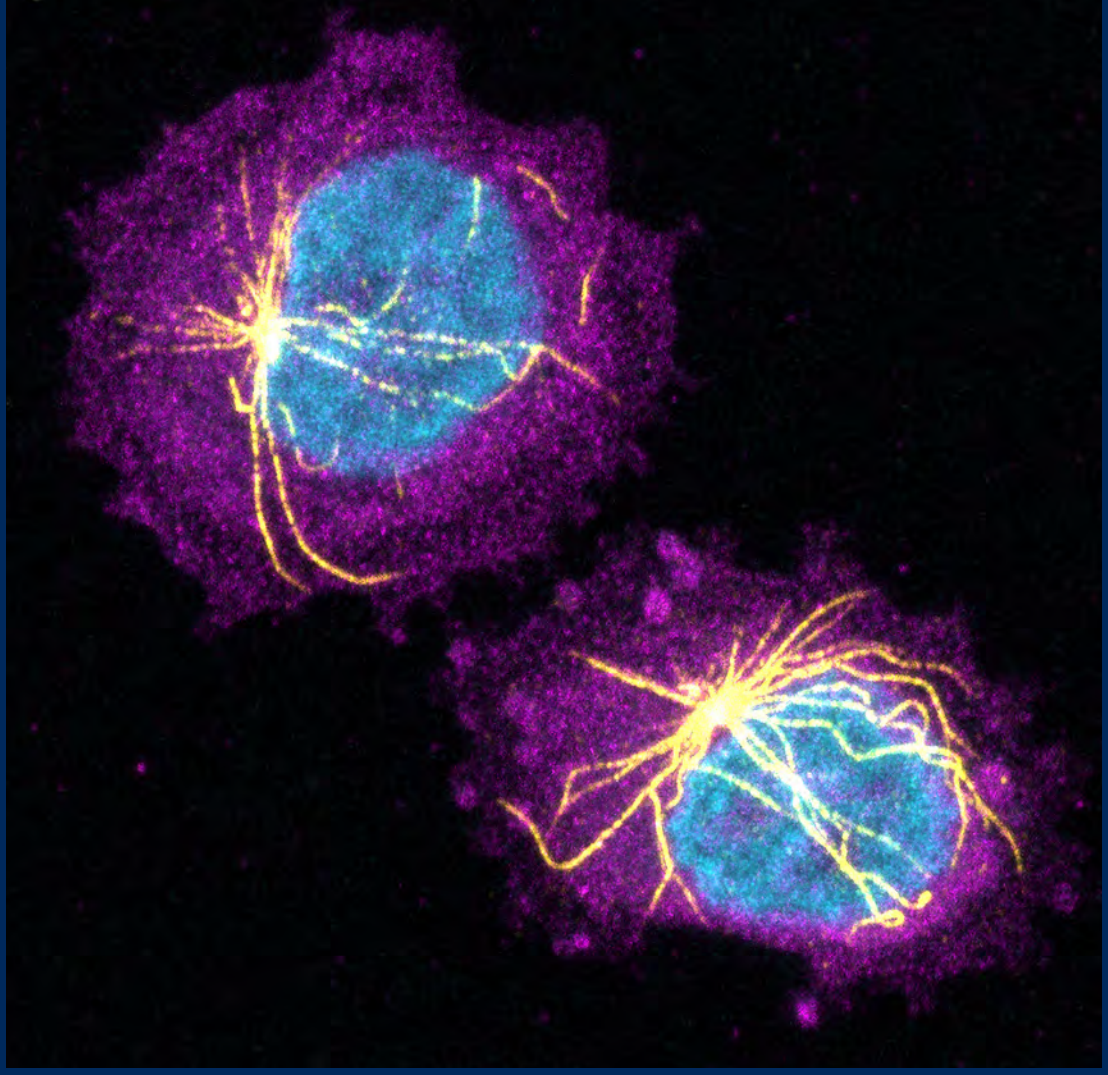


April 2026

Ludwig Link

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

Welcome

Unmesh Kher
Editorial Director

Welcome to the first Ludwig Link of 2026.

Veteran readers have probably noticed that the magazine is not only bulkier than it used to be a few years ago, but far prettier too. For the latter, we thank our researchers, many of whom shared with us images of arresting beauty. The bulk, similarly, comes from their labors, whose products are exceptional.

Take a gander through the Research news section and you'll agree. There's a brief in there, for example, about how cramped quarters make melanoma cells so claustrophobic they literally invade their neighbors. In another pair we describe the findings of two independent studies reporting unique mechanisms by which metastasizing cancer cells guard against death by ferroptosis, each revealing a vulnerability to exploit for cancer therapy. And that's just a bit of the great science in store for you in these pages.

We also, sadly, share news of the death of Richard Hynes, Daniel K. Ludwig Professor for Cancer Research, Emeritus, at Ludwig MIT. We recall with great pride and no less respect his important contributions to cancer research and extend our condolences to his friends and family.

Along with the usual news of awards won by Ludwig-affiliated researchers and snapshots from the Ludwig Harvard retreat last November, we introduce you to Manav Pathania, an accomplished investigator of pediatric brain tumors who joined Ludwig Oxford in February. And, finally, we report the launch of the Ludwig Laboratory for Cell Therapy at Weill Cornell Medicine, which is to be Directed by George Coukos. We take this opportunity to take a quick look back over George's extraordinary tenure as the founding director of the current Lausanne Branch. You will be impressed.

We hope you enjoy this issue of the Ludwig Link.

With warm regards,

Unmesh Kher
Editorial Director

On the cover

Researchers led by Ludwig Oxford's Richard White and Miranda Hunter of the Memorial Sloan Kettering Cancer Center have discovered that the tight physical confinement of tumor cells by surrounding tissues has epigenetic consequences that can influence melanoma progression. Rather than continuing to divide rapidly, squeezed cancer cells in such circumstances activate a program of 'neuronal invasion' and spread into neighboring tissues. Aside from fleeing, confined melanoma cells also build a cytoskeletal cage (yellow) around their nuclei (blue) that helps protect the nucleus from rupture and DNA from damage caused by confinement-induced stress.

Page 36

Image by Miranda Hunter

In this issue

Richard White awarded Academy of Medical Sciences Professorship

We were delighted to learn in November that Ludwig Oxford's Richard White had been awarded an Academy of Medical Sciences (AMS) Professorship, one of three researchers so honored last year. Part of a broader effort to attract top scientific talent to the U.K., the award provides up to £500,000 over five years in flexible research funding to outstanding biomedical researchers who have recently taken up a full professor position in the country. Richard models cancer using zebrafish and human stem cells to investigate, among other things, how gene expression programs involved in embryonic development are co-opted in cancer, with a focus on melanoma. He is especially interested in how processes beyond mutation—such as a cell's anatomical zip code, developmental antecedents and cellular neighbors—contribute to the plasticity of cancer cells and the genesis and progression of tumors. Richard has developed the concept of "oncogenic competence" as a framework for understanding these factors and their possible targeting for cancer therapy. His group has lately taken a keen interest in where biophysical factors, like thermal and mechanical stress, slot into that framework (see story, page 36). Richard plans to apply his AMS award to explore how the thermoregulatory properties of melanin, the pigment produced by both benign and malignant melanocytes, influence the fitness and function of melanoma cells. Our congratulations to Richard on this well-deserved recognition.

Richard White

Yang Shi and Xin Lu elected to prominent Chinese academies

Our congratulations to Ludwig Oxford's Yang Shi and Director Xin Lu, who we learned in December were elected to two prestigious scholarly academies in China as international or foreign academics. Xin was elected to the Chinese Academy of Engineering (CAE), while Yang was elected to the Chinese Academy of Sciences (CAS). CAS and CAE are China's two highest national institutions for science, technology and engineering. CAS focuses on basic and strategic scientific research, spanning the fields of life science, physics, chemistry, mathematics and information technology. The CAE, meanwhile, concentrates on the applied sciences and encompasses medicine, energy, transport, materials, and agriculture. Xin was recognized for her contributions to our understanding of tumor suppression, most notably through the discovery of the ASPP family of proteins as key regulators of the tumor suppressor p53, the most frequently mutated gene in human cancers. Yang was recognized for his discovery of the first histone demethylase, LSD1—and subsequently many other such enzymes—which overturned the long-held dogma that histone methylation is static and irreversible. A total of 51 foreign scholars were elected to the Academies this year.

Yang Shi

Xin Lu

Michael Skinnider

Ludwig Princeton's Michael Skinnider named a Packard Fellow

Ludwig Princeton's Michael Skinnider was chosen as a 2025 Packard Fellow for Science and Engineering in October. The Packard Fellowships honor researchers the David and Lucile Packard Foundation considers "the nation's most promising early-career scientists and engineers." This year's cohort includes 20 such researchers, who will each receive $875,000 over five years to support their studies. The Foundation has awarded more than half a billion dollars to 735 scientists and engineers from 55 universities since the Fellowships were launched in 1988. Mike will apply the flexible funding he gets from the Foundation to support his ongoing efforts to chart the vast and extremely underexplored universe of small molecule metabolites in the body, many of which are likely to play an important role in physiology and disease. The challenge here has more to do with analysis than the availability of experimental tools: mass spectrometry-based metabolomics generates copious data on the small molecules teeming in any given bodily sample, but defining their structures at a reasonable pace and scale remains a problem of staggering complexity. Mike integrates artificial intelligence with biochemical analysis to address that problem and has already shown, in a paper recently published in *Nature*, how large language models can be powerful allies in the effort (see story, page 15).

Ludwig Institute joins Chancellor's Court of Benefactors at Oxford

The Ludwig Institute for Cancer Research was admitted into the University of Oxford's Chancellor's Court of Benefactors in October in recognition of its generous contributions to medical sciences at the university, which has hosted a Ludwig Institute Branch since 2007 under the directorship of Xin Lu. Membership in the Court is a high honor offered to individuals and organizations that the legendary university considers its most significant supporters. Chairman of the Ludwig Institute's Board of Directors Edward McDermott—shown here with Xin and Sir John Bell, former Regius Professor of Medicine at Oxford and a trustee of the Ludwig Institute for Cancer Research Charitable Trust—attended the admissions ceremony and will represent the Ludwig Institute at the Court of Benefactors.

Richard Hynes

1944–2026

It is with great sadness that we learned that Richard Hynes, Daniel K. Ludwig Professor for Cancer Research, Emeritus, at Ludwig MIT died on January 6. He was 81. A scientist as productive as he was inspired, Richard was best known for his discovery of integrins—a family of cell-surface receptors critical to cell adhesion—and his many subsequent contributions to related biology, ranging from embryonic development to cancer to immunology. Born in Kenya, Richard grew up during the 1950s in Liverpool, in the U.K., where he attended school with a couple of the future Beatles, George Harrison and Paul McCartney (the latter, he said, was also a Boy Scout troopmate of his). He earned his PhD from MIT in 1971, returning there four years later as a founding member of the MIT Center for Cancer Research—now known as the Koch Institute. Widely honored for his scientific contributions, not least with the prestigious Albert Lasker Basic Medical Research Award in 2022, Richard also co-founded a biotech, Matrisome Bio, that seeks to develop therapies for cancer and fibrosis by targeting the extracellular matrix. We extend our condolences to the family, friends, colleagues and countless trainees who benefited from his kind and generous guidance and note that, above all else, his was a life truly well lived.

Lahav lab's David Miller presents his work to Jasbeer Khanduja as lab-mate Roubina Tatavosian looks on.

Lahav lab's Joshua François discusses his research.

Constantine Mitsiades, asking a question. The speed talks elicited lively discussion.

Ludwig Harvard's annual retreat

The Ludwig Center at Harvard held its annual retreat, as usual, on the Monday before (the American) Thanksgiving. Also as usual: it was a giant success. Members of the sprawling community assembled by the Center's Co-directors Joan Brugge and George Demetri gathered at the Joseph B. Martin Conference Center with their typical air of scientific gusto, goodwill and mutual support. A day of biomedical show-and-tell and lively discussion followed. The retreat consisted of four differently themed sessions of speed-talks by PIs and trainees, with a few minutes set aside for questions after each talk. Attendees were also treated to a pair of poster sessions—the last enlivened by snacks and what seemed to be a very happy hour. As co-directors, Joan and George shared a vision to link the talent scattered across Harvard's research facilities to create a genuinely collaborative cancer research community. The experiment clearly worked: The Center has become something of a canvas for richly textured cancer research, drawing on a wide palette of scientific and clinical expertise. Partnerships forged across Center laboratories, the directors noted, have yielded at least 110 collaborative publications. Many other studies have benefited as much from the insights and engagement of the Center's formidable brain trust as they have from its funding. Speaking of her fellow director, Joan noted at the start of the retreat: "We really have a true partnership, and I think you all recognize that." The same thing might be said of the Center as a whole.

