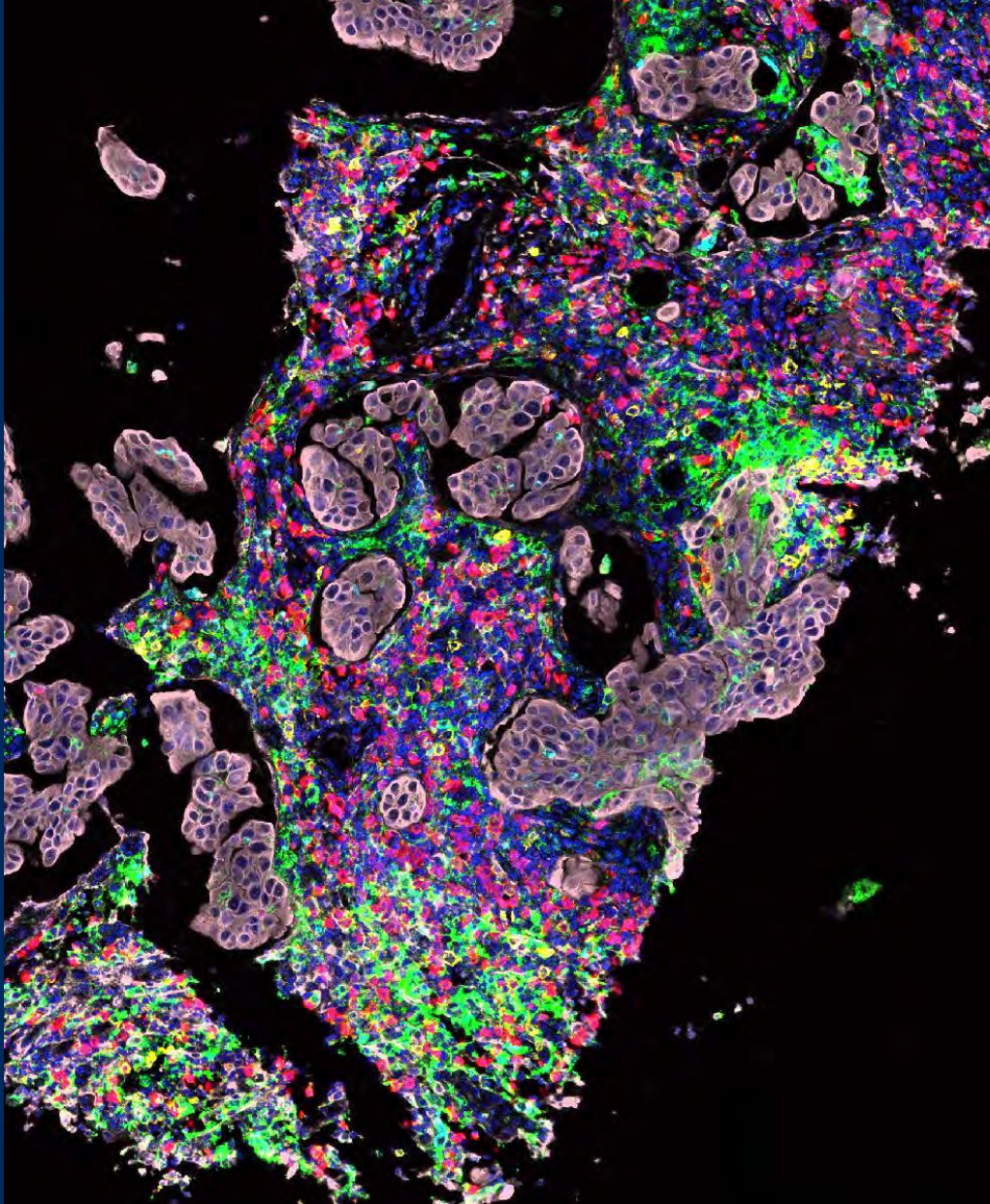




Ludwig Link

7 Team including Ludwig scientists wins Cancer Grand Challenges award

26 Q&A with three newly appointed Ludwig Clinical Scholars

**LUDWIG
CANCER
RESEARCH**

LIFE-CHANGING SCIENCE

Welcome



Unmesh Kher
Editorial Director

Among the many pleasures of publishing this magazine, two stand out, and both have to do with the people behind the science we share.

One is the general tour of cancer research we get as we prepare, with the gracious assistance of Ludwig scientists, the research briefs at the core of this publication. The other is the stories we occasionally get to tell about the scientists themselves. Not only about their lives, accomplishments and scientific vision, but also those moments when a striking result or arresting image brings the abstractions of cellular and molecular biology vividly to life.

These pleasures are in abundant evidence in this issue of the Ludwig Link. Check out our interviews with three newly appointed Ludwig Clinical Scholars—one affiliated with Ludwig Princeton and two at Ludwig Lausanne—in which they tell us a little about their lives, careers and scientific interests. Join us in welcoming them aboard (page 26). Or flip to the back of the book and you'll see our second installment of the Image gallery, a small collection of striking images, along with a little note about each, shared with us by researchers across the Ludwig community.

Along the way to those features, you'll get your usual sampling of Ludwig news, including recent awards and honors earned by colleagues (page 5), the first publication out of Ludwig Oxford's MPN Program and a Cancer Grand Challenges award issued to a team that includes two Ludwig leaders (page 7). Our research briefs (page 10) cover early clinical trials examining new strategies and technologies for immunotherapy—harnessing monocyte-derived macrophages for drug delivery; using low-dose radiotherapy to turn cold tumors hot (see cover)—and a rich assortment of applied science and fundamental discoveries touching on subjects ranging from CAR-T cell design to metabolomics to tumor biogeography.

Welcome to the fall 2026 issue of Ludwig Link!

Sincerely,

Unmesh Kher
Editorial Director

On the cover

Micrograph of a section from a high-grade ovarian cancer metastasis. The biopsy was obtained from a woman who experienced a durable complete response in the RACIN trial, which examined whether low-dose radiotherapy (LDRT) can turn "cold" (immune-excluded) tumors of various types "hot" in preparation for checkpoint blockade immunotherapy. Researchers led by Ludwig Lausanne's Denarda Dangaj Laniti and Fernanda Herrera collected the sample shown here ten days after the patient received low-dose radiotherapy and before anti-PD-1 immunotherapy had started. The pale epithelial islands are cancer cells (pink). These are surrounded by CD8+ T cells (red), B cells (green), dendritic/myeloid cells (cyan) and other antigen-presenting cells, such as macrophages (orange). (PD-1 is stained yellow.) Find out more about this image and its context in our Image gallery (page 36) and in our Research news section (page 18).

Image by Dangaj Laniti lab

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26 | Q&A WITH THREE LUDWIG CLINICAL SCHOLARS

A warm welcome to Bernhard Gentner and Caroline Arber of Lausanne University Hospital and the University of Lausanne, who join Ludwig Lausanne, and to Christian Hinrichs of the Rutgers Cancer Institute, who joins Ludwig Princeton, as Clinical Scholars of the Ludwig Institute for Cancer Research.

How HER2+ breast cancers resist ADC therapy

A clue to triggering ferroptosis for pancreatic cancer therapy

How mitochondrial dysfunction triggers T cell exhaustion

A new manager of metabolic health

How traveling tumor cells evade immune attack

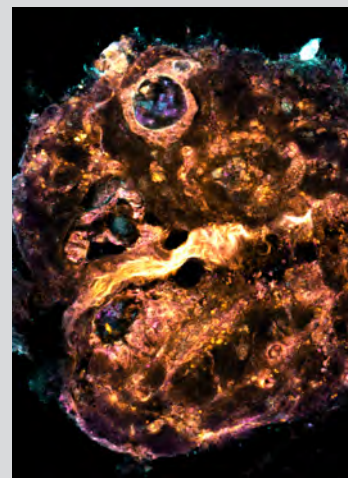
A key trigger for immunosuppression in bladder cancer

A DROP-CAR-T cell for control and safety

Liquid biopsy could aid management of bladder cancer therapy

A single neutrophil state supports tumor growth across cancer types

IMAGE GALLERY



Check out this sampling of arresting images, with explanations and assorted thoughts about each, proudly shared with us by researchers from across the Ludwig community. [PAGE 36](#)

Ludwig Lausanne's Ping-Chih Ho elected AAAS Fellow

We congratulate Ludwig Lausanne's Ping-Chih Ho on his election in March as Fellow of the American Association for the Advancement of Science (AAAS). Ping-Chih was recognized by the AAAS for his continuing and "distinguished contributions to the field of immune metabolism, particularly in elucidating its role in anti-tumor immunity and advancing cancer therapy." A leader in his field, Ping-Chih explores how metabolic byproducts and effects influence the function of immune cells and mediate a conversation between them and their malignant targets. A recent publication out of his lab, for instance, [detailed](#) how an accumulation of malfunctioning mitochondria induces a rewriting of gene expression programs in the

immune system's T cells that pushes them into a state of terminal exhaustion (see page 20). Another recent study led by Ping-Chih identified a specific mode of fat uptake by immune cells within tumors that serves as a metabolic [checkpoint](#) against anti-cancer immune responses and evaluated a candidate antibody drug to undermine this effect. It has since received Fast Track designation from the U.S. Food and Drug Administration for the treatment of liver cancer and is being evaluated in clinical trials by Pilatus, a biotech startup spun out of Ping-Chih's laboratory in partnership with the Ludwig Institute for Cancer Research. Ping-Chih was inducted into the AAAS during a ceremony in Washington, D.C., on May 29.



Ping-Chih Ho

Two Ludwig Lausanne researchers win Robert Wenner Prizes

Our congratulations to Ludwig Lausanne's Michal Bassani-Sternberg and Camilla Jandus, who were named winners of this year's Robert Wenner Prize, which was awarded for the first time to two scientists. Issued by the Swiss Cancer League and established by a bequest left by the eponymous Basel gynecologist, who died in 1979, the award honors outstanding young scientists in the field of oncology. They each received a 50,000 Swiss franc grant to support their research. Michal is a pioneer in the field of immunopeptidomics—the integrated use of mass spectrometry and computational analysis, including machine learning, to predict which antigens out of the thousands displayed to the immune system's T cells are most likely to provoke

effective immune responses. Aside from its contributions to our understanding of the rules that govern antigen presentation and recognition, her work is already being applied to [design](#) personalized cancer vaccines. Camilla's research focuses on the therapeutic potential of innate lymphoid cells (ILCs) and helper T cells. Her lab is exploring changes to ILCs in cancer patients and examining their [crosstalk](#) with immune and cancer cells (see page 23). Her team has also developed innovative technologies to examine tumor-specific CD4+ T cells and their receptors, revealing that, beyond their helper functions, these cells can directly kill cancer cells, a capacity that could potentially be exploited for cancer immunotherapy.



