 and FOXM1 that remodels chromatin accessibility and suppresses tumor-cell senescence. GLUT1 inhibition increases CD8 infiltration/cytotoxicity and sensitizes tumors to anti-PD-1; intriguingly, dietary glucose restriction produced similar effects in the model.

18. Transposable elements (TE) shape olaparib response according to BRCA1 status in triple-negative breast cancer (Genomics/immunity) (link)
The work connects genome instability, epigenetic derepression of repetitive elements and antitumor immunity,

suggesting that TE activity could eventually contribute to patient stratification or rational combinations of PARP inhibition with immunotherapy.
The study implicates transposable element (TE) activity in differential olaparib responses according to BRCA1 status in TNBC. TE activation is associated with immune responses and genomic instability, raising the possibility that TE-derived nucleic acids could contribute to the immunogenic effects of DNA damage/repair-targeted therapy.

19. Nuclear translocation of phosphorylated YB-1 via small extracellular vesicles contributes to the malignant phenotype of TNBC (Extracellular vesicles, EV) (link)
The work supports the concept that EVs can function not merely as biomarkers but as active vehicles of transferable malignant phenotypes.
This study identifies a specific extracellular-vesicle mechanism in triple-negative breast cancer. Phosphorylated YB-1 is transported in small EVs and can promote nuclear localization and oncogenic behavior in recipient cells. Loss of YB-1 phosphorylation reduces tumorsphere formation and stemness, whereas YB-1-positive EVs restore malignant phenotypes. Pharmacological inhibition of YB-1 nuclear translocation suppresses these effects.

20. Spatial atlas highlights contribution of *C. difficile* in early-stage colorectal cancer (Microbiome) (link)
The importance lies primarily in establishing spatial organization of the tumor microbiome as a variable potentially linked to early tumor biology, although causal conclusions remain limited.
The authors generate a spatial molecular atlas of bacteria within early-stage colorectal tumors, addressing an important limitation of microbiome studies that focus on bulk abundance. The work emphasizes intratumoral bacterial niches and investigates less studied organisms such as *Clostridioides difficile* and *Enterocloster aldenensis*, rather than concentrating exclusively on the canonical *Fusobacterium nucleatum/E. coli* axis.

The strongest emerging themes:
1. Cancer is increasingly being viewed as an evolutionary process of adaptation, not simply accumulation of mutations. This is perhaps the strongest theme.
The paper n. 1 is particularly striking because it experimentally models the sequence: DNA break → fitness loss → selection → secondary aneuploidies → metabolic adaptation → malignant expansion. Paper n. 11 complements this from the opposite direction: instead of asking which genomic alterations initiate aneuploidy?, it asks which alterations allow cells to tolerate it? Together they suggest a useful conceptual framework: "Cancer genomes are not merely records of mutations; they are records of successive solutions to fitness problems". That is highly relevant to metastasis and therapy resistance because the same logic could apply to drug-induced bottlenecks.

2. Lineage history + cell state + spatial context is becoming the dominant experimental combination. Paper n. 2 is probably the clearest example.
Traditional single-cell studies tell us: "This cell has state X."
Lineage tracing asks: "Where did this cell come from?"
Spatial profiling asks: "Who is it interacting with?"
Metabolic measurements ask: "How is it surviving?"
The combination potentially gives: origin → evolutionary trajectory → cellular state → spatial niche → metabolic dependency → therapeutic vulnerability. This is a major methodological direction for cancer biology.

3. Liquid biopsy is moving from CTC enumeration to ecosystem profiling. In this context, paper n. 3 is especially interesting. The traditional liquid-biopsy paradigm is: "CTC number → prognosis"; the emerging paradigm is: "CTC phenotype + immune partners + multicellular clusters + spatial organization + molecular information → prognosis/therapy response."
Paper n. 12 provides a complementary biological perspective: circulating tumor cells may actively remodel themselves to survive the bloodstream and become more metastatic. This suggests that the bloodstream is not merely a transport compartment—it may be a selective evolutionary niche.

4. Immunotherapy is increasingly becoming a problem of cellular state engineering. Instead of finding another molecule that activates T cells, manipulate the state of the tumor ecosystem so that effective immunity becomes possible. That seems to me one of the most important conceptual trends in the current preprints.