Stefan Harry, presenting his work on targeting cancer-driving protein complexes with COUPLrs, molecular glues developed in the Bar-Peled lab.

Ozge Somuncu of the D'Andrea lab talks science with a colleague at the retreat's closing happy hour.

Guerriero Lab's Gabriella Antonellis presents her work.

Peter Sorger with Agudo lab's Debolina Ganguly, who presented her work on metastasis and anti-tumor immunity.

Photos by Unmesh Kher

Ludwig Harvard Co-directors Joan Brugge and George Demetri. "We really have a true partnership, and I think you all recognize that," Joan noted in her opening remarks.

Eric Deroze / CHUV

A new Ludwig lab, and an accomplished director, at Weill Cornell Medicine

The Ludwig Laboratory for Cell Therapy will be led by George Coukos, former founding director of the current Lausanne Branch of the Ludwig Institute.

The Ludwig Institute for Cancer Research announced in February the opening of the Ludwig Laboratory for Cell Therapy at Weill Cornell Medicine. Its Director is George Coukos, who recently returned stateside following an extraordinarily productive tenure as the founding director of not only the current Lausanne Branch but also of the Department of Oncology at the University of Lausanne (UNIL) and its hospital, CHUV. Ludwig Distinguished Scholar Douglas Hanahan will serve as interim director of Ludwig Lausanne until a permanent director is appointed.

The Ludwig Laboratory for Cell Therapy will explore tumor immunology and apply cell engineering, synthetic biology and AI to translate its discoveries into next-generation personalized T cell therapies for cancer patients. The launch of the laboratory marks a strategic step for Ludwig, continuing and expanding the Institute's focus on next-generation cell therapies and integrating their underlying discovery science with clinical translation at a top medical institution.

You'd be hard pressed to find a better candidate than George to lead such an effort. As director of Ludwig Lausanne, he conceived, built and ran an ambitious and highly collaborative bench-to-bedside research program for the development, production and clinical evaluation of cellular immunotherapies and cancer vaccines. All this he did while continuing to contribute impressively to the basic and translational exploration of tumor immunology.

None of this was by accident. A physician and renowned scientist, George was already an authority on ovarian tumor immunology with a tenured job when he surprised his colleagues at the University of Pennsylvania more than a decade ago

Gilles Weber / CHUV

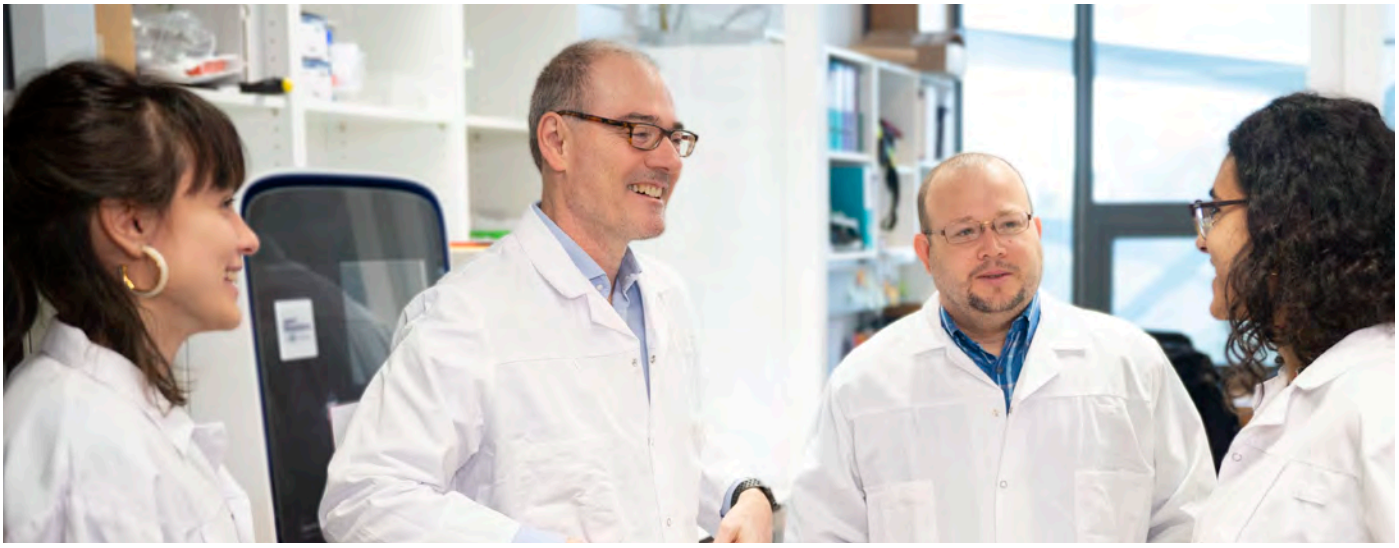
Findings from studies led by George, shown here with Arthur Mulvey (left) and Catherine Ronet, were often applied to devise experimental cell therapies for cancer patients.

with the news that he was heading off to Switzerland to run an ambitious and entirely different kind of experiment in Lausanne. With the Ludwig Institute's support, he told them, he would try to establish a world-class center for personalized immunotherapy in Lausanne.

"I felt the time was right to think big and capitalize on key scientific breakthroughs and technological advances in the field to develop personalized cell-based immunotherapies that would fill a key gap in modern cancer therapeutics," George recalls.

And fill that gap he certainly did. Chief among his accomplishments at Lausanne was the advancement of dendritic cell (DC)-based cancer vaccines and adoptive

Gilles Weber / CHUV



George in his lab, chatting with members of his former Ludwig Lausanne team, Ioanna Rota (left), Jesus Corria and Laura Cabizzosu (right).

Jeanne Martel / CHUV

"I felt the time was right to think big and capitalize on key scientific breakthroughs and technological advances in the field to develop personalized cell-based immunotherapies."

cell therapies (ACT) and development of streamlined production methods for their clinical use. ACT involves the isolation from patients of T cells, their expansion in the lab and subsequent reinfusion for cancer therapy. In collaboration with George, Ludwig Lausanne researchers developed increasingly sophisticated, AI-driven computational methods to identify neoantigens—which are unique to the tumors of individual patients and most likely to elicit a productive therapeutic response. These "neoAg peptides" are being applied to develop DC vaccines and T cells for ACT in clinical trials.

George and his colleagues also devised methods to home in on tumor-infiltrating T lymphocytes (TILs) for ACT that might most effectively target those antigens. They then combined the technologies to create NeoTIL-ACT, which selectively enriches therapeutic TIL cultures with T cells most likely to target a given patient's tumor. They applied neoAg peptides to the production of DC cancer vaccines as well.

Early phase clinical trials in Lausanne evaluating DC vaccines and ACT—including NeoTIL-ACT—have produced encouraging results against several types of highly advanced cancers. Beyond that, George continued his exploration of basic and applied tumor immunology with considerable success. His studies at Lausanne contributed invaluably to identifying mechanisms of immune evasion employed by tumors and markers of anti-tumor immunity. He has also led efforts to engineer T cells to optimize their efficacy as cellular immunotherapies.

As important, George recruited to Ludwig Lausanne an exceptional team of investigators who have become global leaders in their respective fields of study—ranging from myeloid cell biology to the interplay of cancer metabolism and immune responses. The fruits of their research are already being applied to develop new drugs and strategies for cancer therapy.

The team George pulls together at his new base in New York, located at the Sandra and Edward Meyer Cancer Center, will enjoy ready access to world-class expertise in immunotherapy at the Ludwig Collaborative Laboratory at Weill Cornell led by Taha Merghoub and Jedd Wolchok. In addition, its researchers can tap a deep well of expertise in cancer metabolism at Ludwig Princeton. That Branch is also affiliated with the Rutgers Cancer Institute (RCI), which, notably, has an established cell therapy research program. The Laboratory for Cell Therapy will collaborate with RCI, leveraging the established cell therapy manufacturing and clinical infrastructure there for the clinical translation of its products.

Stay tuned for some groundbreaking science out of New York City. The Link will keep you posted.

Eric Deroze / CHUV

George with Ludwig Distinguished Scholar Douglas Hanahan, who will serve as interim director of Ludwig Lausanne until a permanent director is appointed.

Eric Deroze / CHUV

George, meeting here with Sylvie Rusakiewicz (left) and Kalliopi Ioannidou, continued his investigations on the basic mechanisms of tumor resistance and susceptibility to immune clearance.

An AI model for peptide design

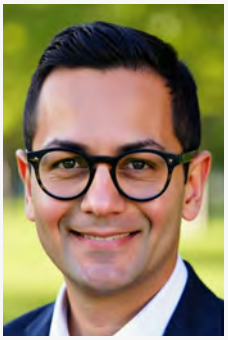
Sangeeta Bhatia

Deep learning guided design of protease substrates | *Nature Communications*, 2026 January 6

Researchers led by Ludwig MIT's Sangeeta Bhatia reported in a January issue of *Nature Communications* a deep learning model for the design of peptides that are clipped with high specificity by defined proteases, a useful tool for cancer therapeutics and detection. Capitalizing on the tendency of cancers to overexpress particular proteases—which help enable metastasis, among other things—the Bhatia lab has over the past 10-plus years developed nanoparticles coated with peptides as diagnostic reporters and established proof of concept for their use in detecting lung, ovarian and colon cancers. The peptide substrates of proteases are roughly 10 amino acids long, which works out to 200 billion possible sequences for each. To work as diagnostic reporters, the peptides must be cleaved both efficiently and selectively by specific proteases. Previously, Sangeeta and her colleagues employed a trial-and-error approach to identify candidate peptides that was informed by published sequences. The end-to-end AI pipeline presented in their paper, CleaveNet, dispenses with that approach. The researchers showed that when applied to matrix metalloproteinases (MMPs), CleaveNet dramatically improved the scale, tunability, and efficiency of substrate design and, in the case of MMP13, captured not only known cleavage motifs but also many that hadn't yet been identified. Aside from its utility in cancer diagnostics, CleaveNet could also be used to design peptide linkers that release antibody-guided drugs exclusively into tumors.

People on the move

A boost to brain tumor research at Ludwig Oxford



Manav Pathania

We extend a warm welcome to Manav Pathania, who joined Ludwig Oxford in February as an assistant member. Manav comes to us from the University of Cambridge, where he led a research group at the Cancer Research UK Children's Brain Tumour Centre of Excellence exploring the role of epigenetics, immune cells and the tumor microenvironment (TME) on the biology of pediatric gliomas. As a postdoc at the UCL Cancer Institute, Manav developed an approach to modeling brain tumors that yielded the first model of H3K27M-driven pediatric glioma whose characteristics closely reflected its human counterparts. His work with that model demonstrated for the first time that mutation of a core chromatin component can drive the genesis of brain tumors by disrupting the normal development of fetal progenitor cells. At Cambridge, Manav applied his techniques to devise 16 additional preclinical models of pediatric glioma along with novel tools to elucidate their drivers and dependencies. These pioneering models have proved useful for translational research, showing, for example, how the crosstalk between tumor and immune cells in the TME might be targeted to enhance therapy. Manav's group at Ludwig Oxford will continue its work on pediatric gliomas while widening its ambit to other brain cancers and the development of novel immunotherapies, such as next-generation CAR-T cells, for brain cancer.