Michal Bassani-Sternberg



Camilla Jandus



Johanna Joyce

Ludwig Lausanne's Johanna Joyce begins EACR presidency

Ludwig Lausanne's Johanna Joyce began in June a two-year term as President of the European Association for Cancer Research (EACR). In addition to promoting broad scientific collaboration, exchange and training, the EACR President oversees organizational strategy and leads efforts to support early-career scientists, advocate for the field and foster an inclusive international research community. Johanna brings to this role internationally recognized scientific and institutional leadership. An authority on the tumor microenvironment (TME), she has made seminal contributions to understanding how interactions between cancer cells and the surrounding immune, vascular and stromal microenvironments drive tumor

progression, metastasis and responses to therapy. Beyond her research, Johanna has addressed challenges facing scientists and the broader scientific enterprise. She has explored the structural factors that contribute to the widening gender gap at senior levels of academic research and [proposed](#) strategies to reduce this disparity while improving the retention of early-career scientists in academia. She has also helped shape discussion of the growing global burden of cancer, identifying [policy](#) priorities that could strengthen Europe's response to this challenge. We are confident that the EACR and the wider cancer research community will thrive under her leadership.



Michael Skinnider

Ludwig Princeton's Michael Skinnider named Pew Scholar

Our congratulations to Ludwig Princeton's Michael Skinnider, who was named a Pew Scholar in mid-June. He is one of 21 scientists selected for the organization's Program in the Biomedical Sciences. Aside from recognizing the scientific capabilities and contributions of early-career researchers, the prestigious award provides each scholar with \$300,000 in flexible funding over the next four years for their studies. The funds will support Mike's ongoing efforts to enlist AI in his exploration of the so-called "dark matter" of the metabolome—the profusion of largely unidentified small molecules that are generated by our cells and commensal microbes or enter our bodies from the outer environment and play a significant yet poorly understood role in health and

disease. Earlier this year, Mike [reported](#) his group's development of DeepMet, a chemical language model that learns from the structures of known metabolites to anticipate the existence of previously unrecognized ones. The group demonstrated that its integration with mass spectrometry-based metabolomics data facilitates metabolite discovery, applying DeepMet to describe several dozen new and structurally diverse mammalian metabolites. Mike will use Pew support to introduce an entirely new AI framework for the acquisition and analysis of mass spectrometry data and explore how genetic variation influences the spectrum of metabolites, work that should identify new metabolic pathways and mechanisms of disease.

Team including Ludwig scientists receives Cancer Grand Challenges award

Ludwig Oxford Director Xin Lu and the Ludwig Institute's CEO and Scientific Director Chi Van Dang were named in March among the recipients of a 2026 Cancer Grand Challenges award as members of the ATLAS (for Antibody Tracking for Long-term Avoidance and Surveillance) team.

Launched in 2020 by Cancer Research UK and the U.S. National Cancer Institute, Cancer Grand Challenges invites scientists to collaborate across borders and disciplines to devise innovative approaches to solving some of the most perplexing problems of cancer biology and care. Led by Paul Bastard of Institut IMAGINE in Paris, Team ATLAS will address the challenge of "Cancer Avoidance". It will receive up to \$25 million over roughly five years to develop a Cancer Antibody Atlas to explore how a subset of the aged and people thought to be predisposed to cancer ultimately evade malignant disease.

Most of the research into the body's immunosurveillance of cancer over the past several decades has focused on the cellular immune response and the evolution of tumors against its pressure. But how the humoral—or antibody—response reflects and influences the risk, avoidance and progression of cancer and its response to therapy has gone largely unexplored. Yet antibodies, and the B cells that produce them, persist in the blood and collectively represent a serological memory bank whose vast deposits include events and biochemical phenomena associated with cancer incidence, avoidance and therapeutic

efficacy. The ATLAS team aims to discover antibodies of this kind that, they expect, will open unforeseen avenues for early detection, prevention and treatment of cancer.

The team proposes to build a Cancer Antibody Atlas based on studies involving more than 10,000 individuals, including centenarians who have escaped cancer diagnoses, discordant identical and fraternal twins and patients at high risk for malignant disease. The researchers will seek out antibodies that bind to a broad range of antigens, such as those that target cancer cells or are associated with T cell responses to cancer. It will also look for antibodies the body produces against its own cells and secreted molecules, or autoantibodies, which have already been shown to influence outcomes of checkpoint blockade immunotherapy. The team will, further, catalog antibodies to pathogens, commensal microbes, food and other exposures that correlate with cancer incidence or therapeutic outcomes. (Xin, Chi and their Team ATLAS colleagues discussed the evidence that underpins their hypothesis and their strategy for its examination in a July [Commentary](#) in *Cell*.)

Ludwig Institute scientists are now involved in two currently active Cancer Grand Challenges teams. The second is the CANCAN team, which is co-led by Ludwig Princeton Associate Director Eileen White and has since 2022 been investigating cachexia, a wasting condition associated with advanced cancer. Stay tuned for exciting science from both teams.



Xin Lu

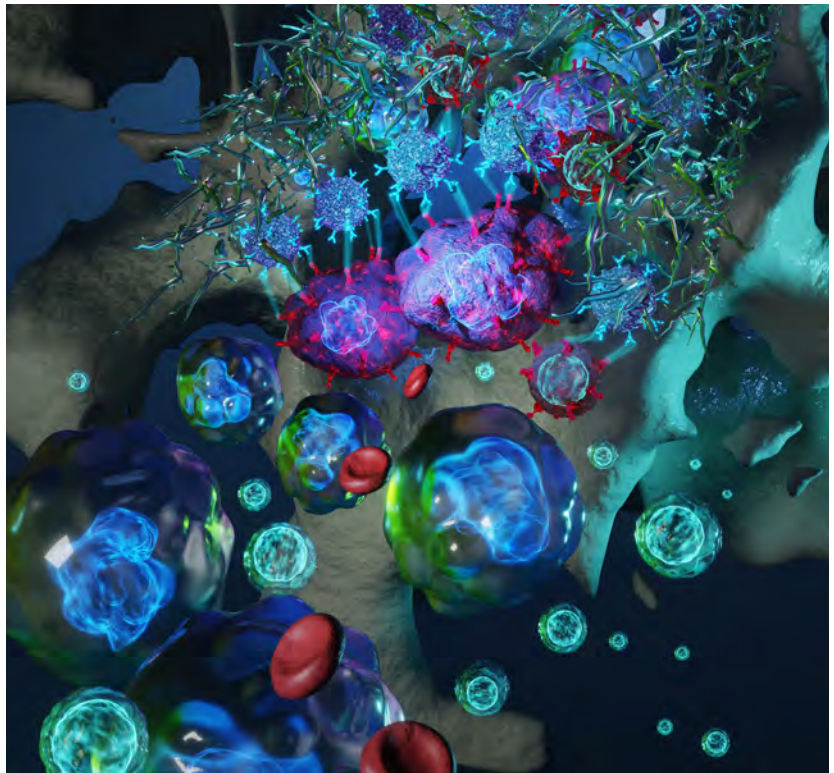


Chi Van Dang

A CAR-T for a big basket of MPNs

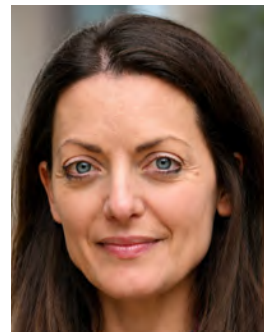
Ludwig Link readers might recall that the Oxford Branch, in collaboration with colleagues at the University of Oxford, launched a [Program on Myeloproliferative Neoplasms](#) (MPNs) in 2025 focused on developing new approaches to treating, diagnosing and assessing risk for MPNs. The first research partially supported by the Program was published in *Science Translational Medicine* in July. MPNs are slow-growing blood cancers. Over time, about a third of patients progress to a stage called myelofibrosis—where extensive scarring of the bone marrow develops—at which point the median life expectancy is 5–7 years. One in five of these patients progress further to an aggressive and incurable leukemia known as blast-phase (BP) MPN. About a third of MPNs are driven by mutations to the chaperone protein calreticulin (CALR). In these cases, the mutant CALR protein binds to the thrombopoietin receptor (TpoR), migrating to the cell membrane and aberrantly activating TpoR signaling in blood stem cells and megakaryocytes.

Spotting an opportunity in that phenomenon, Ludwig Oxford's Bethan Psaila collaborated with Alexandros Rampotas and Martin Pule's lab at University College London to design a CAR-T cell to target the cell-surface mutant CALR-TpoR complex. They showed using samples from myelofibrosis patients that their CAR-T cells selectively killed mutant stem cells while sparing healthy ones and demonstrated in orthotopic mouse models of mutant CALR+ leukemia that they could also improve survival. In an organoid model of myelofibrotic marrow, the CAR-T cells efficiently infiltrated densely fibrotic tissue



A substantial portion of MPNs are driven by mutant CALR, which aberrantly forms a complex with TpoR and migrates to the cell surface to trigger oncogenic signaling, generating a cancer-specific antigen that can be targeted by CAR-T cells. This graphic, generated in partnership with DrawImpacts, depicts CAR-T cells killing bone marrow cells that express mutant CALR, which is depicted here as a red 'flag' on the cell surface.

to kill their quarry. However, the CAR-T cell therapy worked less well on samples from patients with BP-MPN due to the relatively low levels of CALR expressed on target cells. This was disappointing, as these patients have the greatest need for more effective therapies. To address this challenge, the team developed an innovative strategy to boost CAR-T cell targeting of mutant cells in patients with BP-MPN: pretreatment with a TpoR agonist therapy. This novel immunotherapy represents a promising new strategy to more effectively treat malignancies driven by mutant CALR.