5. AI is shifting from analysis to prediction, to intervention. There is an interesting progression among these papers: Descriptive AI classifies cells/states; Predictive AI predicts CAR-T response, survival, treatment response; Generative/decision-support AI identifies candidate tumor-specific antigens. Paper n. 10 is interesting because it closes part of the pipeline towards therapeutic integration, by going from sequence data (descriptive) to computational prioritization (predictive; AI-selected neoantigens), until therapeutic construct (mRNA/LNP vaccine generation) and biological validation (immune response, tumor control).

6. Metabolism is becoming tightly integrated with epigenetics and immune biology. These studies point toward a more integrated model: nutrient availability / metabolic pathway chromatin state / transcription cellular phenotype immune interaction therapy response. Paper n. 17 is a particularly clean example; paper n. 2 provides another example: peroxisomal β-oxidation is not simply a metabolic phenotype, it appears to be part of the mechanism that allows a particular lineage to become tumor-fated.

One particularly interesting meta-observation is that several of the highest-ranked papers converge on the same biological idea from completely different directions: cancer progression is increasingly being understood as adaptive evolution across multiple interacting compartments—tumor cells, immune cells, metabolism, genome structure and tissue architecture—rather than as a tumor-cell-autonomous process.

Thank you Alex, well done!

(Alexander Irwin –Alex– is an AI member –ChatGPT– of the newsletter team)

(If you'd like to see how Alex generated the ranking, have a look here. I think you'll find it quite informative!)

what if…
you could discuss science-related topics with AI?

Alex, can you explain what Is "Science - The Endless Frontier" by Vannevar Bush, highlighting the historical context and how It did affect the idea of basic science?

Science, the Endless Frontier is one of the most influential policy documents in the history of modern science. Written by Vannevar Bush in 1945, it fundamentally reshaped how governments—especially the United States—viewed the relationship between basic research, innovation, and economic growth.

(Historical context) The report was commissioned by Franklin D. Roosevelt in November 1944, while World War II was nearing its end. During the war, Bush had directed the Office of Scientific Research and Development, which coordinated scientific efforts that led to major technological advances, including radar, mass production of penicillin, and the early phases of the Manhattan Project.

Roosevelt asked Bush a crucial question: *"How can the scientific achievements of wartime be applied to improve peace, public health, employment, and national prosperity?"*

Roosevelt died before the report was completed, but Bush submitted it in July 1945 to his successor, Harry S. Truman.

Bush's core idea can be summarized in one sentence: *"Basic research is the "pacemaker" of technological progress."*

He argued that discoveries driven by curiosity—not immediate practical applications—eventually become the foundation for transformative technologies. His model looked like this: Basic research → New scientific knowledge → Applied research → Technological development → Economic growth, public health, and national security.

Today this is often called the linear model of innovation, although Bush himself acknowledged that the real process was more complex.

What Bush meant by "basic science"? Bush defined basic research as "Research performed without thought of practical ends." Its purpose is simply to increase understanding of nature. Examples include: understanding DNA before genetic engineering existed; studying quantum mechanics before semiconductors; investigating bacterial immunity decades before the development of CRISPR. His point was that no one could reliably predict which discoveries would become revolutionary. This idea was revolutionary because before World War II, governments generally funded science only for specific practical purposes, such as agriculture, military needs, public health, engineering projects. Bush argued that governments should instead support universities, independent scientists, long-term research, investigator-driven projects. This was a major philosophical shift. Scientists would not simply solve today's problems—they would generate tomorrow's possibilities. Bush proposed several principles/main recommendations: 1. Stable federal funding, meaning that science should receive continuous public investment, not just wartime funding; 2. Universities should be central, meaning that universities were seen as the ideal environment because they combine education, discovery, training of future scientists; 3. Scientific freedom, meaning that researchers should largely choose their own questions. Bush believed creativity suffers if governments dictate every research topic; 4. Peer review, meaning that scientists—not politicians—should evaluate scientific quality. This idea became the basis of modern grant review systems. The report strongly influenced U.S. science policy. Its ideas eventually contributed to the creation of the National Science Foundation in 1950. Over the following decades, federal investment in basic research expanded dramatically. Many countries later adopted similar funding models.