A method to pick patients for BCG therapy

Non-muscle invasive bladder cancer (NMIBC) can be treated with the BCG vaccine, an old vaccine for tuberculosis. But not all patients respond to this unique immunotherapy and there is no way to predict who these responders might be. Analysis of tumor DNA in urine (utDNA) from patients could help but liquid biopsies are confounded by the "field effect", or mutations in noncancerous cells around the tumor. Researchers co-led by Ludwig Stanford's Max Diehn and Ash Alizadeh with a Stanford colleague reported in a *Cell* paper in January that such mutations increase with age—as does the incidence of bladder cancer. They also described a method to identify and remove field effect mutations in utDNA analysis to improve the accuracy of such prediction in patients who have undergone surgery and are being considered for adjuvant BCG therapy. Analyzing 261 samples from NMIBC patients who received BCG following surgery, Max and his colleagues identified three classes of patients: nonresponders, BCG responders and surgery responders. They found that BCG responders show evidence of pre-existing immune activation and tumors with a higher burden of mutations than patients who did not respond to BCG. They also identified potential biomarkers for the identification of patients most likely to benefit from either surgery alone or BCG therapy and, by elimination, those who are likely to need alternative therapies.

Field-effect-informed urine liquid biopsy for bladder cancer | *Cell*, 2026 January 27

Max Diehn

Ash Alizadeh

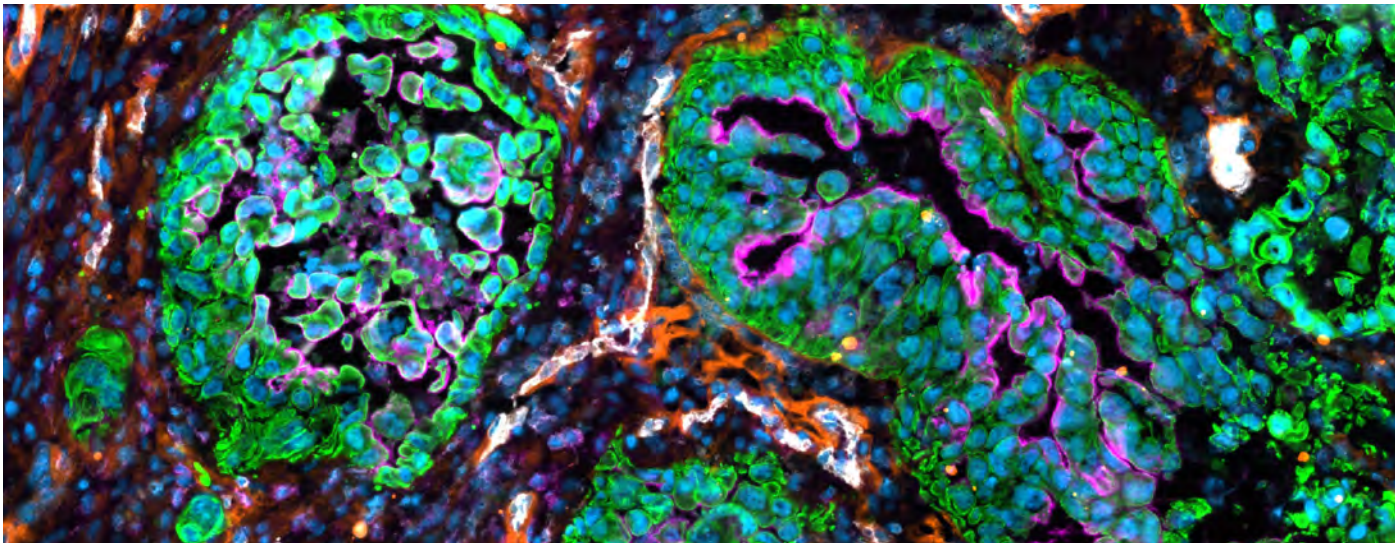
Hantao Qiang

Michael Skinnider

Unleashing AI on the metabolome

Although metabolism has been a focus of relatively intense study for more than a century, a huge number of its molecular byproducts remain unknown. Even when small-molecule metabolites are detected by technologies such as mass spectrometry, they often cannot be identified or structurally described. Large language models (LLMs), which can be trained on the chemical structures of small molecules via formats that represent these structures as short strings of text, could help solve this problem. Such models are already widely and productively applied to predict the structures of macromolecules like proteins, discern their functions and design variants with specific functions based on the evolutionary forces that have shaped the original molecule. The application of LLMs to small molecules, however, has been restricted primarily to generating structures of potential utility as drugs. Researchers led by Ludwig Princeton's Hantao Qiang and Michael Skinnider reported in a January paper in *Nature* their development of an LLM named DeepMet to explore the vast space of unknown metabolites—often called the "dark matter of the metabolome". DeepMet learns from the structures of known metabolites to anticipate the existence of previously unrecognized metabolites. Its integration with mass spectrometry-based metabolomics data facilitates metabolite discovery and the researchers illustrated its power by applying DeepMet to describe several dozen structurally diverse mammalian metabolites.

Language model-guided anticipation and discovery of mammalian metabolites | *Nature*, 2026 January 14



Leire Bejarano

Micrograph showing the diversity of interacting cell types in the microenvironment of a brain metastasis. CD13 (pink) is enriched in cancer cell nests (pan-cytokeratin, green) located in proximity to the tumor vasculature (endothelial cells, white, and stromal cells, orange). All nuclei are visible in blue (DAPI staining).

Leire Bejarano

Johanna Joyce

A tool for metastatic seeding in the brain

Major cancers such as melanoma and those of the lung and breast often spread to the brain. But establishing a viable colony in the unique microenvironment of the brain is a major challenge for the itinerant cancer cell. It entails passage across the formidable blood-brain barrier, followed by the manipulation of the brain microenvironment to engender conditions amenable to tumor growth and survival. This includes the recruitment of resident cells such as microglia—specialized macrophages in the brain—astrocytes and neurons, which are now known to play a central role in brain tumor growth. But the intrinsic characteristics of cancer cells also contribute to metastatic success. Researchers led by Ludwig Lausanne's Leire Bejarano and Johanna Joyce reported in a January paper in *Cell Reports* their discovery of one such factor: aminopeptidase N (or CD13), a membrane-bound enzyme that snips proteins whose elevated expression is associated with poor outcomes in colon, lung and other cancers. They showed that aminopeptidase N is specifically expressed at high levels during the early establishment of metastatic colonies in the brain. Disrupting expression of the protein in mouse models of cancer delayed the growth of metastatic brain tumors and extended survival, while boosting its expression increased metastatic seeding of the brain. Their findings identify a potential drug target for the prevention or treatment of brain metastases, a major unmet need of cancer care.

Tumor-derived aminopeptidase N promotes early stages of brain metastatic colonization
Cell Reports, 2026 January 21

A target and a tweak for CAR-T cell SCLC therapy

Small cell lung cancer (SCLC) tumors resist checkpoint blockade immunotherapy by disabling the machinery of antigen presentation that would otherwise betray their presence to T cells, whose receptors bind only to antigens presented by MHC molecules on sick and cancerous cells. So chimeric antigen-receptor (CAR)-T cells, which detect cancer antigens using an antibody fragment that requires no such presentation, could be a viable alternative for SCLC immunotherapy. The trouble here is that only a couple of CAR targets have been identified for this cancer, and those are mainly expressed in neuroendocrine SCLCs. Researchers co-led by Ludwig Stanford's Crystal Mackall reported in *Cell Reports Medicine* in January that SCLC and thoracic SMARCA4-deficient undifferentiated tumors (UTs)—which clinically mimic SCLC—both express another antigen, B7-H3/*CD276*, that can be targeted for CAR-T therapy. SCLC cells unfortunately express this antigen parsimoniously. SMARCA4-deficient UTs, on the other hand, express it at high levels. They, however, resist CAR-T therapy by secreting TGF-β. Cell culture and animal studies demonstrated that both mechanisms of resistance can be overcome by engineering the CAR-T cells to co-express c-Jun. When knocked in to the CAR-T cell genome using CRISPR-Cas9 editing, c-Jun enhances CAR-T activity by inducing the expression of type I/II cytokines and preventing CAR-T cell exhaustion. The researchers also showed that their manufacturing method is suitable for clinical applications.

Crystal Mackall

c-JUN enhances CRISPR knockin anti-B7-H3 CAR T cell function in small cell lung cancer and thoracic SMARCA4-deficient undifferentiated tumors | *Cell Reports Medicine*, 2026 January 20

A math model suggests how to improve CAR-T cell efficacy

Although chimeric antigen-receptor (CAR) T cell therapies are now being put to the test in the treatment of glioblastoma, neuroblastoma and, most remarkably, the swiftly lethal pediatric cancers known as diffuse midline gliomas, the strategy has proven decidedly less than effective for the treatment of most solid tumors. This is in large measure because CAR-T cells face the same challenges as ordinary anti-tumor T cells: they have trouble infiltrating the tumor and then are swiftly pushed into exhaustion or otherwise disabled by the harsh conditions they find in its microenvironment. The abnormal and dysfunctional blood vessels that feed tumors play no small part in this and several studies spearheaded by Ludwig Harvard's Rakesh Jain have shown that normalizing these vessels using anti-angiogenic drugs, i.e. VEGF inhibitors, can restore the efficacy of both chemo and immunotherapy. In a November paper published in *PNAS*, researchers led by Rakesh reported a mathematical model for the optimization of CAR-T therapy against solid tumors. Their simulations show that vascular normalization with VEGF-blockade can lift immunosuppression considerably and reduce—by roughly fivefold—the dosage of CAR-T cells required to elicit a therapeutic effect. Their model, notably, also captures the benefits of optimal scheduling of the therapy and suggests that direct delivery of CAR-T cells to tumors could mitigate T cell exhaustion and improve outcomes.

Rakesh Jain

Physiologically based pharmacokinetic model for CAR-T cell delivery and efficacy in solid tumors | *PNAS*, 2025 November 11

The benefits, and potential cost, of membrane ethers

Researchers co-led by Ludwig MIT Co-director emeritus Robert Weinberg, alumnus Whitney Henry—who now leads her own lab at MIT—and a colleague at the Institut Curie in France employed a combination of genetic approaches, lipid reconstitution assays, three-dimensional microvascular network systems and animal models to examine how ether lipids in the membrane contribute to cancer cell metastasis and survival. Highly drug-resistant stem-like cancer cells (CSCs) with mesenchymal traits—those essential to metastasis, such as motility and structural plasticity—tend to accumulate iron. The element is essential to cellular energy generation. But it also makes the cells susceptible to iron-dependent cell death, or ferroptosis, which is fueled by the oxidation of membrane lipids. The researchers previously found that ether lipids are major substrates for such oxidation. Robert, Whitney and colleagues reported in a January publication in *Nature Communications* that ether lipids support motility and morphological plasticity by establishing a low tension and high fluidity in the CSC's external membranes. Further, they enable the clathrin-free, CD44-mediated uptake and hoarding of iron. Accordingly, loss of ether lipids from the membrane compromises the stemness of the cancer cells as well as their extravasation, a key step in metastasis. Ether lipid loss, the researchers showed, diminishes metastatic burden in mouse models. So a membrane property that confers a functional advantage to metastatic cells also exacts a cost: ferroptotic vulnerability.

Ether lipids influence cancer cell fate by modulating iron uptake | *Nature Communications*, 2026 January 27

Robert Weinberg

Whitney Henry

Rakesh Jain

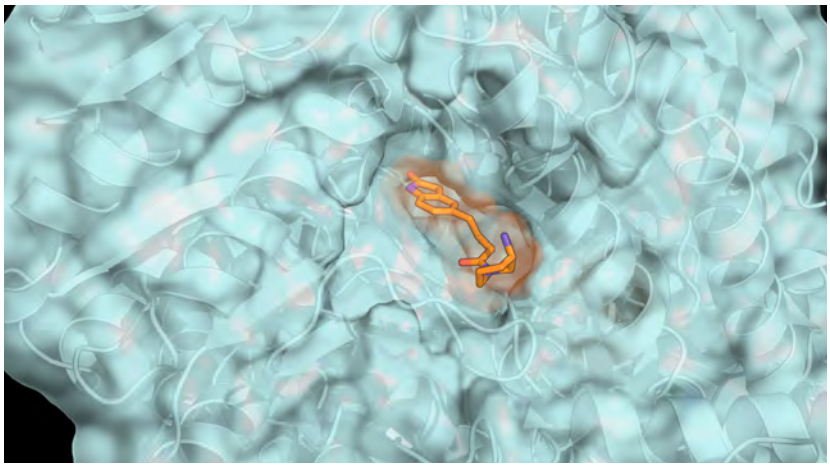
Matthew Vander Heiden

How nutrient availability affects breast cancer metastasis

The factors that determine where in the body breast cancer can metastasize are not well understood. It is likely, however, that the metabolic profile of any given tissue plays a role. Researchers led by Ludwig Harvard's Rakesh Jain and Ludwig MIT's Matthew Vander Heiden and their Harvard colleague George Church reported in a January issue of *Nature* their findings from a sweeping examination in mice of the metabolic conditions that make tissues amenable to breast cancer metastasis. The researchers quantified the absolute levels of 124 nutrients in various mouse tissues to chart the metabolic landscape encountered by metastasizing cells. They then examined how this relates to the ability of tissues to host breast cancer metastases by engineering breast cancer cells to disrupt their synthesis of specific nutrients and testing their ability to grow in those tissues. They found that no single nutrient accounts for such ability in any tissue. Rather, it is the interplay of intrinsic cancer cell traits and multiple nutrients in the tissue microenvironment that determines whether a breast cancer cell can seed a metastatic tumor. However, purine synthesis did emerge as an indispensable requirement for breast cancer metastasis and tumor growth across multiple tissues. That dependency was unaltered by the availability of nucleotides in any given tissue or their synthesis by tumor cells. This finding suggests a general terrain for the discovery of therapeutic targets.