Bethan Psaila

 [CAR T cell therapy selectively depletes disease-driving mutant calreticulin cells in xenotransplants and human organoid models of myelofibrosis](#) | *Science Translational Medicine*, 2026 July 1



The Ludwig Institute and Keystone co-sponsor meeting on cancer metabolism

The Ludwig Institute for Cancer Research and Keystone Symposia announced a joint meeting, titled *Tumor and Host Metabolism: Integrating, Molecular Cellular and Systemic Interactions*, to be hosted by the Ludwig Institute's Branch at Princeton University on March 7-10, 2027. This is the first of a series of symposia planned by the two organizations—and hosted at each of the Ludwig Institute Branches—on topics of critical importance to cancer research. The current meeting is being organized by Ludwig Harvard's Marcia Haigis and Ludwig Princeton's Lydia Lynch. Its proceedings will revolve around the crosstalk between tumor and systemic metabolism, with an emphasis on how cancers exploit and engineer both to support their growth, thwart immune surveillance and resist therapy. Presentations and discussions will also cover how the metabolic health of the host influences these processes and how information gleaned from the metabolic chatter between tumor and host might be harnessed for cancer prevention and therapy. Finally, talks will address the application of machine learning and artificial intelligence to extract useful information from the daunting



Lydia Lynch



Marcia Haigis

mass of biochemical data typically generated by metabolomics studies. Ludwig Institute Scientific Advisor Karen Vousden of The Francis Crick Institute in London will be giving the keynote address. Other invited speakers include authorities on various aspects of cancer metabolism, metabolomics, the tumor microenvironment and immunology. Merit scholarships to defray the costs of attendance are available to qualifying applicants and the meeting welcomes submissions for small talks and posters on related research. For more, scan the QR code (right), visit the [Ludwig Cancer Research](https://ludwigcancerresearch.org) website or Google up [Keystone meeting P12027](https://keystone.org) and browse the dedicated website.

Some key deadlines to keep in mind:

Scholarship deadline:
November 12, 2026

Short talk abstract
deadline: November 12,
2026

Early registration
deadline: January 7, 2027

Poster abstract deadline:
February 16, 2027





Richard White



Yilun Ma



Tuulia Vallius



Peter Sorger

How keratinocytes hit the brakes on melanoma invasion

Keratinocytes account for 90% of the cells in the outer layer of skin and are among the cell types incipient melanomas interact with most frequently. They play varying roles in the skin cancer. Growth factors they secrete have, for example, long been known to stoke tumor progression. More recently, Ludwig Oxford's Richard White and his colleagues discovered that desmosome mutations in these nonmalignant cells can drive melanoma cell proliferation. On the other hand, keratinocytes can inhibit cancer initiation by confining transformed melanocytes to the epidermis. In a June issue of *eLife*, researchers led by Richard and Yilun Ma at the Memorial Sloan Kettering Cancer Center—including Ludwig Harvard's Tuulia Vallius and Peter Sorger—reported an alternative mechanism by which keratinocytes can restrain the cancer.

Employing a zebrafish model to observe the earliest stages of melanoma, they discovered that keratinocytes around melanoma cells undergo an epithelial-to-mesenchymal transition (EMT) reminiscent of their behavior during wound-healing. Overexpressing the EMT-orchestrating transcription factor Twist in keratinocytes improved zebrafish survival, apparently by curtailing melanoma invasion. Single-cell analysis revealed that melanoma cells around those keratinocytes tended to be more differentiated and less invasive. The researchers also identified the molecular interactions between melanoma cells and keratinocytes responsible for this effect. It is noteworthy that EMT—which is typically engaged by invasive cancer cells in tumors—can, in the melanoma microenvironment, inhibit cancer invasion.

 [Restraint of melanoma progression by cells in the local skin environment](#) | *eLife*, 2026 June 30

Upending a metabolic assumption

Generated by the breakdown of tryptophan, phenylalanine and tyrosine, indole and phenol metabolites play important roles in physiology, ranging from the maintenance of healthy body weight to immune regulation. They are also currently the focus of intense investigation for their roles in multiple diseases, including those of the liver and kidney, as well as their widely varying and even opposing influences on cancer pathogenesis and therapy. This species of metabolites is generally believed to be produced by gut bacteria, an assumption researchers led by Ludwig Princeton's Jenna AbuSalim and Director Joshua Rabinowitz thought they'd put to the test. They reported in a June publication in *Nature Metabolism* that their isotope-tracing studies in mice, rats and human cells reveal that many indole and phenol metabolites—including such physiologically important ones as aryl-pyruvates, aryl-lactates, aryl-

acetates, aryl-carboxylic acids and cinnamic acid—are, in fact, produced abundantly by mammalian metabolism. Circulating levels of the metabolites remained robust following treatment with antibiotics, which disrupt the microbiome. This finding was reflected in samples from patients on antibiotics, including cancer patients. Meanwhile, metabolites produced exclusively by microbes, such as indole-3-propionate and p-cresol sulfate, decreased following antibiotic treatment. Jenna, Josh and their colleagues also detailed the source of indole and phenol metabolites, information critical to understanding their physiological function and developing tools to manipulate their levels for therapy.

 **Host metabolism can produce many indoles and phenols independently of the microbiome** | *Nature Metabolism*, 2026 June 23



Jenna AbuSalim



Joshua Rabinowitz

A potential marker of T cell exhaustion

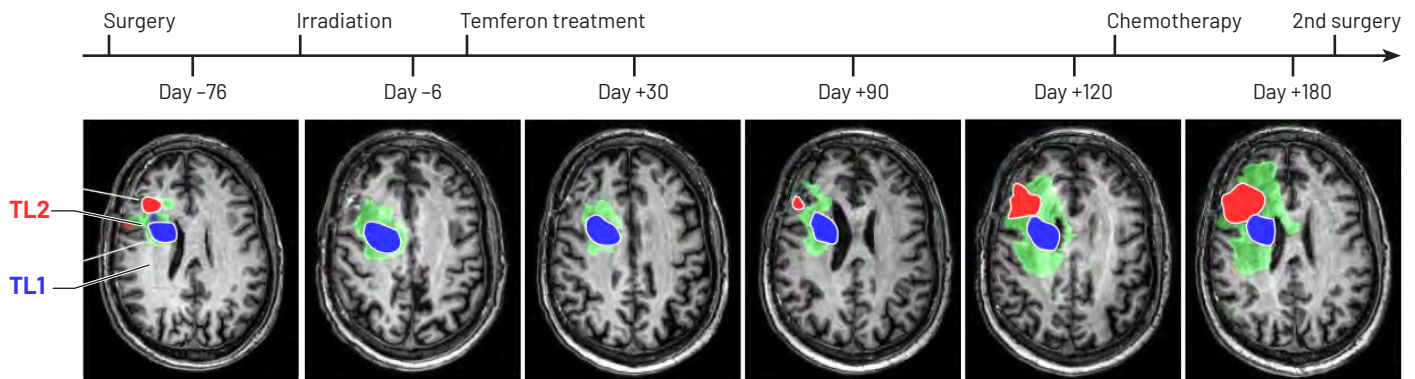
Activated CD8+ T cells increase mitochondrial mass and membrane potential to generate the energy needed for their work. As might be expected, dysfunctional and depolarized mitochondria are associated with T cell exhaustion and have been the focus of many tumor immunology studies. But poor mitochondrial quality and efficiency in T cells can also cause abnormally elevated membrane potential, or hyperpolarization, of mitochondria. In fact, studies of adoptive cell therapy in preclinical models have shown T cells with low mitochondrial potential to be associated with memory phenotype and improved effector function and those with high potential to have better initial effector function but a propensity for exhaustion and shorter survival. Researchers led by Ludwig

Chicago Co-director Jeffrey Rathmell and his Vanderbilt University colleague Kathryn Beckermann assessed the mitochondrial membrane potential (MMP) of tumor-associated T cells in the peripheral circulation as an indicator of T cell phenotypes and a marker of responses to immune checkpoint inhibitors (ICIs) in non-small cell lung carcinoma and clear cell renal cell carcinoma patients. They reported in a June issue of *The Journal of Immunology* that MMP^{high} CD8+ T cells tended to be exhausted, while those in an MMP^{low} state were more often memory cells. They also identified gene signatures associated with anti-tumor MMP^{high} T cells that are negatively correlated with patient response to ICIs and could be biomarkers of T cell exhaustion.



Jeffrey Rathmell

 **Mitochondrial potential reflects T cell fitness and function during cancer immunotherapy**
The Journal of Immunology, 2026 June 17



The MRI scans show the evolution of GBM over time in a patient treated with Temferon. After partial surgical resection, the largest target lesions (TL) remaining were TL1 (blue) and TL2 (red). The light green areas are perilesional edema. TL2 disappeared after radiotherapy, while TL1 was radioresistant. Over time, TL1 remained stable, and a biopsy revealed a high frequency (16% of TAMs) of TIE2+ macrophages (TEMs) and the presence of a strong interferon response signature, consistent with infiltration of Temferon progeny and activation of the TIE2 promoter-driven IFN- α transgene. The opposite was true for TL2, which recurred at 3 months and continued to grow.



Bernhard Gentner

Gene-engineered stem cell therapy for GBM passes its first test

Monocyte-derived macrophages and microglia help maintain an immunosuppressive microenvironment in glioblastoma (GBM) tumors. During chemo and radiotherapy, these macrophages are often replenished by hematopoietic stem/progenitor cell (HSPC)-derived monocytes recruited from bone marrow. Researchers led by Ludwig Lausanne's Bernhard Gentner figured they'd turn those recruits into double agents and reported in a June issue of *Nature Medicine* the first clinical evaluation of a genetically engineered stem cell transplant, Temferon, devised for that purpose. Temferon harnesses HSPC-derived macrophages for the targeted delivery to tumors of interferon- α 2 (IFN- α) to locally activate antitumor immunity. Bernhard and his colleagues used it to treat patients with an aggressive subtype of GBM

tumors that bears an unmethylated *MGMT* promoter. No dose-limiting toxicities were observed in 24 newly diagnosed GBM patients. Median overall survival and progression-free survival were 16.7 months (median survival for this subtype of GBM is 11-14 months) and 8.1 months from diagnosis, respectively. Two of the trial enrollees have, remarkably, survived more than three years following their initial surgery. The study resulted in an enduring engraftment of engineered HSPCs in the bone marrow and minimal systemic exposure to IFN α , which is notably toxic. The researchers also demonstrated that Temferon progeny were recruited into GBM tumors, where they locally secreted IFN α to reprogram myeloid and T cell compartments capable of tumor control.