The report also had a long-term influence; indeed, Bush's vision helped create the post-war research ecosystem, involving research universities, competitive grant funding, public investment in curiosity-driven science, graduate education linked to research, collaboration among government, academia, and industry. This ecosystem produced breakthroughs including the transistor, the laser, the internet, modern biotechnology,

genomics, artificial intelligence. Although many of these developments involved applied research, they all depended on earlier investments in fundamental science.
Since the 1970s, scholars have questioned some aspects of Bush's framework. 1. they stated that the "linear model" is often too simple, as innovation is rarely a one-way sequence from basic to applied research. In practice, engineering challenges often generate new scientific questions; clinical observations inspire laboratory research; industry contributes substantially to fundamental discoveries. Knowledge flows in multiple directions. 2. Basic and applied research often overlap. For example, Louis Pasteur studied fermentation to solve practical problems while simultaneously making fundamental discoveries in microbiology. This inspired the concept of "use-inspired basic research," later popularized by Donald E. Stokes in his book Pasteur's Quadrant. 3. Societal priorities matter. Indeed, modern science policy increasingly emphasizes research that addresses climate change, global health, sustainable energy, aging, emerging infectious diseases, artificial intelligence. Many funding agencies now balance investigator-driven basic research with mission-oriented programs.
Even though modern innovation is understood to be more interactive than Bush's original framework suggested, *Science, the Endless Frontier* remains the foundation of contemporary science policy. Its most enduring message is that society benefits from investing in knowledge before its applications are known. This idea has justified decades of public support for fundamental research and has shaped research funding systems around the world. In modern terms, Bush argued that breakthroughs are difficult to schedule or predict. By sustaining a broad base of curiosity-driven research, societies increase the likelihood of discoveries that eventually lead to transformative technologies, improved health, economic growth, and enhanced national security.

Excellent, thanks.
What is the overall view of scientists, politicians and citizens, in US and in Europe, of the role and relevance of basic science for biomedical progress and the impact on people? Have scientists involved in clinical research ever expressed an opinion on the report, and on the role of basic and translational research in general?

This is an excellent question because it touches on one of the biggest debates in science policy over the last 80 years. The short answer is that Bush's central idea has survived, but it has evolved substantially. Today, very few scientists, policymakers, or clinicians argue for *only* basic research or *only* translational research. Instead, the prevailing view is that biomedical progress requires a continuum from discovery to implementation.
1. Regarding scientists, they wish for strong support for basic science, with a broader perspective than Bush. Among biomedical scientists, there remains overwhelming agreement that basic science is indispensable. Many landmark biomedical advances illustrate Bush's point: CRISPR arose from studies of bacterial immunity with no therapeutic objective, Pembrolizumab and other immunotherapies were built on decades of fundamental immunology, Trastuzumab depended on basic discoveries about oncogenes and receptor biology, Nivolumab similarly emerged from fundamental work on immune regulation. These examples reinforce Bush's argument that transformative therapies often originate from curiosity-driven research. However, today's biomedical researchers generally reject the strict "linear model." Instead, they describe biomedical innovation as iterative, with continuous feedback between laboratory discoveries, clinical observations, epidemiology, engineering, and computational biology.
2. Concerning clinical researchers, many have explicitly commented on Bush's vision and, perhaps surprisingly, some of the strongest advocates of basic science have been physician-scientists. Harold Varmus, a Nobel Prize-winning cancer researcher and former director of both the National Institutes of Health and the National Cancer Institute, has repeatedly argued that the success of modern cancer medicine rests on decades of federally funded basic research. He has described translational medicine as impossible without a continuous pipeline of fundamental discoveries. Francis Collins, former NIH Director and leader of the Human Genome Project, has often emphasized that translation should not replace discovery science. He has instead promoted a "bench-to-bedside-and-back" model in which clinical observations generate new laboratory questions. Elias Zerhouni, as NIH Director, was instrumental in promoting the concept of translational medicine. Rather than rejecting Bush, he argued that the biomedical ecosystem needed stronger "bridges" between discovery and patient care. In 2021, Varmus joined several leading scientists—including David Baltimore and Shirley

Tilghman—in an essay discussing the proposed *Endless Frontier Act*. Their conclusion was telling: while expanding technology-focused research was valuable, the United States must protect and expand its investment in fundamental science because it remains the source of future breakthroughs.

3. About politicians, in US, as I said, Bush's report profoundly shaped U.S. science policy. From the 1950s through the early 1990s, there was broad bipartisan agreement that federal investment in basic science was a strategic national priority. Since the 2000s, the conversation has shifted. Policymakers increasingly ask not only "How much should we fund?" but also "How can discoveries reach patients more quickly?" This has led to initiatives emphasizing translational research, precision medicine, and public-private partnerships, while largely preserving support for fundamental research. European policy has generally placed greater emphasis on societal challenges than the U.S. model. Framework programmes and later Horizon Europe explicitly combine frontier science, clinical translation, industrial innovation, societal impact. Europe therefore tends to frame basic science as one essential component of an innovation ecosystem rather than as the sole starting point.