Nutrient requirements of organ-specific metastasis in breast cancer | *Nature*, 2026 January 7

A tour de force of retinoid biology



Kang lab

For more than a century, efforts to develop viable drugs to block retinoid signaling have met with failure. This image depicts the putative binding mode of one of the identified inhibitors to ALDH1A3 active site. The inhibitor, developed in the Kang lab, was identified using a hybrid computational and experimental approach.

Researchers led by Ludwig Princeton's Yibin Kang and Cao Fang detailed in a *Nature Immunology* paper in January how all-trans retinoic acid (atRA) produced by dendritic cells (DCs) alters them to induce tolerance of tumors. This tolerance diminishes the efficacy of DC vaccines—partly explaining why such immunotherapies have met with limited success. Retinoic acids (RA) are produced by a family of aldehyde dehydrogenase (ALDH1A) enzymes. ALDH1a3 is often overexpressed in human cancer cells, while ALDH1a2 is produced by certain immune cells. Cao, Yibin and colleagues found that under conditions commonly employed to produce DC vaccines, differentiating DCs begin expressing ALDH1a2, producing high levels of RA. The nuclear signaling pathway activated by RA suppresses the maturation of DCs, diminishing their ability to trigger anti-tumor immunity. RA also favors the development of macrophages that are less efficient than DCs in presenting tumor antigens for immune recognition, further undermining the efficacy of DC vaccines. The researchers also reported the design of a candidate drug that inhibits RA production by both cancer cells and DCs by targeting both ALDH1a2 and ALDH1a3. The compound, KyA33, not only boosted the efficacy of DC vaccines in preclinical studies but also holds promise as an independent cancer immunotherapy. This comes on the heels of a separate study led by Yibin and former graduate student Mark Esposito, reported in *iScience* last November, that described the rational design and preclinical development of drugs that inhibit retinoic acid production. For more than a century, efforts to develop viable drugs to block retinoid signaling have failed. The process of drug discovery developed in the latter study provided the blueprint for the design of KyA33. The study also resolved an enduring paradox of retinoid signaling in cancer. atRA has been shown to induce the growth arrest and death of cancer cells in laboratory cell cultures. Yet, much evidence, including the findings of large clinical trials, indicates that high intake of vitamin A or RA increases cancer incidence and mortality. The team showed that ALDH1a3 is overexpressed in diverse cancers to generate RA, but that cancer cells lose their responsiveness to retinoid receptor signaling. Further, atRA secreted into the tumor microenvironment suppresses anti-cancer immune responses, including those mediated by T cells. The researchers showed that their novel ALDH1a3 inhibitors serve as a potent immunotherapy in mouse models of cancer.

Yibin Kang

Cao Fang

Targeting autocrine retinoic acid signaling by ALDH1A2 inhibition enhances antitumor dendritic cell vaccine efficacy | *Nature Immunology*, 2026 January 5

Development of retinoid nuclear receptor pathway antagonists through targeting aldehyde dehydrogenase 1A3 *iScience*, 2025 November 21

Shared DNA targets enable cancer cell plasticity

Multiple transcription factors can target a given DNA sequence to control gene expression. Having related transcription factors target the same genes with divergent outcomes could be a mechanism of nongenetic adaptation by which cancer cells accommodate the demands of a changing microenvironment (by, for example, switching from brisk proliferation to differentiation, or simply fleeing the scene). Researchers led by Ludwig Oxford's Pakavarin Louphrasitthiphol and Colin Goding explored such co-targeting by three closely related transcription factors—TFEB, TFE3 and MITF—in melanoma. They detailed in a December publication in *Cell Reports* how the three transcription factors influence melanoma progression and cooperate to enable cellular adaptations to the harsh microenvironment of the tumor. Pakavarin, Colin and their colleagues show that far from being redundant, each transcription factor regulates different and often opposing gene expression programs that coordinate differentiation, metabolism and protein synthesis and limit immune cell infiltration of the tumor. MITF, for example, promotes proliferation and glycolysis while TFEB drives differentiation and, along with TFE3, mitochondrial respiration. The regulated exchange of MITF, TFEB and TFE3 enables phenotypic switching that flips cancer cells from proliferation into states conducive to invasion. Significantly, TFE3 suppresses T cell and macrophage immune infiltration into tumors whereas loss of both MITF and TFE3 reverses the effect of loss of TFE3 alone, but instead leads to increased NK cell infiltration.

MITF, TFEB, and TFE3 drive distinct adaptive gene expression programs and immune infiltration in melanoma | *Cell Reports*, 2025 December 23

Pakavarin Louphrasitthiphol

Colin Goding

Alexander Rudensky

Xiao Huang

How a subtype of regulatory T cells aids anti-tumor immunity

Tumor-associated regulatory T cells (Tregs), which restrain autoimmune reactions in healthy tissues, are generally associated with adverse outcomes across cancers. In colorectal cancers (CRCs), however, increased numbers of intratumoral Tregs have been linked to improved survival. Researchers co-led by Ludwig MSK's Alexander Rudensky and Xiao Huang with MSK colleague Christina Leslie reported in a December issue of *Immunity* that this is because two subtypes of Tregs in CRC tumors, defined by their expression of immunomodulatory cytokine IL-10, have opposing effects on the cancer's progression in mouse models. Found mainly in tissue adjacent to the tumor, IL-10^{+} Tregs suppress the production of IL-17—an interleukin that drives tumor growth—by Th17 T cells. Meanwhile, IL-10^{-} Tregs, which are found within tumors, drive tumor growth by inhibiting the anti-tumor activity of cytotoxic T cells. The opposing effects of IL-10$^{+/-}$ Tregs on outcomes are reflected in human CRCs. A meta-analysis of single-cell gene expression datasets revealed that similar Tregs are present in lung, stomach and skin cancers. Further, IL-10^{-} Tregs express CCR8, suggesting they might be depleted by antibodies to CCR8—a target already under evaluation in several clinical trials for cancer therapy. The functional differences between the two types of Tregs could permit selective targeting of pro-tumoral Treg cells while preserving the anti-tumor variety.

Opposing functions of distinct regulatory T cell subsets in colorectal cancer | *Immunity*, 2025 December 15

Jiaxin Ge

Kenneth Kinzler

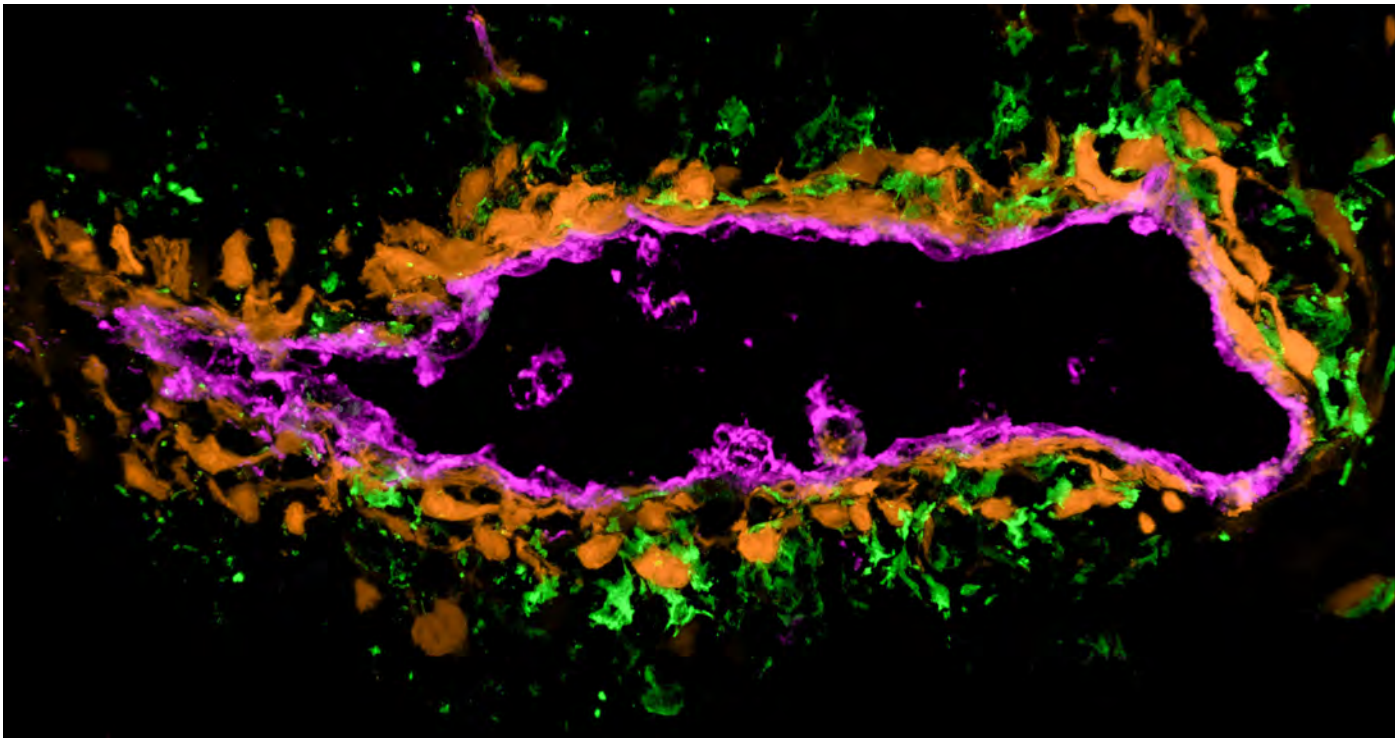
Bert Vogelstein

Suman Paul

A possible targeted therapy for T cell cancers

One of the challenges of developing effective therapies for T cell lymphomas and leukemias—for which few treatments exist—is that patients are extremely sensitive to the loss of these versatile immune cells. Enough T cells must be left alive following therapy to ensure patients can still battle infections. In pursuit of that goal, researchers led by Ludwig Johns Hopkins' Jiaxin Ge, Kenneth Kinzler, Bert Vogelstein and Suman Paul reported in *Nature Cancer* in December the second iteration of a therapeutic strategy for selectively killing T cells recently developed at the Johns Hopkins Center that could enable the development of an off-the-shelf therapy for these cancers. Their strategy exploits the fact that healthy T cell pools in people express a mix of two T cell receptor alleles: TRBC1 (about 40%) and TRBC2 (60%). Cancerous T cell pools, being descendants of a single transformed clone, express only one of those alleles. The researchers described the design and preclinical evaluation of an antibody-drug conjugate (ADC) that selectively targets TRBC2-expressing T cells, following up on one reported in 2024 that similarly eliminates T cells expressing TRBC1. The high-affinity anti-TRBC2 ADC specifically targeted TRBC2+ cancers *in vitro* and in mouse models, opening a new approach to treating T cell malignancies that targets one clonotype that characterizes a T cell cancer while sparing the other to sustain T cell-mediated immune responses.