 [Tumor-targeted interferon- \$\alpha\$ gene therapy for glioblastoma: a phase 1 trial](#) | *Nature Medicine*, 2026 June 1

From mechanistic insight to a targeted GIST therapy

Most gastrointestinal stromal tumors (GISTs) are driven by mutations to the KIT or PDGFRA genes. But some 10%-15% of GISTs show no mutation to these or other canonical oncogenes. They are instead characterized by the functional loss of the mitochondrial succinate dehydrogenase (SDH) complex caused by mutation of an SDH subunit or—remarkably—epigenetic silencing without any sign of a causal mutation. In both cases, the SDH loss results in genome-wide DNA hypermethylation. Ludwig Harvard's Bradley Bernstein, Co-director George Demetri and colleagues described in a 2019 *Nature* study how these epigenetic changes alter DNA packaging to induce the oncogenic expression of fibroblast growth factor (FGF) and activate an autocrine signaling loop through the FGF receptor (FGFR). These findings prompted clinical investigators Priscilla Merriam and Suzanne George of

the Dana-Farber Cancer Institute to launch a phase 2 trial evaluating the responses of SDH-deficient GIST patients to the FGFR inhibitor rogaratinib. They reported, along with Brad and George, the results of this trial in a May publication in *Nature Medicine*. Two dozen patients received rogaratinib and ten experienced partial responses, for an objective response rate of 41.7%. Median progression-free survival (PFS) was 31.0 months, and 1-year PFS was 77.4%. Toxicities were manageable. The researchers note that their "trial illustrates a successful demonstration of targeted cancer therapy predicated on an epigenetic mechanism of oncogene activation."

 **Fibroblast growth factor receptor inhibition for succinate dehydrogenase-deficient gastrointestinal stromal tumors: a phase 2 trial** | *Nature Medicine*, 2026 May 26



Bradley Bernstein



George Demetri



Crystal Mackall

 **Cell-autonomous control of CAR signaling and receptor shedding via ADAM17-mediated proteolysis** | *Cell*, 2026 May 15

At long last: an AIR CAR

Chimeric antigen receptor (CAR)-T cells show a greater propensity to exhaustion. They also tend to induce cytokine-related toxicities at a higher rate than naturally occurring T cells. The former is due to the elevated tonic—or idling, non-antigen induced—signaling by chimeric receptors; the latter by the intense and persistent activation of CAR-T cells upon antigen stimulation. Researchers led by Ludwig Stanford's Crystal Mackall reported in a May *Cell* paper a strategy to address these challenges by exploiting protein shedding, an intrinsic mechanism by which cells control the activity of cell surface proteins, including T cell receptors. The researchers inserted a short canonical sequence cut by the protease

ADAM17—which kicks into action in T cells upon activation—into the outer, membrane-proximal stretch of the CAR to create an activation-induced release (AIR)-regulated CAR. They show here that CAR levels on the surface of these cells were reduced in proportion to their tonic signaling, curtailing their exhaustion and improving their anti-tumor efficacy. Receptors that suppress immune responses (like TGF- β) or induce cell death (like FAS) following T cell activation could also be equipped with the AIR motif to boost CAR-T cell potency. AIR also permits the design of logic-gated CARs, in which the activation of one CAR leads to the AIR-enabled unmasking of a second CAR at an appropriate site.

Hijacking a myeloid receptor for self-defense



Chien-Huan Weng



Jedd Wolchok



Taha Merghoub

Expressed on the surface of phagocytic myeloid cells, SIRPα transmits a “don’t eat me” signal to macrophages when it is engaged by its cognate receptor CD47. Many types of cancer cells aberrantly express CD47 at high levels as a mechanism of immune evasion. CD47 blockade, a therapeutic approach pioneered by the laboratory of Ludwig Stanford Director emeritus Irv Weissman, is therefore being evaluated as a monotherapy and in combination with other agents as a cancer immunotherapy. But SIRPα is also aberrantly expressed on melanoma and other types of cancer cells, though what it does for them has so far been unclear. Researchers led by Ludwig Weill Cornell’s Chien-Huan Weng and Co-directors Jedd Wolchok and Taha Merghoub found that when expressed by melanoma cells, SIRPα suppresses anti-tumor immune responses through an entirely different mechanism: by suppressing CD8+ T cell infiltration into tumors. They described in a May issue of *Cell Reports* how its deletion in melanoma cells results in the upregulation of the chemokine CXCL10, driving immune infiltration and control of tumor growth. In line with that posited mechanism, CXCL10 deletion suppresses infiltration by CD8+ T cells and accelerates tumor growth. The findings indicate that selective targeting of tumor-expressed SIRPα—which is already being targeted as a potential immunotherapy—might also enhance immune infiltration and T cell-mediated tumor control across SIRPα-expressing cancers.

 **Tumor-intrinsic expression of signal regulatory protein α contributes to the suppression of anti-tumor immune responses** | *Cell Reports*, 2026 May 29

Viral mimicry for CRC therapy

Endogenous retroelements, including retrotransposons, are normally epigenetically silenced. When this repression is lost, they can be transcribed into RNAs containing inverted repeat Alu sequences that fold into double-stranded RNA (dsRNA). These are recognized as viral elements by innate sensors, triggering type I interferon responses—a process known as viral mimicry—which can enhance cell-intrinsic anti-tumor immunity. In a May issue of *Nature Communications*, researchers led by Ludwig Oxford's Parinaz Mehdipour, Yucheng Wang and Alice Daddi identified an RNA-level mechanism that suppresses viral mimicry in colorectal cancer (CRC). They demonstrated that the m⁶A RNA methyltransferase METTL3 limits the accumulation of Alu-derived dsRNA in CRC cells, suppressing innate immune signaling, and that its inhibition activates viral mimicry in a subset of CRCs. CRCs with high basal m⁶A methylation and the capacity to generate Alu-derived dsRNA responded to METTL3 inhibition alone. Tumors with lower m⁶A levels, however, required combination treatment with DNA methyltransferase inhibitors (DNMTis), which increase retroelement transcription and dsRNA production. These findings identify METTL3 as an RNA-level immune checkpoint that suppresses viral mimicry in CRC and suggest its inhibition may improve anti-tumor immunity. Combined METTL3 and DNMT inhibition could be a promising therapeutic strategy for CRCs that are otherwise resistant to METTL3 inhibition alone.

 **m⁶A modification suppresses innate anti-tumour immunity in colorectal cancer by limiting alu-derived dsRNA accumulation** | *Nature Communications*, 2026 May 14



Parinaz Mehdipour



Yucheng Wang



Alice Daddi

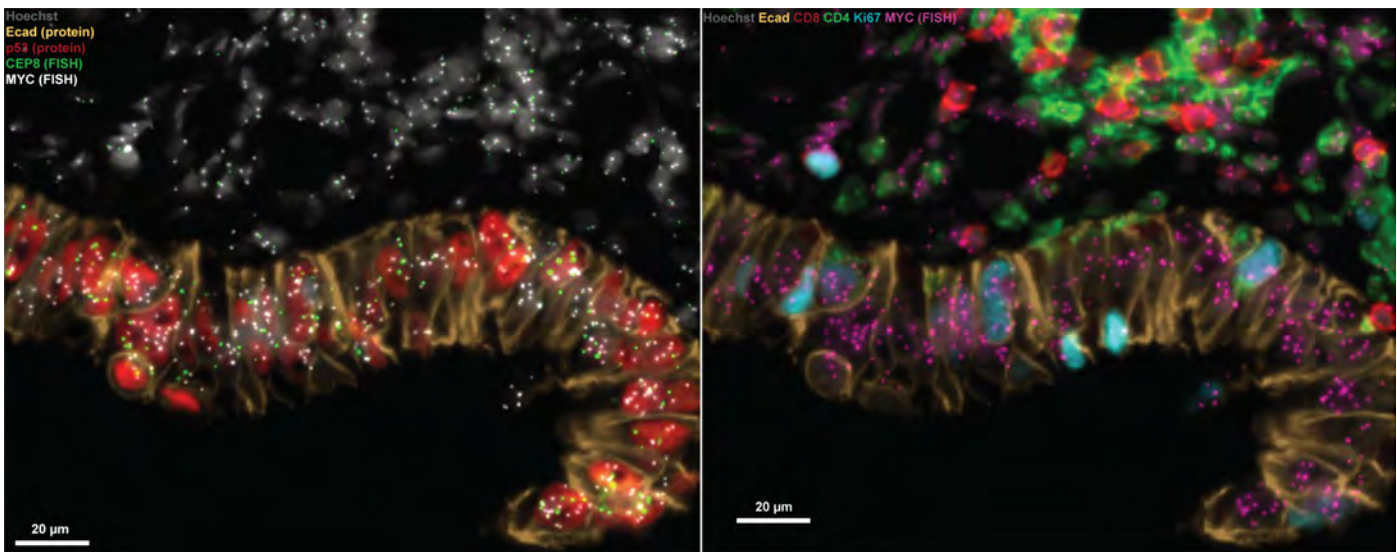


Ping-Chih Ho

A metabolite for T cell vitality

The tumor microenvironment (TME) is profoundly immunosuppressive, not least due to its tendency to induce a state of dysfunction known as exhaustion in cytotoxic (CD8+) T cells (CTLs). Researchers led by Ludwig Lausanne's Ping-Chih Ho and colleagues in China reported in a May paper that made the cover of *Science Immunology* that citraconate—an isomer of the anti-inflammatory metabolite produced by macrophages, itaconate—maintains the stemness of CTLs, attenuating their exhaustion and augmenting their anti-tumor activity. The isomer, they show, is depleted in CTLs from mouse models and patient samples that have been subjected to the hypoxia and chronic antigen stimulation in the TME that induces exhaustion. Treating exhausted T cells from human tumors with citraconate in cell culture restored their activation and stemness while reducing their expression of markers associated with exhaustion. Probing deeper, the researchers found that citraconate inhibits phosphodiesterase1A/C (PDE1A/C) expression and maintains adequate levels of cAMP, supporting mitochondrial integrity. This, in turn, leads to protein kinase A signaling and repression of arachidonate-5-lipoxygenase (ALOX5) transcription, which suppresses arachidonic acid peroxidation and prevents a type of cell death known as ferroptosis. Patient samples revealed that low ALOX5 or PDE1A expression correlate with less CTL exhaustion and improved responses to immune checkpoint blockade therapy, supporting the clinical relevance of the citraconate-PDE1-cAMP-ALOX5 axis as a target for the enhancement of cancer immunotherapy.