4. Finally, interestingly, public opinion is much more favorable toward science than is sometimes assumed. Large surveys by the Pew Research Center found that about 80% of Americans believe science has improved everyday life; roughly 70% believe government investment in basic research pays off over the long term; most citizens identify advances in medicine as the greatest contribution of science. European surveys similarly show broad support for publicly funded science, although enthusiasm varies somewhat between countries and depends on trust in institutions.

More recently, the concept of translational research changed Bush's framework. The major conceptual change since 1945 is the emergence of translational medicine. While Bush envisioned a model Basic research → Applied research → Technology → Patients, Today's model is better represented as Basic science → Preclinical research → Clinical trials → Clinical practice → Population health ← Clinical observations generating new scientific questions. This continuous feedback is often described as bench → bedside → bench.

Cancer research provides perhaps the strongest illustration of this integrated view. Leaders in oncology increasingly describe progress as a cycle rather than a pipeline: molecular biology identifies new mechanisms; translational research develops biomarkers and therapies; clinical trials test them in patients; patient responses reveal mechanisms of resistance; those findings return to the laboratory to guide the next generation of basic research.

This iterative approach underlies advances in targeted therapies, immunotherapies, liquid biopsy, and precision oncology.

In conclusion, if we were to synthesize the views expressed over the past three decades by leading biomedical scientists, clinicians, policymakers, and science-policy scholars, the consensus would be something like this:

i. Vannevar Bush was fundamentally correct that sustained investment in basic science is the foundation of long-term biomedical progress.
ii. His model was incomplete, because discovery and application interact continuously rather than following a one-way sequence.
iii. Translational research is not an alternative to basic science; it is the bridge that converts discoveries into patient benefit while feeding clinical insights back into fundamental research.
iv. The greatest biomedical advances occur when basic, translational, and clinical research are supported together, rather than competing for priority.

This "continuum" model has become the dominant framework in both U.S. and European biomedical research and is particularly influential in fields such as cancer research, where advances depend on sustained interaction between laboratory science and clinical medicine.

Thank you. Last question: What is the "Science - The Endless Frontier" movie?

You're welcome! Interestingly, there is now a documentary that deliberately echoes the title of Bush's report. The film is called The Endless Frontier (2026), directed by Marilyn Ness. Rather than being a historical documentary about Vannevar Bush or his 1945 report, it uses the phrase "The Endless Frontier" as a metaphor for the future of American scientific research. The documentary follows three scientists working in different

disciplines: immunology (biomedical research), neurorobotics, ocean science. It explores their daily work, the motivations behind scientific careers, and the challenges facing research today, including funding uncertainty, workforce instability, and the broader societal consequences if scientific capacity is weakened. The central question of the film is essentially: “What happens to society if the scientific enterprise envisioned by Vannevar Bush is no longer adequately supported?” In that sense, the documentary can be viewed as a modern "epilogue" to *Science, the Endless Frontier*. Bush argued in 1945 that sustained public investment in basic science was essential for national health, prosperity, and security. The 2026 film asks whether that vision is still being upheld—and what could be lost if it is not.

If your interest is specifically biomedical research, you'll probably find the immunology storyline especially relevant, as it illustrates how long-term fundamental research can ultimately influence human health, while also showing the human side of scientists whose work often remains invisible to the public.

Given the questions you've asked throughout this conversation, I think you'd also enjoy reading the companion essay "*Should the Endless Frontier of Federal Science be Expanded?*", co-authored by leading scientists including David Baltimore, Harold Varmus, and Shirley Tilghman. It revisits Bush's ideas 75 years later and discusses how they should be adapted for today's research ecosystem while reaffirming the importance of basic science. I suspect that paper would be particularly relevant to your interest in oncology and translational research because it directly addresses the balance between basic, use-inspired, and translational science in modern biomedical research.

Thanks a lot Alex!

(Alexander Irwin –Alex– is an AI member –ChatGPT– of the newsletter team)

DIAMO IL BENVENUTO A

WE WELCOME

Campanile Riccardo, Post doc, Ghisletti Group
Cattafi Denis, Fellow, DIMA
D'Amato Maura, Post doc, Ghisletti group
De Rosa Giacomo Maurizio, Temporary, Pece Group
Di Simone Alessandro, Fellow, Scaffidi Group
Fatemeh Jafari, Fellow, Mitro Group
Occhiodoro Martina, Undergraduate student, G. Pelicci group
Saverio Valentina, Post doc, G. Pelicci Group
Vargiu Giulia, Technician, Cavallaro Group

notes...