TRBC2-targeting antibody–drug conjugates for the treatment of T cell cancers | *Nature Cancer*, 2025 December 22



F. Duval

Immune hubs within tumors can either strengthen or dampen the body's anti-tumor response. These structures form in close proximity to blood vessels (pink, endothelial cells; orange, pericytes) and contain CCR7+ dendritic cells (green), which can either activate or suppress anti-tumor immunity

Mikaël Pittet

Positioning and reversible suppression of CCR7+ dendritic cells in perivascular tumor niches shape cancer immunity
Immunity, 2025 December 19

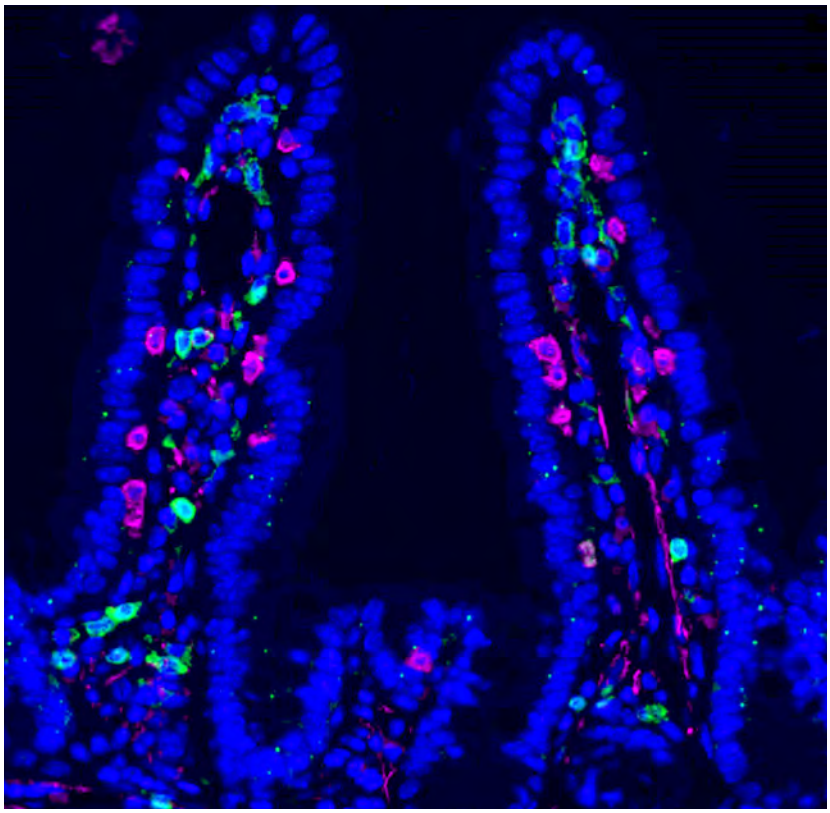
On cDC clustering and anti-tumor immunity

Researchers led by Ludwig Lausanne's Mikaël Pittet described in a December paper in *Immunity* the localization of CCR7+ conventional dendritic cells (cDCs) within tumors and showed how their positioning influences anti-tumor immune responses. The chemokine receptor CCR7 is expressed by activated type 1 and 2 cDCs, professional antigen-presenting immune cells that activate and direct anti-tumor T cell responses. Their relative abundance in tumors is associated with better survival outcomes and responses to immunotherapy in cancer patients. Single-cell, spatial and intravital analyses of tumors from patients and in mouse models revealed that fibroblasts surrounding venous blood vessels produce the chemoattractant CCL19 to guide CCR7+ DCs into perivascular niches, where they cluster and activate T cells. CCR7+ DCs in these clusters are often contacted by regulatory T cells (Tregs), which suppress their expression of CD40 and inhibit their ability to activate CD4+ and CD8+ T cells. Mikaël and colleagues showed that depleting Tregs reverses this effect and improves T cell-mediated tumor control. Notably, anti-PD-1 immunotherapy promotes not only CCR7+ DC clustering but also interaction with Tregs via a CCL22-mediated mechanism, mitigating the efficacy of checkpoint blockade therapy. The authors suggested that the pharmacologic targeting of these cellular interactions in perivascular immune hubs may offer a path to improving patient responses to cancer immunotherapy.

A positive side-effect of chemotherapy

Researchers led by Ludwig Lausanne's Ludivine Bersier and Tatiana Petrova reported in a December publication in *Nature Communications* a gut-to-bone marrow axis of signaling that helps prevent liver metastases of colorectal cancer (CRC) and is induced by the indirect effects of chemotherapy on gut microbes. They show that intestinal inflammation, or mucositis, caused by chemotherapy alters nutrient availability in a manner that promotes the growth of bacteria that metabolize tryptophan into indole-3-propionic acid (IPA). This molecule reprograms immune cell generation in the bone marrow to favor the development of macrophages over immunosuppressive monocytes, effectively giving a surprising, positive spin to a common side-effect of chemotherapy. The immune shift enhances the anti-tumor activity of CD4+ T cells and spatially reorganizes their interactions with CD8+ T cells at metastatic sites. Moreover, the observed reprogramming of the immune system outlasts the duration of therapy, disfavoring the post-treatment spread of the cancer to the liver. Ludivine, Tatiana and their clinical colleagues also showed that IPA levels in CRC patients are a fifth of those seen in healthy people and higher circulating IPA levels after chemotherapy in a subset of patients correlated with fewer monocytes and better outcomes. This suggests IPA might have therapeutic potential as an agent that prevents relapse in patients receiving chemotherapy.

Chemotherapy-driven intestinal dysbiosis and indole-3-propionic acid rewire myelopoiesis to promote a metastasis-refractory state | *Nature Communications*, 2025 December 15



Ludivine Bersier

Immunostaining of mouse small intestine for DNA (blue), CD4+ (red), and CD8+ (green) T cells.

Ludivine Bersier

Tatiana Petrova

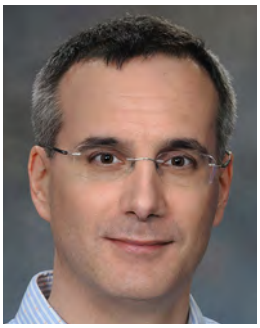
The pentose phosphate pathway and anti-tumor immunity

The oxidative pentose phosphate pathway breaks down glucose to generate nicotinamide adenine dinucleotide phosphate (NADPH), which is critical for biosynthesis and redox defense in cells. The pathway involves two key NADPH-producing enzymes: glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (PGD). Previous studies have suggested that G6PD supports but PGD limits T cell-mediated immunity. Researchers led by Ludwig Princeton's Joshua Rabinowitz and Zihong Chen reported in a December issue of *PNAS* that both enzymes are important for T cell-mediated immune responses. PGD loss in T cells causes systemic depletion of T cells, while G6PD loss results in activation-induced T cell apoptosis. The latter effect cannot be rescued by supplementation with the biosynthetic products of oxidative phosphorylation but could be partially remedied by removal of the oxidized dimeric amino acid cystine from cell culture media. Redox stress induces uptake of cystine, which is normally a precursor to reduced antioxidant molecules like glutathione. But in the absence of sufficient NADPH, the cystine remains stuck in its oxidized dimeric form causing disulfide stress and ultimately apoptosis. The findings establish the pentose phosphate pathway as a driver of anti-tumor immunity and support clinical examination of the efficacy of checkpoint blockade immunotherapies in people with G6PD deficiency—the most common enzyme deficiency in humans.

Oxidative pentose phosphate pathway is required for T cell activation and antitumor immunity | *PNAS*, 2025 December 3

Joshua Rabinowitz

Zihong Chen



Patrick Barth

Caroline Arber

Fortifying therapeutic T cells with synthetic receptors

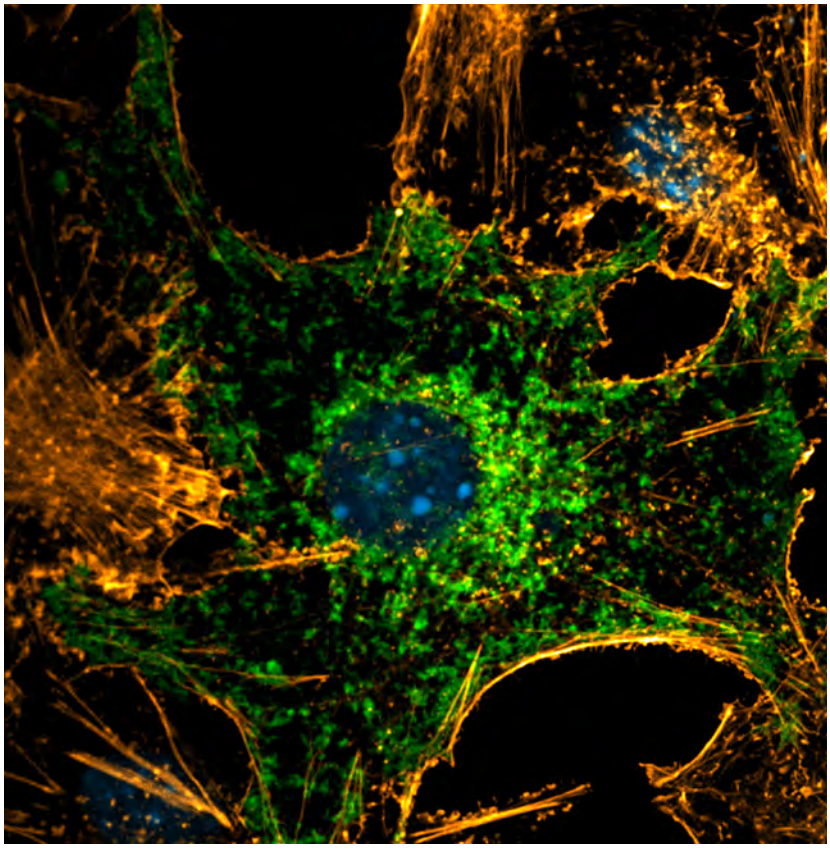
Cytotoxic T cells (CTLs) become dysfunctional in the tumor microenvironment (TME) for a variety of reasons. These include an abundance of inhibitory factors in the TME and a paucity of stimulatory ones, such as cytokines. Researchers led by Ludwig Lausanne's Patrick Barth and Caroline Arber reported in an October publication in *Nature Biomedical Engineering* a computational platform that addresses these challenges through the design of co-stimulatory cell-surface receptors that can be engineered into T cells or CAR-T cells used for adoptive cell therapies to enhance their anti-tumor efficacy. Called T-SenSERs (for TME-sensing switch receptors), the synthetic receptors are built by mixing and matching functional protein domains so that they convert the signals transmitted by factors abundant in the TME into co-stimulatory signals known to boost T cell function. The researchers demonstrated the utility of their platform by engineering T-SenSERs that bind either vascular endothelial growth factor or colony-stimulating factor-1, which both promote tumor growth and are selectively enriched in a variety of tumors. CAR-T cells equipped with these engineered receptors, which transmit a signal that boosts T cell proliferation and cytotoxicity when activated, showed enhanced anti-tumor activity in models of lung cancer and multiple myeloma.

Computational design of synthetic receptors with programmable signalling activity for enhanced cancer T cell therapy | *Nature Biomedical Engineering*, 2025 October 28

A target specific to metastatic melanoma cells in lymph nodes

Cancer cells often suppress ferroptosis—an iron-fueled mechanism of cell death driven by the rampant oxidation of membrane lipids—by expressing high levels of antioxidant proteins. Researchers led by Ludwig Harvard's Mario Palma and Jessalyn Ubellacker reported in a November issue of *Nature* that melanoma cells that metastasize to the lymph nodes become highly dependent on one such protein known as ferroptosis suppressor protein 1(FSP1). They show that FSP1 inhibitors significantly curtailed tumor growth in a mouse model of melanoma that favors lymph node metastases. Notably, FSP1-dependency is an adaptation of melanomas spreading through the lymph nodes; subcutaneous melanoma tumors are not susceptible to FSP1 inhibition. Jessalyn and her colleagues showed that a metabolic shift likely leads to FSP1 dependency. Melanoma cells traveling through the bloodstream rely on another protein, GPX4, to resist ferroptosis. Those in lymph nodes lose that dependency. GPX4 is lost to ubiquitination and degradation by proteasomes in hypoxic conditions comparable to those found in the microenvironment of the lymphatic niche, leaving the cells dependent on FSP1 to guard against ferroptosis. Aside from identifying a potential drug target for metastatic melanoma, the study illustrates how important it is to examine ferroptosis and other processes targeted for cancer therapy in the context of their natural tissue microenvironment.