 **Citraconate preserves T cell stemness and antitumor immunity** | *Science Immunology*, 2026 May 1



Tanjina Kader

A precursor lesion (STIC) shows early genetic changes and immune engagement using ORION-FISH. Left: This STIC lesion (a precursor of HGSOC) shows p53 protein overexpression (red), confirming a p53 mutation, along with extra copies of the MYC gene (white). E-cadherin (brown) marks the epithelial cells, confirming that the MYC gain occurs specifically within the STIC lesion itself. Right: Surrounding the STIC epithelium (which carries the MYC gain), immune cells—including CD8 (red) and CD4 (green) T cells—are enriched in close contact with the lesion.

A spatially contextualized lens on tumor evolution

Tumors are complex ecosystems in which cancer cells carrying different somatic mutations and chromosomal copy-number changes interact with stromal and immune cells across distinctive tissue regions. Because these relationships may influence tumor behavior, preserving their geography is essential to understanding how cancers emerge and evolve. Single-cell sequencing can capture cellular heterogeneity, but it typically requires dissociation, while bulk approaches average signals across many cells. Both can obscure the spatial relationships and fine-scale interactions that are central to tumor biology. In the April issue of *Cancer Discovery*, Ludwig Harvard investigators Tanjina Kader and Sandro Santagata and their colleagues described ORION-FISH, a spatially resolved workflow designed to preserve that context. ORION-

FISH combines multiplexed protein imaging with DNA fluorescence in situ hybridization (FISH) to map genomic alterations and the functional states and local environments of individual cells in intact tissue. Applied to high-grade serous ovarian carcinoma (HGSOC), the method recapitulated known chromosomal alterations and revealed subclonal cellular heterogeneity missed by targeted sequencing. In serous tubal intraepithelial carcinomas (STICs), precursors of HGSOC, ORION-FISH identified intermixed epithelial populations with *MYC* or *CCNE1* copy-number gains and showed that these genomic changes were associated with distinct immune microenvironments. Some alterations were also detected in morphologically normal-appearing fallopian tube epithelial cells, providing new insight into the earliest stages of HGSOC initiation and evolution.

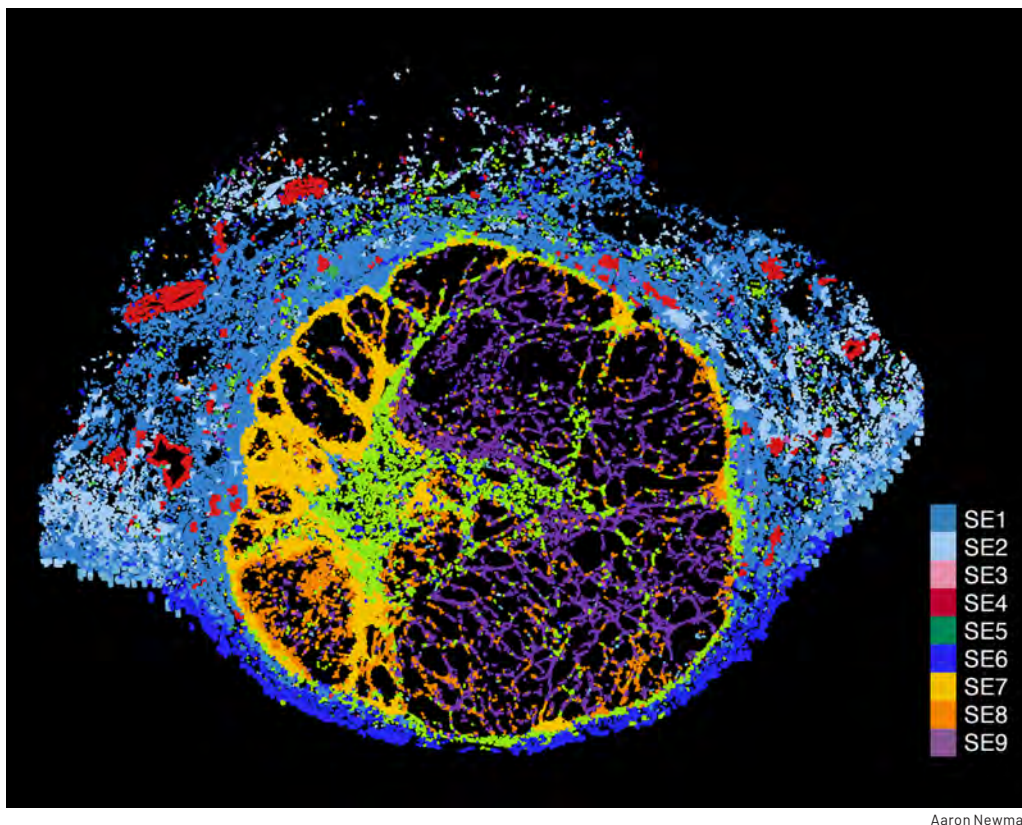


Tanjina Kader



Sandro Santagata

 **Spatial integration of protein and chromosomal states reveals early copy number changes and genotype-associated immune neighborhoods in serous ovarian cancer evolution** | *Cancer Discovery*, 2026 April 18



Nine multicellular environments, called spatial ecotypes, are shown here for a melanoma tumor sample. Spatial ecotypes are associated with patient survival and treatment.

Aaron Newman

Tumor cartography by liquid biopsy

Tumors are topographically diverse ecosystems of cancerous and noncancerous cells, and their distinct biogeographies have a significant bearing on cancer progression and responses to therapy. Researchers led by Ludwig Stanford's Aaron Newman and Aadel Chaudhuri of the Mayo Clinic reported in a May issue of *Nature* a machine-learning framework for multi-analyte profiling of spatial ecotypes (SEs), which describe spatially dependent cell states and multicellular ecosystems in the tumor microenvironment (TME). By integrating more than 10 million single-cell and spot-level spatial transcriptomes from ten human carcinomas and melanomas, the researchers identified nine widely conserved SEs, each having unique biological and spatial features and associations with clinical outcomes. Some of the SEs were correlated with distinct

responses to immunotherapy. The locations and core characteristics of the SEs were also conserved across tumor types. Aaron and his colleagues then showed that these SEs can be identified from plasma cell-free DNA (cfDNA) using DNA methylation profiling and deep learning, developing a model for this purpose named *Liquid EcoTyper*. Using whole-genome cfDNA methylation profiles of nearly 100 patients with melanoma, the researchers found faithful concordance between plasma-derived SE levels, SE levels confirmed by tumor biopsy and known outcomes of checkpoint blockade immunotherapy. Their findings reveal fundamental units of TME organization and demonstrate a multimodal platform for profiling TMEs for risk stratification and the personalization of therapy.

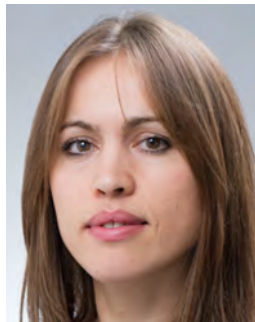


Aaron Newman

 **Non-invasive profiling of the tumour microenvironment with spatial ecotypes**
Nature, 2026 May 6

A little zap before immunotherapy

The immunosuppressive microenvironment of solid tumors poses a daunting challenge to immunotherapy. Researchers led by Ludwig Lausanne's Denarda Dangaj Laniti and Fernanda Herrera reported in an April publication in *Clinical Cancer Research* the findings of a phase 1 clinical trial (RACIN) examining whether low-dose radiotherapy (LDRT) can be used to gently turn "cold" (immune-excluded) tumors of various types "hot" in preparation for immune checkpoint blockade (ICB) therapy. The researchers found the LDRT + ICB combination to be manageably safe, with an overall disease control rate of 42%. One ovarian cancer patient even sustained a complete response three years after receiving the combination. Analysis of tumor samples, collected before and ten days after LDRT, revealed that DNA damage response (DDR)-prone tumors that already harbored a few anti-tumor CD8⁺ T cells showed more anti-tumor T cell activity after LDRT. Those that resisted therapy had, at baseline, a paucity of immunostimulatory myeloid cells and an abundance of suppressive immune cells, such as mucosal-associated invariant T (MAIT) and regulatory natural killer (NK) cells. The study provides rare clinical evidence that low-dose radiation can reprogram immune-excluded metastases and bolster a CD8⁺ T cell response before immunotherapy is even started, opening a path to potentially expand immunotherapy to cold tumors (see cover image and Page 36). It also identifies biomarkers (like DDR features and immune cell niches) for patient selection in future trials.



Denarda Dangaj Laniti



Fernanda Herrera



Cameron Flower

A shared pathway of resistance

Cancers are frequently driven by the hyperactive signaling of tyrosine kinases, and many targeted cancer therapies have been developed over the past quarter century that inhibit their activity. Although many of these drugs have benefited patients, tumors frequently resist their effects despite being driven by the kinases they target. A study by former Ludwig MIT Graduate Fellow Cameron Flower—now a postdoc in Franziska Michor's lab at Ludwig Harvard and in Leonard Zon's lab at Boston Children's Hospital—and his former advisor Forest White used phosphotyrosine immunoaffinity enrichment and high-sensitivity mass spectrometry on cancer cell lines to identify signaling networks that drive sensitivity or tolerance to tyrosine kinase inhibitors (TKIs). The pair quantified endogenous levels of 1,222 phosphotyrosine sites across the proteomes of tyrosine kinase-driven human cancer cell lines that show variable response to genotype-matched TKIs. They found that TKIs are equally effective at inhibiting tyrosine kinase activity in both TKI-sensitive and insensitive cells but that more robust phosphotyrosine signaling was associated with reduced sensitivity to TKIs. They reported in a March issue of *PNAS* that cells that tolerate a variety of TKIs share high activity of the SRC/ABL family of kinases, which may be a general survival pathway conferring intrinsic resistance to therapy. A number of clinical trials now underway co-target signaling by SRC/ABL family kinases, offering a fortuitous clinical test of their hypothesis.