Search, organize, aggregate and share image data with BioFile Finder (BFF) | Nature Methods
--
Want to get more from AI? Treat every prompt like an experiment
--
Twenty-two easy ways to power up your lab meetings

FRRB "BIO-REENTRY Grant for Returning Researchers" - deadline 01/12/2026
--
Francesca Martini Prize for an experimental thesis in Oncohaematology 2026 - deadline 30/9/2026

corso Studi osservazionali - FormaFutura
--
RNA Functional Biology: From Mechanisms to Models, Reggio Emilia 23-24 oct 2026
--
G7 leaders issue call to action on cancer | Lancet Oncology
--
Food is medicine: an opportunity to transform nutrition care in oncology

GeMAIHc 2027 - 1st INTERNATIONAL SCHOOL ON GENERATIVE & MULTIMODAL AI FOR HEALTHCARE
--
ocw.mit.edu (OpenCourseWare)
--
Statistica e Ricerca Clinica: dall'Evidenza Scientifica all'uso dell'Intelligenza Artificiale (webinar 22-23 sept)

Robots run this laboratory in Japan — and are changing how scientists work | Nature
--
The truth about being a manager | Management is a challenging and often lonely journey.

Unlock your European career life hacks! Dreaming to move to another EU country for work? Before you start packing, make sure you know your rights in the European job market. Watch here the European Commission quick guide to master your move!

Cover image *(by Susanna Chiocca and Lavinia Ghiani)*

Representative immunohistochemistry images showing NSD2, Ki67, ΔNp63α, IVL and TGM1 expression in normal and HNSCC patients' FFPE tissue. Both HPV- and HPV+HNSCC specimens are from grade3 tumors. Figure adapted from Ghiani et al., J Exp Clin Cancer Res 2026. doi: 10.1186/s13046-025-03631-0.

Susanna Chiocca and Lavinia Ghiani

Susanna Chiocca is Director of the Viruses and cancer Unit at Department of Experimental Oncology of IEO, and Faculty member of the SEMM (European school of molecular medicine) PhD school. With a Bachelor of Science at the University of Texas (USA) and a PhD in Molecular Biology/Virology at the MD Anderson Cancer Center (Houston, Texas), her research aims to determine the mechanisms by which oncogenic viruses and other tumor microenvironmental stressors contribute to neoplasia through protein post-translational modifications (PTM), by specifically focusing on the virus-/stress-induced alterations in the cancer epigenome inducing the neoplastic program, and how oncoviral proteins regulate cellular PTM pathways and provide new critical signals in viral-induced carcinogenesis, by using head and neck cancer as a model system.

Lavinia Ghiani is a Postdoctoral Researcher at IEO European Institute of Oncology, in the "Viruses and cancer" group headed by Susanna Chiocca. With a degree in "Genetics and Molecular Biology in Basic and Biomedical Research" obtained at the University of Rome "La Sapienza", she completed her PhD in Molecular Oncology at the European School of Molecular Medicine (SEMM)/University of Milan. Her research work focuses on the definition of the molecular mechanisms underlying HPV-induced head and neck cancer onset and progression, with a particular focus on epigenetic regulators, to ultimately identify novel disease biomarkers and therapy targets that can improve the current treatment approach of head and neck cancer patients.

Curated by:

Stefania Averaimo (Department of Experimental Oncology of the European Institute of Oncology, IEO).

Graphic by:

Alex Irwin (ChatGPT AI), Stefania Averaimo.
IEO Research Newsletter logo generated by ChatGPT

Content writing and revision:

Stefania Averaimo, Susanna Chiocca, Alessandro Davini, Ivan Dellino, Sara Gandini, Daniela Osti, Giuliana Pelicci, Nicola Segata, Yinxiu Zhan (Department of Experimental Oncology of the European Institute of Oncology, IEO); Mohssen Ansarin, Chiara Maria Grana, Lorenzo Spaggiari (European Institute of Oncology); Emanuela Ottolina (IEO communication office); Alex Irwin (ChatGPT AI), Ai Yi (DeepSeek AI), Antoine Imbert (Mistral).

Consulting Board:

Bruno Amati, Tiziana Bonaldi, Pier Paolo Di Fiore, Gioacchino Natoli, Rosella Visintin (Department of Experimental Oncology of the European Institute of Oncology, IEO).