Lymph node environment drives FSP1 targetability in metastasizing melanoma | *Nature*, 2025 November 5



Mario Palma

Fluorescence microscopy image of lymph node metastatic melanoma cells, showing ferroptosis suppressor-1(FSP1) in green, cytoskeletal actin filaments in orange, and cell nuclei in blue.

Mario Palma

Jessalyn Ubellacker

A driver of T cell exhaustion hides in the matrix

Researchers led by Ludwig Weill Cornell's Chien-Huan Weng and Co-directors Taha Merghoub and Jedd Wolchok reported in a November issue of *Nature Immunology* an underappreciated mechanism by which anti-cancer T cells in tumors are pushed into functional exhaustion and showed in preclinical studies how it might be sabotaged to boost the efficacy of cancer immunotherapy. They found that thrombospondin-1 (TSP-1), an extracellular matrix protein, can bind CD47, a receptor on the surface of CD8+ T cells (CTLs), to drive their functional exhaustion. The study stemmed from observations made several years ago in Jedd and Taha's lab that CD8+ T cells bearing the markers of exhaustion also express CD47 at noticeably high levels. The researchers discovered that TSP-1 engagement of CD47 activates the calcineurin-NFAT signaling pathway and drives the expression of TOX, a master regulator of T cell exhaustion, along with other markers of exhaustion. Disruption of TSP-1 binding to CD47 by a small peptide snapped exhausted anti-tumor T cells out of their functional stupor. This revived the cell-killing capabilities of CTLs, improved their infiltration into tumors—even into "cold" tumors that ordinarily harbor few CTLs—and improved the efficacy of PD-1 blockade, extending survival in mouse models of cancer.

Thrombospondin-1–CD47 signaling contributes to the development of T cell exhaustion in cancer
Nature Immunology, 2025 November 17

Chien-Huan Weng

Taha Merghoub

Jedd Wolchok

Jeffrey Rathmell

Targeting glutamine metabolism to enhance immunotherapy

The amino acid glutamine is critical to cancer cell survival and efforts to inhibit its metabolism for therapy have been underway since the 1950s. Multiple studies have since revealed that glutamine inhibition not only kills cancer cells directly but also supports anti-tumor immunity. But the first inhibitor of glutamine metabolism, DON, proved too promiscuous in its targeting and thus too toxic for clinical use. Researchers led by Ludwig Chicago Co-director Jeffrey Rathmell employed an *in vivo* CRISPR screen on CD8+ T cells in the tumor microenvironment (TME) to identify a more specific inhibitor of glutamine metabolism for cancer therapy. They reported in an October publication in *The Journal of Immunology* that while other glutamine-metabolizing enzymes are essential to T cells, the deletion of glutamine synthetase (GS) uniquely improved CD8+ T cell fitness in the tumor microenvironment (TME), boosting mitochondrial respiration and resistance to reactive oxygen species, among other things. Both GS deletion and pharmacological inhibition improved tumor control in mouse models. GS-deficient CD8+ T cells transferred into mice were more resilient under the metabolic stress of the TME, better at killing cancer cells and expressed genes known to be markers of memory and stemness. Jeffrey and his colleagues argue that their findings suggest GS-inhibition might be a powerful therapeutic companion for multiple cancer immunotherapies.

Glutamine synthetase deficiency enhances CD8 T cell survival and stress resilience in the tumor microenvironment | *The Journal of Immunology*, 2025 October 31

Ralph Weichselbaum

Dapeng Chen

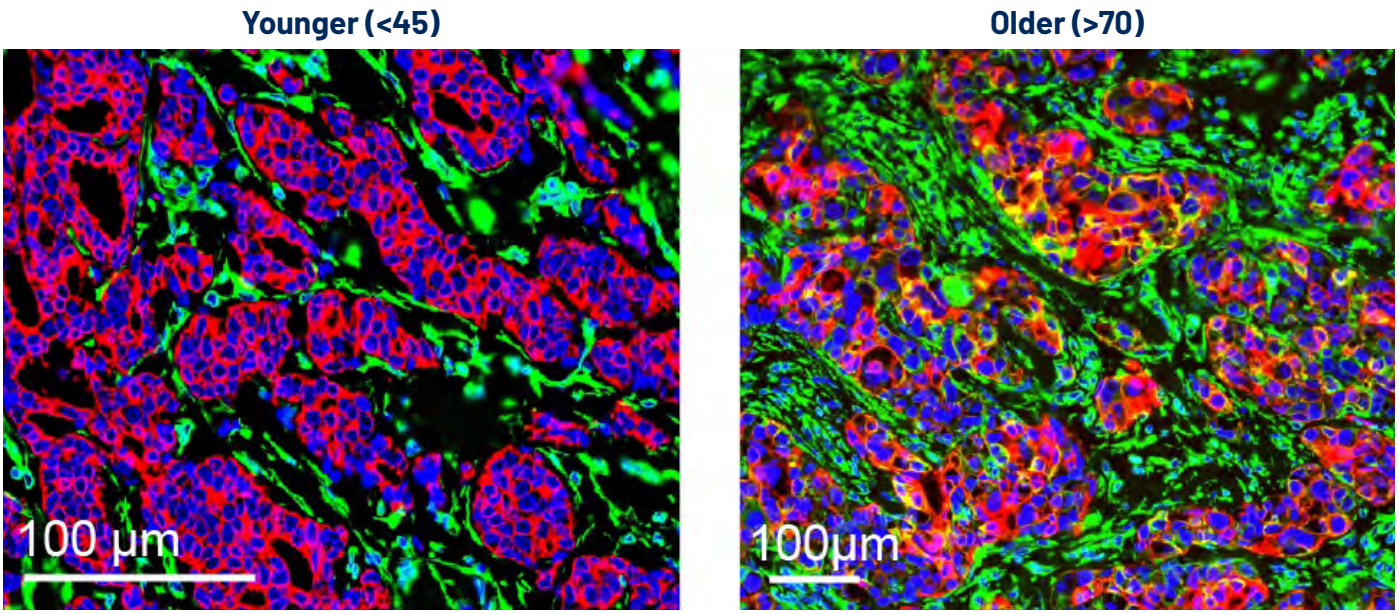
Chuan He

Hua Laura Liang

Radiation calls up YTHDF2 in dendritic cells to resist radiotherapy

Ludwig Chicago researchers have previously demonstrated that the m6A RNA-binding protein YTHDF2, which is expressed at high levels in myeloid-derived suppressor cells following radiotherapy (RT), plays a key role in the immunosuppression induced by those cells—and that its inhibition boosts RT efficacy in mouse models. In a November paper in the *Journal of Experimental Medicine*, a Center team led by Co-director Ralph Weichselbaum, Dapeng Chen, Chuan He and Hua Laura Liang reported that YTHDF2 is also a radiation-induced immune checkpoint in dendritic cells (DCs) and that a spike in its expression in DCs following exposure to ionizing radiation correlates with RT failure in patients. They found that radiation induces the expression of SPI1, which drives YTHDF2 expression in DCs. This promotes the m6A-mediated degradation of Notch pathway regulators, which in turn impairs the ability of DCs to cross-present antigens to CD8+ T cells and stimulate their anti-tumor activity, resulting in immune evasion and metastasis. Targeting YTHDF2 restored DC immunogenicity and enhanced RT-induced tumor control. It also improved the efficacy of DC-based cancer vaccines when combined with RT in animal models, suggesting a strategy to overcome RT resistance and limit metastases.

Radiotherapy induces YTHDF2 in dendritic cells impairing cross-presentation and T cell function | *Journal of Experimental Medicine*, 2025 November 6



The Van Galen and McAllister labs

Representative composite images of TNBC tumor tissue sections from a younger (<45) and an older (>70) patient stained for panCK (red) and vimentin (green). Nuclei are stained with DAPI (blue). Colocalization of vimentin+/panCK+ cells is indicated in yellow, revealing epithelial–mesenchymal transition, which is increased in older patients.

Peter van Galen

Cell populations in human breast cancers are molecularly and biologically distinct with age
Nature Aging, 2025 November 4

Exploring the interplay of age and carcinogenesis in breast cancer

Compared to women between the ages of 55 and 64 who are diagnosed with breast cancer, women both younger and older have worse outcomes, regardless of their particular subtype of the cancer. Why this should be is unclear. Both demographics have long been underrepresented in clinical trials, and not much is known about how age affects the cells of the tumor microenvironment and shapes pathology. Yet the subtypes of disease seen most often in each subgroup do vary with age. The incidence of triple-negative breast cancer (TNBC), for example, is relatively higher in younger women, while hormone receptor-positive disease is markedly more common in older women. Through analysis of existing bulk and single-cell transcriptomic data, researchers co-led by Ludwig Harvard's Peter van Galen and Harvard colleague Sandra McAllister developed a framework for understanding cell-specific, age-associated changes in gene expression, protein levels and cellular interactions within the tumor microenvironment in TNBC and estrogen receptor positive (ER^+) breast cancers. They reported in a *Nature Aging* paper in November an Age-Specific Program ENrichment (ASPEN) analysis pipeline that exposes age-related changes in the malignant and noncancerous cells of the tumor microenvironment for both types of breast cancer, and the signaling pathways potentially underlying those changes. The study identified possible targets for age-adapted therapeutic interventions for breast cancer.

An AI for cellular potency

The cells of multicellular organisms can be hierarchically arranged based on their capacity to generate other cell types. This "potency"—ranging from totipotent to differentiated—declines with each step of that hierarchy. From the observation that the diversity of genes expressed by cells similarly declines with differentiation, researchers led by Ludwig Stanford's Aaron Newman developed in 2020 a computational framework named CytoTRACE to predict the potency of cells based on single-cell RNA sequencing data. In October, Aaron and his colleagues reported in *Nature Methods* their development of CytoTRACE 2, an AI-powered improvement on its predecessor. For CytoTRACE 2, the researchers trained a machine learning algorithm on huge datasets of gene activity known to be associated with various levels of differentiation. They then sorted the cells into six levels of potency and 24 subcategories. While the original CytoTRACE can only compare the potency of cells within a single dataset, CytoTRACE 2 can do so across datasets, assigning an absolute measure of potency to any given cell across tissues. Most notably, its results are interpretable—providing insight into such things as the gene expression programs that determine potency. Illustrating its utility for cancer research, the researchers showed CytoTRACE 2's predictions correspond to established stem cell signatures in a leukemia and could identify the known multilineage potential of oligodendroglioma cells. These results open the door to more precise identification of high potency cells in cancer.

Aaron Newman

Improved reconstruction of single-cell developmental potential with CytoTRACE 2 | *Nature Methods*, 2025 October 27

Foxp3-less Tregs resist identity crisis

Regulatory T cells (Tregs) suppress autoimmunity and inflammation and are exploited by a variety of solid tumors to muffle anti-tumor immunity. The identity of Tregs is defined by Foxp3 and their function depends on the transcription factor. However, it has not been clear just how dependent the gene-expression programs that define Treg cell function are on its continuing activity in differentiated Treg cells. Researchers co-led by Ludwig MSK Director Alexander Rudensky used a mouse model of inducible Foxp3 protein degradation to explore the matter. They reported in an October *Nature Immunology* paper that while Foxp3 is required to establish the identity and function of "young" Treg cells, its loss under steady state has no effect on the immunosuppressive function of mature Tregs and is accompanied by only minimal changes to their gene expression patterns. Foxp3 activity is, however, required for appropriate function and fitness under conditions of intense inflammation, even in mature Treg cells. The researchers also found that Foxp3 loss caused the preferential destabilization and dysfunction of intratumoral Tregs in mouse models, enabling anti-tumor immune responses and the shrinkage of tumors without inducing adverse side-effects. The researchers suggest this presents a unique opportunity to develop immunotherapies for tumors that harbor large numbers of these immunosuppressive cells.