 **Combinatorial delivery of low-dose radiotherapy and immunotherapy to patients with immune-excluded tumors enhances CD8⁺ T cell functionality** | *Clinical Cancer Research*, 2026 April 17

 **Tyrosine phosphoproteome profiling identifies cell-intrinsic signals limiting the efficacy of tyrosine kinase inhibitor therapies** | *PNAS* 2026 March 25

Liquid biopsies could guide AML therapy

Measurable residual disease (MRD) is a strong predictor of relapse in acute myeloid leukemia (AML) patients who have undergone bone marrow transplantation. But the detection of residual leukemic cells requires repeated bone marrow biopsies, which are invasive and painful. Researchers led by Ludwig Johns Hopkins' Yuxuan Wang, Bert Vogelstein and Nickolas Papadopoulos, with their Johns Hopkins colleagues Lukasz Gondek and Richard Jones, reported in a *PNAS* publication in April a personalized, plasma-based assay for detecting MRD called v96. The assay incorporates up to 96 mutations and can be used to detect MRD with far greater ease and accuracy than that achieved by existing assays. The researchers tested v96 on 30 patients and found that it detected MRD in all patients in remission prior to transplantation—where conventional clinical assays found it in only 20% of them. Moreover, in 27 of the 30 patients (90% of patients), evidence of residual disease was found two months after transplantation. Cell-free DNA from plasma detected leukemic cells with far greater sensitivity than DNA isolated from bone marrow cells. In patients who relapsed, the median number of mutants detected in plasma was 352 times higher than in those who remained in remission. The researchers noted that noninvasive assays could reliably guide “the timing of transplantation and subsequent therapeutic measures” for AML, and should be evaluated in larger prospective studies.

 **A plasma-based DNA test for quantification of disease burden in acute myeloid leukemia patients undergoing bone marrow transplantation** | *PNAS*, 2026 April 14



Yuxuan Wang



Bert Vogelstein



Nickolas Papadopoulos

Liquid biopsy could aid management of bladder cancer therapy

Initial results of a recent clinical trial revealed that tumor resection and systemic therapy achieved lasting remissions for some patients with muscle-invasive bladder cancer (MIBC), indicating that not all patients require complete removal of the bladder, or cystectomy, which can have lasting consequences for urinary and sexual function. The cancer, however, recurred in a subset of patients who initially underwent the more limited procedure without cystectomy. Researchers led by Ludwig Johns Hopkins' Yuxuan Wang, Co-director Bert Vogelstein and Matthew Galsky of the Icahn School of Medicine at Mount Sinai, New York, conducted a long-term follow-up of trial enrollees to determine whether tumor DNA in the plasma (ctDNA) or urine (utDNA) could serve as biomarkers to inform prognosis and need for cystectomy. They reported in a February issue of *PNAS* that three-year survival with intact bladders for patients who had a complete clinical response following tumor resection and systemic therapy was 69%. Risk of metastasis was nearly five-fold higher for those with detectable ctDNA prior to systemic therapy, while undetectable ctDNA before or after systemic therapy was associated with extremely low metastatic risk. utDNA was more sensitive than ctDNA in detecting residual disease within the bladder, and detectable utDNA despite complete clinical response was associated with shorter bladder-intact survival. The findings are a first step toward incorporating ut/ctDNA assays in the management of MIBC.

 **Monitoring of plasma and urine tumor-derived DNA to inform bladder-sparing approaches for patients with muscle-invasive bladder cancer** | *PNAS*, 2026 February 18

A clue to triggering ferroptosis for pancreatic cancer therapy

Tumors fueled by a cancer gene named KRAS are often susceptible to ferroptosis, a type of cell death caused by the iron-driven oxidation of membrane lipids. Yet, though more than 95% of pancreatic ductal adenocarcinomas (PDACs) harbor KRAS mutations, they show no such vulnerability. Researchers led by Ludwig Institute CEO and Scientific Director Chi Van Dang and Maimon Hubbi, a postdoc in his laboratory at Johns Hopkins University, reported in an April paper in *Molecular Cell* that the composition of metabolites in the fluid around PDAC cells and the tumor's typically severe hypoxia cooperate to induce resistance to ferroptosis. They also identified hypoxia-inducible factor-2 (HIF-2) as a critical mediator of this effect. Maimon, Chi and their colleagues showed that HIF-2 boosts levels of glutathione, a cofactor for the enzyme GPX4, which counters the lethal membrane oxidation driven by ferroptosis. It does so by stepping up expression of the Xc⁻ transporter, which brings the molecule's precursor (cystine) into the cells, as well as that of enzymes (CBS and CTH) that help convert precursors into glutathione. It also stimulates mitophagy and reduces mitochondrial production of reactive oxygen species, limiting the lipid peroxidation that drives ferroptosis. The findings suggest targeting HIF-2-activated pathways could sensitize pancreatic tumors to ferroptotic therapies.

 **The HIF-2 transcription factor mediates resistance to ferroptosis in pancreatic cancer** | *Molecular Cell*, 2026 April 2



Chi Van Dang



Maimon Hubbi



Yingxi Xu



Ping-Chih Ho

How mitochondrial dysfunction triggers T cell exhaustion

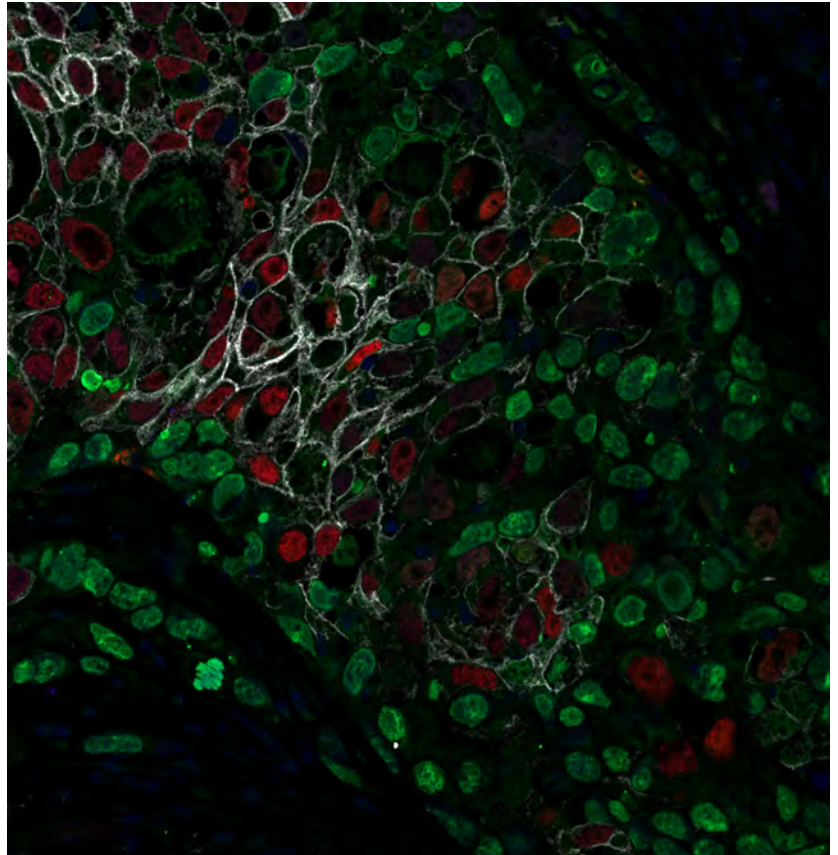
The harsh conditions of the tumor microenvironment often push CD8⁺ T cells into a state of terminal exhaustion, which is characterized by an accumulation of dysfunctional mitochondria and extensive genetic reprogramming. Researchers led by Ludwig Lausanne's Yingxi Xu and Ping-Chih Ho reported in a March paper in *Nature* how the accumulation of depolarized mitochondria drives terminal exhaustion through processes involving the release of the iron-bearing compound heme. They showed that the glut of dysfunctional mitochondria seen in exhausted tumor infiltrating CD8⁺ T cells enhances proteasome activity that preferentially degrades mitochondrial heme-containing proteins. The resulting intracellular buildup of heme leads to the generation of a functionally distinct form of the molecule known as regulatory heme, which shuttles into the nucleus via the nuclear transporter PGRMC. There it binds the transcription factor BACH2, inducing its degradation and awakening gene expression programs that drive terminal exhaustion. The researchers showed that disruption of PGRMC2 abrogates this effect, keeping anti-tumor T cells in a functionally vibrant state. They also demonstrated that transient and low-dose addition of the cancer drug bortezomib—a proteasome inhibitor currently used to treat B cell acute lymphoblastic leukemia—to CAR-T cell cultures during manufacturing reduces exhaustion-associated programs in the cells and maintains them in a proliferative and functionally vibrant state.

 **Proteasome-guided haem signalling axis contributes to T cell exhaustion** | *Nature*, 2026 March 18

How HER2+ breast cancers resist ADC therapy

Antibody-drug conjugates (ADCs) that target HER2, like trastuzumab deruxtecan (T-DXd), are used to treat HER2-positive breast cancer. But HER2 heterogeneity in tumors can drive resistance to such therapies. Understanding why this is so has been hindered by the lack of preclinical models that faithfully mimic HER2 heterogeneous tumors. Researchers led by Ludwig Harvard's Kornelia Polyak, including Center colleague Franziska Michor, reported in an April *Cancer Discovery* publication their development of human cell line models composed of *ERBB2*-amplified (HER2^{hi}) and nonamplified (HER2^{lo}) cell populations from the same tumor and the use of those models to examine the role of HER2 heterogeneity in tumor biology and drug resistance. Their studies uncovered cooperation between clonal sub-populations of HER2^{hi} and HER2^{lo} cells and showed that the latter drive resistance to HER2-targeting ADCs and subsequent disease recurrence but are themselves susceptible to HER2 kinase inhibitors. Employing CRISPR screens on co-cultures of HER2^{hi} and HER2^{lo} cells, the team showed that HER2^{lo} cells can be sensitized to T-DXd by loss of *ABCC1*, a transporter that drives drug resistance in many cancers, and the deubiquitinating enzyme *USP9X*, which prevents the degradation of proteins. Inhibiting the latter, they show, sensitizes HER2^{lo} cells to T-DXd by promoting HER2-degradation and release of the ADC payload. The findings suggest an approach to overcoming therapeutic resistance in HER2+ breast cancers and improving patient outcomes.

 **HER2 heterogeneous breast cancer models reveal novel therapeutic targets and subclonal dynamics during evolution to resistance to HER2-targeted therapies** | *Cancer Discovery*, 2026 April 2



Marie-Anne Goyette

Micrograph of a HER2 heterogeneous tumor. Red and green are HER2 high and low cells, respectively, marked with RFP and GFP, and white is HER2 staining.



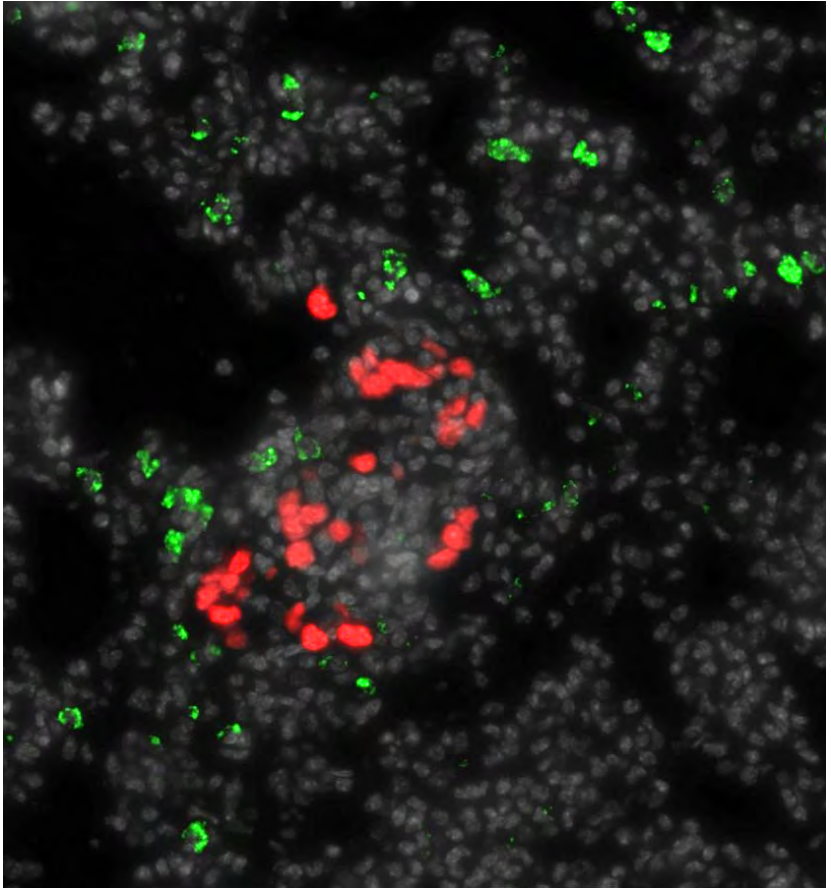
Kornelia Polyak

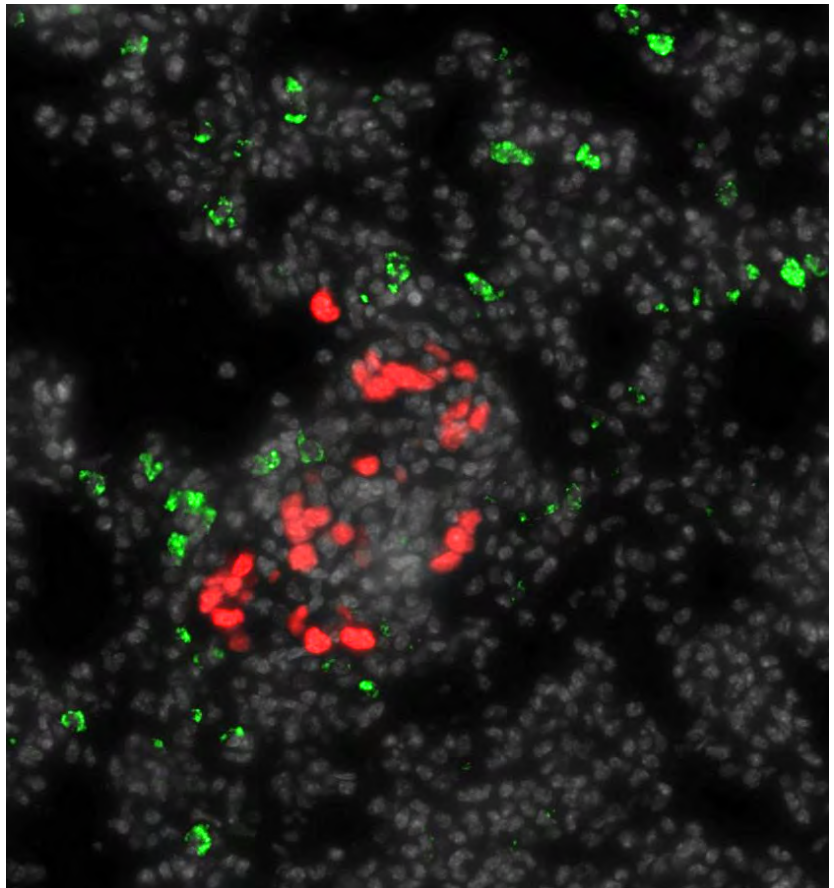


Franziska Michor

How traveling tumor cells evade immune attack

Researchers led by Ludwig Harvard's Monica Cassandras, Xavier Sanchez and Judith Agudo reported in a March publication in *Nature* a potentially new strategy to prevent the metastasis of triple-negative breast cancer (TNBC). The researchers applied JEDI—a model Judith developed to study the immune system's surveillance of cancer stem cells—to locate TNBC cells that evade immune attack and metastasize successfully in mice. They found that many disseminated tumor cells (DTCs) activate the glucocorticoid receptor (GR) to evade targeting by natural killer cells and CD8+ T cells. GR activation suppresses the FAS-FAS ligand pathway, which the researchers show is a key pan-cytotoxic pathway against DTCs. The findings are in line with recent reports suggesting that activation of the glucocorticoid receptor correlates with metastasis and poor outcomes for TNBC patients. Judith, Monica, Xavier and their colleagues showed that mifepristone, a GR inhibitor already in clinical use worldwide, reduced the number of incipient metastases and extended survival in TNBC mouse models. Combining it with anti-PD-1 checkpoint blockade immunotherapy further inhibited TNBC metastasis and extended survival. The researchers note that they have identified a novel mechanism of immune evasion employed by DTCs, underscoring how differently such traveling cells interact with the immune system. They also suggest the GR signaling pathway may be a target for therapies that curtail cancer metastasis, the leading cause of cancer-related mortality.

 A Glucocorticoid-Fas axis controls immune evasion during metastatic seeding | *Nature*, 2026 March 4



Monica Cassandras

Image of a micrometastasis of triple-negative breast cancer in the lung, showing disseminated tumor cells (red) and immune cells (NK cells and CD8+ T cells, green).



Monica Cassandras



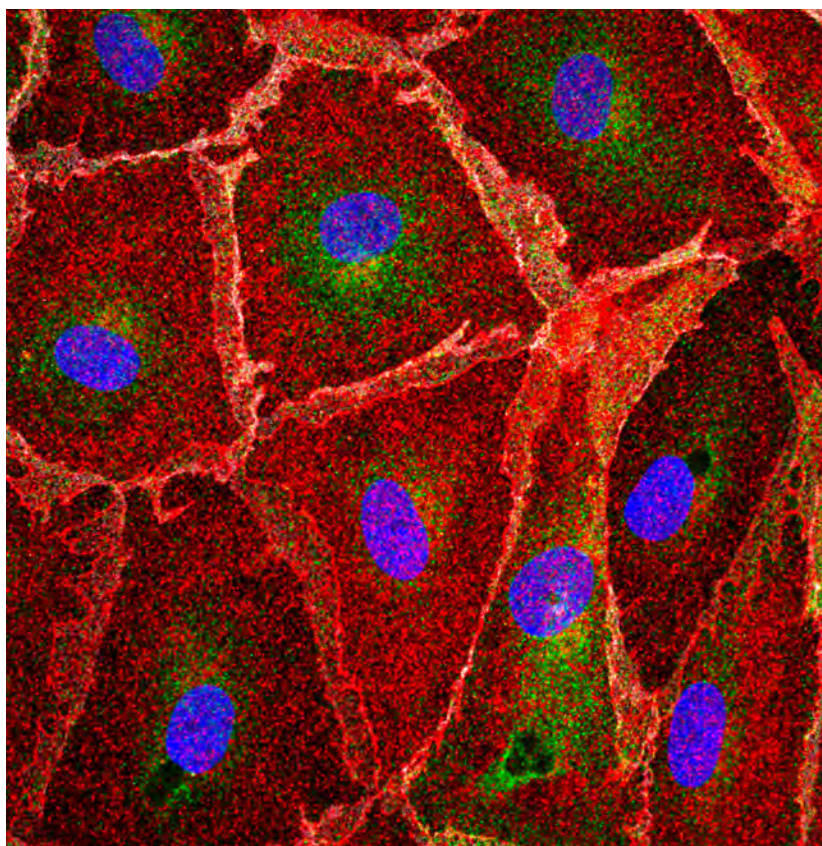
Xavier Sanchez



Judith Agudo

A new manager of metabolic health

The endothelial cells that line blood vessels regulate the passage of nutrients from the blood into the body's tissues. In a March issue of the *Journal of Experimental Medicine*, researchers led by Ludwig Lausanne's Laureline Wetterwald, Anna Köck and Tatiana Petrova uncovered an unexpected, active role for the cells in maintaining metabolic health. The researchers discovered that a newly identified transmembrane phosphoglycoprotein expressed only in endothelial cells, MYCT1, is essential for white adipose tissue (WAT) expansion. In mouse models, deletion of *Myct1* sufficed to limit energy storage in WAT, with the mice remaining much leaner than their normal counterparts even when fed a high-fat diet. Their studies revealed that MYCT1 regulates endolysosomal trafficking through its interaction with small transmembrane proteins IFITM2 and 3. Loss of MYCT1 leads to accumulation of IFITM2/3 in endosomes, driving enhanced endocytic uptake and the delivery of plasma protein cargo to lysosomes for degradation. This causes an intracellular nutrient overload that hyperactivates signaling by mTORC1—a molecular manager of cellular metabolism—leading to the futile use of energy in endothelial cells instead of its delivery to other tissues for storage in fat. The discovery assigns a new role to endothelial cells in regulating metabolism and energy storage. It also suggests a target for drugs that could disrupt the endothelial management of energy transfer to treat metabolic disease and cancer.