Alexander Rudensky

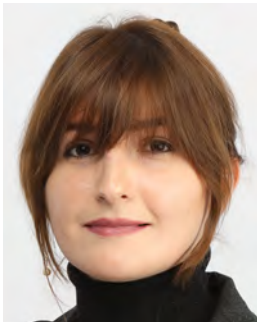
Temporal and context-dependent requirements for the transcription factor Foxp3 expression in regulatory T cells | *Nature Immunology*, 2025 October 8

The how and where of tRNA Ψs

Pseudouridine (Ψ) is one of the most common RNA modifications in human cells. Made to multiple types of RNA by pseudouridine synthases (PUSs), the modifications play an important role in stabilizing RNAs and ensuring their appropriate splicing and translation into proteins. PUS enzymes are increasingly recognized as key players in genetic diseases, including cancer, but their specific biological roles are in most cases undefined. To chart the universe of Ψ modifications and their various PUS authors, researchers led by Ludwig Oxford's Chunxiao Song and Parinaz Mehdipour generated knockouts and knockdowns of individual PUS enzymes and mapped the resulting Ψ profiles using a sequencing method developed in the Song lab known as BACS (for 2-bromoacrylamide-assisted cyclization sequencing). BACS converts Ψ to C mutations in RNAs, enabling direct, quantitative, base-resolution sequencing of the modification. Chunxiao, Parinaz and their colleagues reported in an October publication in *Nature Cell Biology* several previously unknown transfer (t) RNA targets of various PUS enzymes and showed that a pair of them—TRUB1 and PUS10—redundantly catalyze the tightly conserved Ψ55 modification, which is essential to tRNA structure and ribosome binding. They reported in this paper the first comprehensive map of PUS-dependent modifications in human tRNAs that links each PUS enzyme to its tRNA targets, effectively creating a reference map to guide studies of the roles these enzymes play in health and disease.

A comprehensive tRNA pseudouridine map uncovers targets dependent on human stand-alone pseudouridine synthases | *Nature Cell Biology*, 2025 October 24

Chunxiao Song



Parinaz Mehdipour

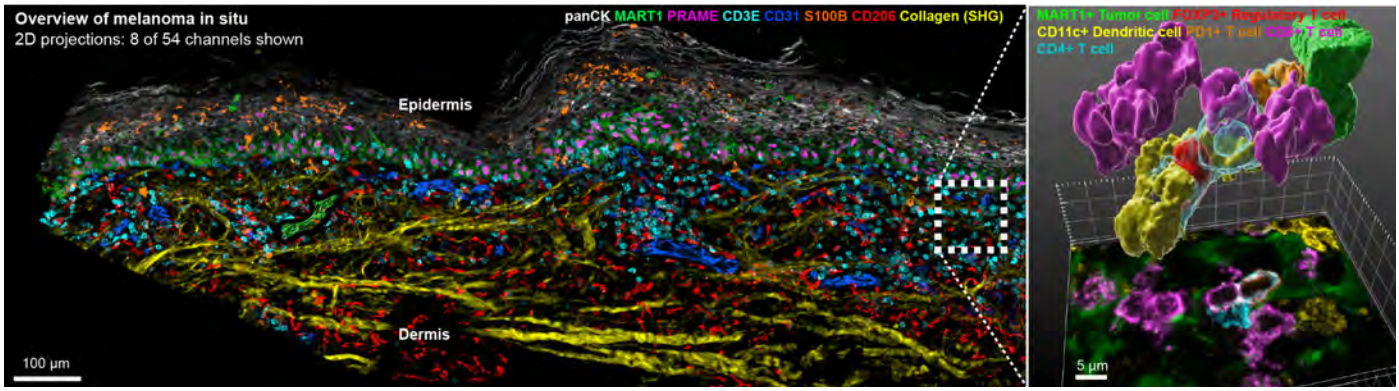
Yuxuan Wang

Bert Vogelstein

ctDNA predicts post-surgical recurrence risk for stage III CRC

Researchers led by Ludwig Johns Hopkins' Yuxuan Wang and Bert Vogelstein with Ludwig Institute alumni in Melbourne, Jeanne Tie and Peter Gibbs, reported in an October publication in *Nature Medicine* their findings from the phase II/III DYNAMIC-III trial, which were also presented at the European Society for Medical Oncology Congress 2025. The study, which compared treatment informed by circulating tumor DNA (ctDNA) analysis to current standard of care in patients with stage III colon cancer, built on a similar study for stage II colon cancer led by the same researchers. That study, reported in March, found such analysis accurately predicted the risk of recurrence and that directing chemotherapy only to ctDNA-positive patients reduced chemotherapy use overall without compromising recurrence-free survival (RFS). The current study similarly found ctDNA to be a reliable risk marker. Treatment de-escalation guided by postsurgical ctDNA analysis led to reduced exposure to chemotherapy and fewer adverse events in patients at low risk for recurrence, with RFS approaching that achieved with standard management (85% vs. 88%). Unfortunately, patients with ctDNA-positive disease did not benefit from a ctDNA-guided escalation of therapy, suggesting a need for better therapy for these high-risk patients. The trial stems from a five-year, $10 million program launched in 2015 by the Conrad N. Hilton Foundation and the Ludwig Institute for Cancer Research for the prevention and early detection of colon cancer.

Circulating tumor DNA-guided adjuvant therapy in locally advanced colon cancer: the randomized phase 2/3 DYNAMIC-III trial | *Nature Medicine*, 2025 October 20



Clarence Yapp and Peter Sorger

Left: High-resolution view of early melanoma from a FFPE patient sample stained by 3D CyCIF for 54 proteins (only 8 shown) in a 35-micron thick tissue specimen. Right, top: Inset shows a community of immune cells interacting with a tumor cell. Thick tissue imaging paired with 3D high-resolution confocal microscopy resolves the full shape of each cell and its contacting neighbors along all 3 axes. Right, bottom: A 2D image simulated below for comparison.

High dimensional imaging in 3D is more revealing

Clarence Yapp

Ajit Nirmal

Sandro Santagata

Peter Sorger

For 150 years, histopathological analysis of hematoxylin and eosin (H&E) stained specimens has been performed using tissue sections that are 4-5 µm thick. Contemporary "spatial biology" approaches have retained this format. The use of thin sections makes fine details of cells and organelles clearer (by preventing interference from out of focus light) but a report in the September issue of *Nature Methods* led by Ludwig Harvard's Clarence Yapp, Ajit Nirmal, Sandro Santagata and Peter Sorger shows that nearly all cells and nuclei are incomplete in standard 5 µm sections. This compromises the accuracy of phenotyping and obscures functionally significant contacts between cells. By extending highly multiplexed spatial profiling to 3D imaging of 30-50 µm thick sections, the Harvard team has shown that it is possible to accurately determine the shapes of intact cells, analyze juxtracrine signaling events, and detect mitochondria, peroxisomes, secretory granules and other intracellular organelles. Analysis of cell–cell interactions in 3D shows that many immune cells within and at the margins of tumors are engaged in multiple (up to ten) simultaneous activating and inhibitory interactions with neighboring cells. 3D tissue imaging therefore promises to improve understanding of tumor, stromal and immune cell interaction in the presence and absence of immunotherapy. Precise mapping of T cell states and niches is a key goal for the next phase of this research.

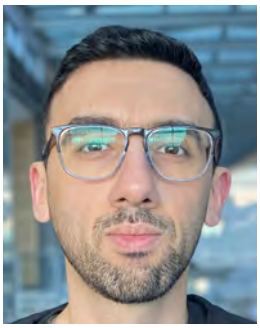
Study data is freely available via QR code

Highly multiplexed 3D profiling of cell states and immune niches in human tumors
Nature Methods, 2025 September 29

A metabolic map of the liver and intestine

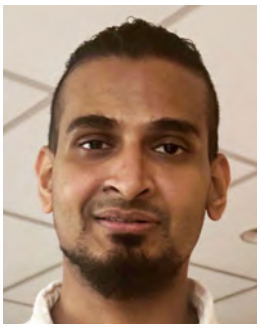
In both the intestines and liver, tissue function is linked to spatial architecture. Gradients of nutrients, oxygen and gene expression along defined structural axes—the portal-central axis in the liver and the crypt-villus axis in the small intestine—underlie specialized, spatially coordinated metabolic functions. To study spatial variations in metabolism in these tissues, researchers led by Ludwig Princeton's Laith Samarah and Director Joshua Rabinowitz, together with Princeton computer scientist Ben Raphael, mapped metabolite abundances and pathway activity at high spatial resolution in mice using imaging mass spectrometry (MALDI-IMS), isotope tracing and a deep-learning approach that inferred the metabolic topography of tissues from metabolomic images. They reported in an October issue of *Nature* that more than 90% of metabolites vary significantly along the portal–central axis in the liver and along the crypt-villus axis in the intestine. Laith, Josh and their colleagues described metabolic activity patterns underlying these concentration gradients. They also traced the metabolic fate of dietary fructose, a major factor in obesity, and showed how, at high doses, the sugar causes profound local disruptions in the levels of ATP—the body's most basic currency of energy—in the liver. The authors note that fructose intake is associated with cancers of both the liver and intestine, and the technologies developed here should be powerful tools for spatial analysis of tumor metabolism.

Spatial metabolic gradients in the liver and small intestine | *Nature*, 2025 October 15

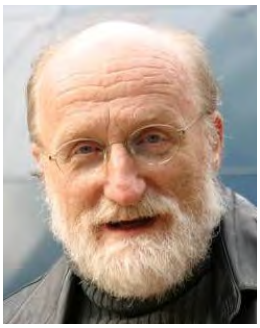


Laith Samarah

Joshua Rabinowitz



Asif Khan



Chris Sander

An AI model to catch pancreatic cancer

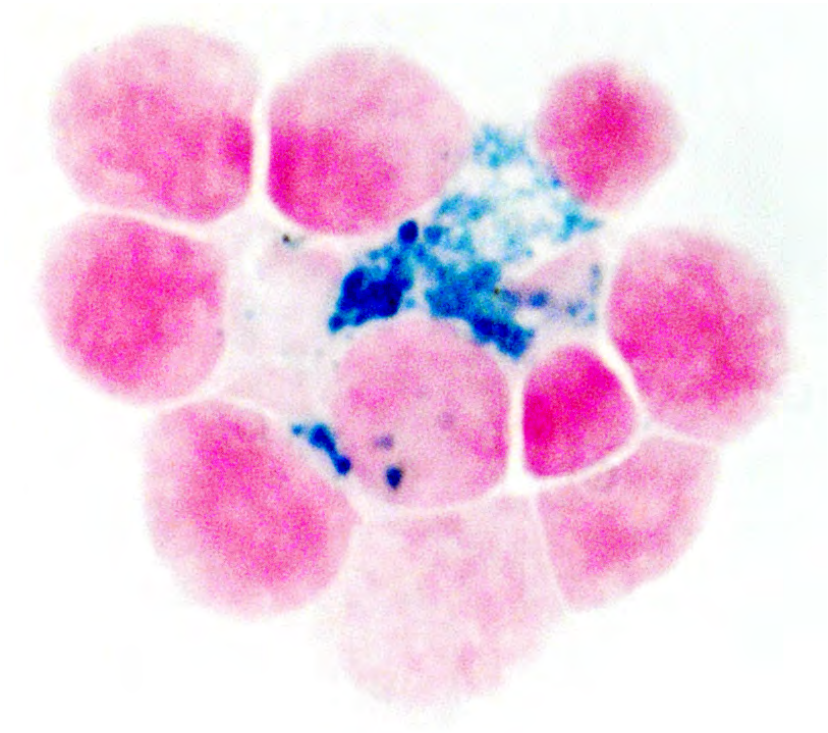
Due to its location deep in the abdominal cavity, its vague symptoms and a paucity of effective, practical and affordable screening technologies, pancreatic ductal adenocarcinoma (PDAC) is often diagnosed at an advanced stage and carries a very poor prognosis. There is therefore a critical need for practical and affordable approaches to screening. Ludwig Harvard researchers led by Asif Khan and Chris Sander described in a September issue of *Cell Reports Medicine* a potentially powerful approach for earlier detection of PDAC: a transformer-based AI model that learns interdependencies among events in patients' longitudinal medical histories. Using longitudinal Veterans Affairs electronic health records from 19,426 PDAC cases and about 15.9 million controls, the model combined diagnostic and medication trajectories to predict PDAC risk within a 6-, 12- or 36-month window. In a cohort of 1 million patients, the top 1,000–5,000 highest-risk patients had a 3-year PDAC incidence 115- to 70-fold higher than a reference estimate based on age and sex alone. The AI-based model also identified diagnosis and medication exposures correlated with elevated risk, such as chronic inflammatory conditions and specific medications taken by patients. The model holds promise as a practical and relatively affordable way to improve early detection of PDAC.

Pancreatic cancer risk prediction using deep sequential modeling of longitudinal diagnostic and medication records | *Cell Reports Medicine*, 2025 September 16

Breast cancer bone mets promote anemia by pilfering iron

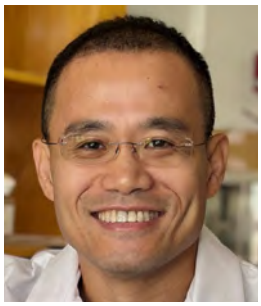
Breast cancers frequently spread to the bone, establishing tumors that are largely impervious to treatment and are associated with poor patient prognoses. Anemia is among the most common complications of such metastases. Researchers led by Ludwig Princeton's Yibin Kang and Yujiao Han described in a *Cell* paper in September a pair of canny strategies breast cancer cells employ to access metabolic support in the oxygen-poor microenvironment of bone marrow that contribute to that anemia. They discovered that specialized iron-recycling immune cells—erythroblast island (EBI) macrophages—cluster around cancer cells in the metastatic niche in bone. Although bone marrow has healthy reserves of iron, an essential mineral, it is not readily available to invading cancer cells. EBI-macrophages ordinarily provide iron to erythroblasts, the precursors of red blood cells. Cancer cells, the researchers found, hijack EBI macrophages to acquire iron, disrupting the generation of red blood cells. Having hoarded the available iron, the cancer cells then begin mimicking erythroblasts, expressing a component of hemoglobin—β-globin—to better survive the hypoxic environment in the bone marrow. Together, these adaptations likely synergize to induce anemia. The researchers show that similar iron-handling macrophages are found in human bone metastases from lung and kidney tumors as well. This suggests that the hijacking of iron-recycling macrophages might be a common phenomenon in cancers that metastasize to the bone.

Tumors hijack macrophages for iron supply to promote bone metastasis and anemia | *Cell*, 2025 September 3



Yujiao Han and Yibin Kang

Upon metastasizing to the bone marrow, tumor cells hijack EBI macrophages, diverting iron from erythroblasts to tumor cells, contributing to anemia. This bright-field image of Prussian blue and nuclear fast red staining shows erythroblasts around an iron-rich, blue-stained macrophage.



Yibin Kang

Yujiao Han

A dietary strategy to enhance neuroblastoma therapy

Researchers led by Ludwig Princeton's Sarah Cherkaoui, Raphael Morscher of the University of Zurich and Michael Hogarty of the University of Pennsylvania with Ludwig Princeton Director Joshua Rabinowitz and Associate Director Eileen White reported in a September publication in *Nature* that, in mouse models, a dietary intervention improves the anti-cancer efficacy of difluoromethylornithine (DFMO), a drug approved for the childhood cancer neuroblastoma. The combination arrests tumor growth not by killing cancer cells but by inducing their differentiation. Neuroblastoma cells depend on polyamines, and DFMO inhibits an enzyme that makes these metabolites via a pathway starting from the amino acids arginine and proline. A diet devoid of those amino acids depletes polyamines and synergizes with DFMO. The mechanism of action of the combination involves altered translation of particular gene transcripts into proteins due to ribosome stalling at codons that have an adenosine in the third position, apparently because polyamines are required for efficient translation of such codons. Such transcripts are selectively enriched in cell cycle genes and low in neuronal differentiation genes. Impaired translation of the former favors a pro-differentiation proteome in the cells, inducing the observed therapeutic effect. Analogous quirks, the authors suggest, may be exploited to treat other pediatric cancers, as the one identified in this study is probably representative of many such mechanisms that have evolved to regulate responses to metabolic stress.

Reprogramming neuroblastoma by diet-enhanced polyamine depletion | *Nature*, 2025 September 24

Sarah Cherkaoui

Joshua Rabinowitz

Eileen White

Michelle Monje

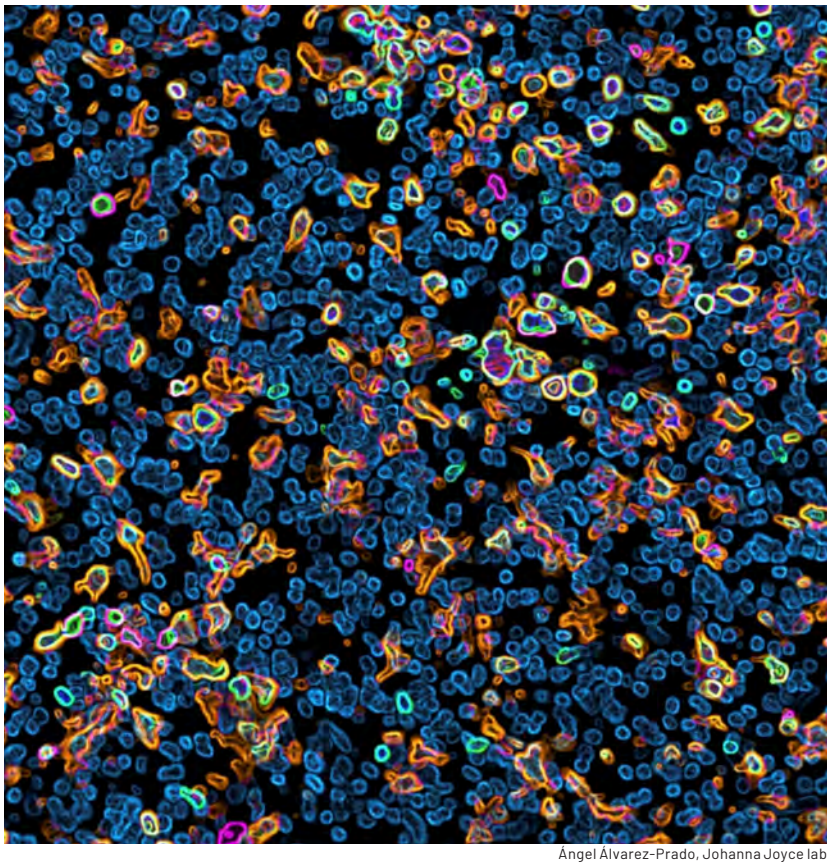
How neurons drive SCLC growth

Neural activity is now known to play a major role in cancer growth. Neurons establish synapses with glioma cells and engage with them via paracrine signaling as well to fuel brain tumor growth. Outside the brain, the innervation of a wide variety of tumors—such as those of the breast and prostate—can also regulate their progression. Researchers co-led by Ludwig Stanford's Michelle Monje reported in a September *Nature* paper that neuronal activity plays a critical role in the pathogenesis of small-cell lung cancer (SCLC). Michelle and her colleagues showed that severing the vagus nerve—which runs between the brain and lung—in a mouse model of inducible SCLC markedly inhibited the initiation and progression of the tumors, highlighting a critical role for innervation in the earlier phases of their growth. In the brain, a favored locale for SCLC metastasis, they found that SCLC cells co-opt neuronal activity-regulated mechanisms to stimulate their growth and progression. Glutamatergic and GABAergic (γ-aminobutyric acid-producing) cortical neuronal activity drive proliferation of SCLC in the brain through both paracrine and synaptic interactions. The synapses established with a subset of SCLC cells transmit neural signals and the depolarization of their membranes in that process suffices to drive the growth of the brain metastases. Tumor growth, they reported, could be attenuated with an antiseizure drug in the mice.

Neuronal activity-dependent mechanisms of small cell lung cancer pathogenesis | *Nature*, 2025 September 10

A one-two punch to knock out GBM

Glioblastoma multiforme (GBM) is notoriously resistant to treatment. This stems, in part, from the dizzying genetic variability of glioblastoma cells and the profoundly immunosuppressive microenvironment the tumor cultivates. Researchers led by Ludwig Lausanne's Johanna Joyce and recent alumnus Ángel Álvarez-Prado identified in a September publication in *Cell Reports* a promising new drug target in GBM cells that could potentially address both these sources of resistance. Recent studies have found that certain types of cancer cells that continuously express interferon-stimulated genes (ISGs) are highly vulnerable to ADAR1 loss, and that deleting its gene in melanoma tumors can improve responses to immunotherapy in mouse models. Ángel, Johanna and colleagues showed that loss or chemical inhibition of ADAR1—which is a regulator of the innate antiviral response induced by type I interferons in mammalian cells—stalls the proliferation of genetically diverse ISG-expressing GBM cells in cultured human tumor samples and in mouse models. Further, disabling ADAR1 amplified ISG-stimulated inflammatory responses, which had the effect of reprogramming the tumor microenvironment of multiple, genetically distinct GBM tumors. This boosted the numbers of anti-tumor immune cells in the TME—such as CD8+ T cells, pro-inflammatory macrophages and natural killer cells—and depleted immune cells that suppress anti-tumor immune responses. ADAR1, the researchers note, is especially enticing as a target because its disruption delivers a one-two punch against the GBM tumor.



Ángel Álvarez-Prado, Johanna Joyce lab

Image rendering of the glioma microenvironment following ADAR1 deletion, showing cancer cells (blue) and infiltration of immune cells (green), including CD8+ T lymphocytes (green+pink) and tumor-associated macrophages (green+orange).

Johanna Joyce

Ángel Álvarez-Prado

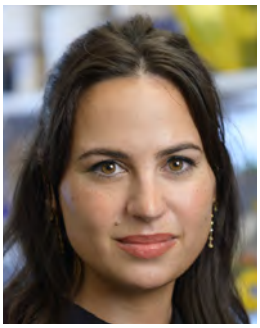
Cancer cell and microenvironmental rewiring by ADAR1 loss impairs glioblastoma tumor growth and extends survival | *Cell Reports*, 2025 September 1

Putting the squeeze on cancer cells makes them invasive

Researchers led by Ludwig Oxford's Richard White and Miranda Hunter of the Memorial Sloan Kettering Cancer Center reported in an August paper in *Nature* how the tight physical confinement of tumor cells by surrounding tissues has epigenetic consequences that can influence melanoma progression. Rather than continuing to divide rapidly, cancer cells in such circumstances activate a program of 'neuronal invasion' and spread into neighboring tissues. Using a zebrafish model of melanoma, the researchers showed that HMGB2, a DNA-bending protein, responds to the mechanical stress of confinement by binding to chromatin, altering its structure and exposing regions of the genome encoding genes linked to invasiveness. Cells with high levels of HMGB2 thus become less proliferative but more invasive and resistant to treatment. They also remodel their cytoskeleton, forming a cage-like structure around the nucleus. This protective shield involves the LINC complex, a molecular bridge that connects the cell's skeleton to the nuclear envelope, helping to protect the nucleus from rupture and DNA from damage caused by confinement-induced stress. The findings highlight an underappreciated dimension of microenvironmental influence on cancer cell behavior, showing how physical cues can prompt them to adapt their skeletal and genomic architecture to shift between states of growth and invasion. Most notably, however, the study also demonstrates how physical stress is a potent—and barely explored—driver of epigenetic change.

Mechanical confinement governs phenotypic plasticity in melanoma | *Nature*, 2025 August 27

Richard White



Miranda Hunter

Chetan Bettegowda

Christopher Douville

A more informative liquid biopsy for brain cancers

The only definitive way to diagnose most brain cancers is by surgical biopsy, a potentially dangerous procedure that is sometimes not even an option. Researchers led by Ludwig Johns Hopkins' Chetan Bettegowda and Christopher Douville reported in an August issue of *Cancer Discovery* a multianalyte test that can accurately detect brain cancers using small quantities of cerebrospinal fluid (CSF). They also demonstrated that combining multiple biomarkers significantly improves the specificity of such tests. Their workflow, named CSF-BAM, simultaneously identifies B cell and T cell receptor sequences, aneuploidy—abnormal numbers of chromosomes in cells, a common feature of advanced cancers—and mutations using amplification of both strands of DNA obtained from CSF samples. The researchers validated CSF-BAM using 209 samples from patients with high-grade gliomas, medulloblastomas, brain metastases, and central nervous system lymphomas. The workflow detected the most common and aggressive brain tumors—accounting for 129 samples—with a sensitivity of 81%. None of the 30 CSF-BAM assays run on samples from people without brain cancer generated a false positive. Aside from detecting brain cancers, the researchers note, the test also provides potentially useful information about the genetics and immune microenvironment of brain tumors.

Detection of human brain cancers using genomic and immune cell characterization of cerebrospinal fluid through CSF-BAM | *Cancer Discovery*, 2025 August 25