Anna Köck

Endothelial cells stained for MYCT1 (red), VE-cadherin (white) and IFITM2/3 (green).



Laureline Wetterwald



Anna Köck



Tatiana Petrova

 **MYCT1-IFITM2/3 interaction links endothelial endolysosomal trafficking to white adipose tissue expansion** | *Journal of Experimental Medicine*, 2026 March 25

A key trigger for immunosuppression in bladder cancer

Innate lymphoid cells type 2 (ILC2s) can support tumor growth and survival by increasing the population of myeloid-derived suppressor cells (MDSCs), which inhibit effector T cell mediated anti-tumor immunity. But it is not clear what triggers their pro-tumoral activation. Researchers led by Ludwig Lausanne's Maryline Falquet and Camilla Jandus reported in a February publication in *Nature Communications* the nature of that trigger and an additional mechanism by which activated ILC2s induce immunosuppression in the tumor microenvironment in bladder cancer (BC). They showed using patient samples and mouse models that nerve growth factor (NGF) produced by mast cells, which accumulate in the BC tumor microenvironment, activates ILC2s. NGF binding to the high-affinity NGF receptor TrkA, which is specifically expressed by ILC2s, induced IL-5 and IL-13 secretion, a hallmark of ILC2 activation. Maryline, Camilla and colleagues found that activated ILC2s also directly induce the differentiation of naïve CD4⁺ T cells into regulatory T cells, which sustain their pro-tumoral effects. Further, the researchers demonstrated that an existing inhibitor of the TrkA improves survival in an orthotopic mouse model of BC and sensitizes the mice to checkpoint blockade immunotherapy. In patients, high NGF levels were associated with shorter survival in ILC2-rich bladder tumors, supporting the clinical relevance of these findings and nominating the targeting of TrkA⁺ ILC2s as a potential immunotherapy for this cancer.

 **Mast-cell derived nerve growth factor drives ILC2 pro-tumoral functions in bladder cancer** | *Nature Communications*, 2026 February 21



Maryline Falquet



Camilla Jandus



Melita Irving



Greta Maria Paola
Giordano Attianese

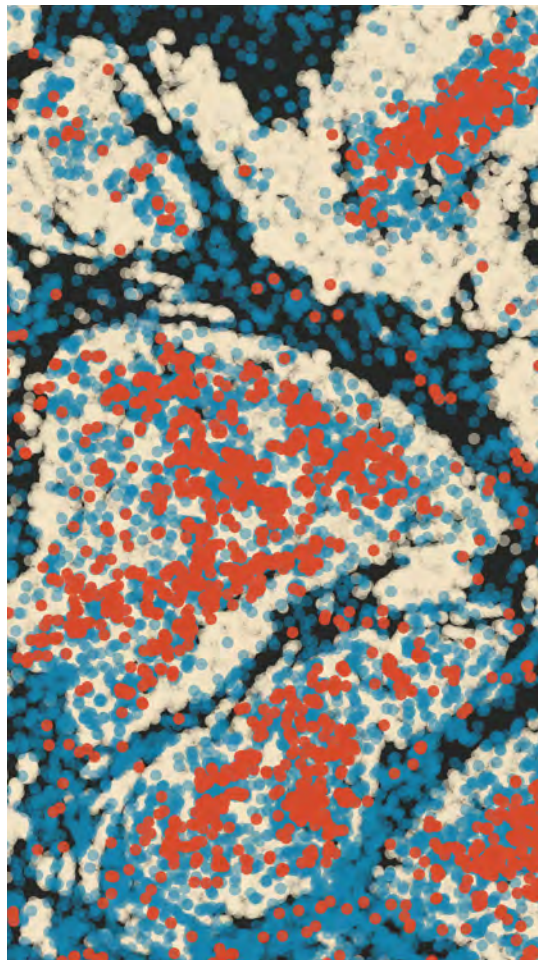
A DROP-CAR-T cell for control and safety

For all their promise, chimeric antigen-receptor (CAR)-T cells do have their limitations. For one thing, they can inadvertently kill healthy cells along with cancerous ones—or, separately, provoke a systemic immune overreaction—causing serious and sometimes even lethal side effects. Researchers led by Ludwig Lausanne's Melita Irving and Greta Maria Paola Giordano Attianese and colleagues at the École Polytechnique Fédérale de Lausanne reported in a February issue of *Nature Chemical Biology* their design and preclinical evaluation of a CAR-T cell that elegantly addresses this risk. Their construct, dubbed the DROP (for drug-regulated off-switch PPI)-CAR-T cell, can be swiftly switched off by a clinically approved cancer drug, venetoclax, and then restarted upon withdrawal of the drug. The signaling component of the CAR inside the cell is linked, via its transmembrane segment, to a protein domain on the outside of the cell carrying the computationally designed human domain dmLD3. This binds to a BCL-2 domain attached to the tumor-targeting component of the CAR. Venetoclax disrupts this protein-protein interaction (PPI), releasing the tumor-targeting component and disengaging the CAR T cell from its targeted cancer cell while preserving the T cell for subsequent therapeutic revival. The researchers show that their DROP-CAR-T cells effectively kill cancer cells and can be switched off and reactivated as intended in mouse models of cancer.

 **Drug-controlled CAR T cells through the regulation of cell-cell interactions** | *Nature Chemical Biology*, 2026 February 19

A single neutrophil state supports tumor growth across cancer types

Though they've been linked to the growth of multiple cancers, neutrophils can assume multiple functional states, only some of which have that effect. Identifying those states has proved to be a challenge. Researchers led by Ludwig Lausanne's Mikaël Pittet reported in a February publication in *Cancer Cell* a gene expression program in tumor-associated neutrophils (TANs) that uniformly supports cancer cell survival and tumor progression across human and murine tumors. The program pushes TANs into a terminal 'aged' state characterized by high CCL3 expression. These senescent, CCL3^{hi} neutrophils preferentially occupy hypoxic niches in the tumor microenvironment (TME). Induced by hypoxia, CCL3 binds to its receptor CCR1 on the TANs themselves to drive senescence, activate gene expression programs that induce TAN adaptations to the TME and activate genes that promote tumor growth. The researchers showed that mice lacking CCL3 or CCR1 in their neutrophils failed to support tumor growth. They also identified TANs expressing this conserved genetic program as a key component of the TME linked to cancer progression, described a biomarker of prognosis for further evaluation and suggested signaling pathways that maintain CCL3^{hi} TANs as potential targets for cancer therapy. These findings, together with Mikaël and colleagues' 2023 *Science* study identifying the CXCL9-to-SPP1 macrophage polarity axis, establish neutrophil abundance and macrophage polarization as two independent, key TME variables that broadly influence cancer progression and patient outcomes.



Pittet lab

Sample from a human head-and-neck tumor containing infiltrating neutrophils. Tumor cells appear in light grey. Among the infiltrating neutrophils, some do not express CCL3 (blue), while others do (red). Mikaël and colleagues found that CCL3-positive neutrophils are highly conserved across tumor types and promote the growth of tumors.



Mikaël Pittet

 **CCL3 is produced by aged neutrophils across cancers and promotes tumor growth** | *Cancer Cell*, 2026 February 5



Christian Hinrichs
Ludwig Princeton



Caroline Arber
Ludwig Lausanne



Bernhard Gentner
Ludwig Lausanne

Interviews with three new Ludwig Clinical Scholars

Our founder, Daniel K. Ludwig, made it abundantly clear that he wanted the cancer research supported by his legacy to be translated, whenever possible, into clinical interventions. In keeping with that vision, on July 1 the Institute appointed three accomplished physician-researchers as Ludwig Clinical Scholars: Bernhard Gentner and Caroline Arber of Lausanne University Hospital (CHUV) and the University of Lausanne, who join Ludwig Lausanne; and Christian Hinrichs of the Rutgers Cancer Institute, who joins Ludwig Princeton.

"These appointments reflect the Institute's longstanding commitment to bringing

exceptional clinical insight together with the basic and translational science conducted at our Branches," said Ludwig Institute Deputy Scientific Director and Communications Director Pat Morin. "Bernhard, Caroline and Christian are outstanding physician-scientists whose expertise will strengthen those connections and help turn discoveries made in our laboratories into new cancer therapies."

To welcome them on board, the Link recently caught up with each to learn a little more about their lives, careers and avocational pursuits. Here are some excerpts from those conversations.

LUDWIG PRINCETON

Christian Hinrichs

Tell us a bit about yourself—your family, where you grew up.

I grew up in St. Louis. I actually committed to medicine when I was 17, in high school, and went to a combined six-year BA/MD school at the University of Missouri–Kansas City (UMKC). I have a brother who’s a couple years younger than me, and my mom and dad are no longer living, but we all grew up in a house in St. Louis. I loved science, and my grandfather was a physician—he was actually a third-generation physician, I think, so it makes me the fourth in my family. I really admired him and was kind of inspired by him. He actually ended up being one of the early physicians in what was at the time called industrial surgery, but it evolved in his lifetime into occupational medicine. He started an occupational health practice in downtown St. Louis when he got back from World War II—he was an Army doctor.

How did you wind up in the world of cancer research?

After the six-year BA/MD, I stayed at UMKC and I did a five-year general surgery residency there. When I was doing surgery, I realized that a lot of general surgery, at least at that time, was actually oncologic surgery. But I thought that should really be a specialized field, where you understand the disease you’re treating. So I wanted to learn more about cancer surgery, and did a two-year fellowship at Roswell Park Cancer Institute, in Buffalo.

During the fellowship, the limitations of surgery in treating cancer became even more apparent. We had some particularly compelling and emotional cases, where we did big operations on young people,



and their cancer came back before they were even healed. That had a big impact on me. I was able to obtain a position in a research fellowship at the National Cancer Institute (NCI), in what’s called the surgery branch, which was known as more of an immunotherapy center than actually a surgery place. That’s where the early development of IL-2, under Steve Rosenberg, was happening. IL-2 was an early immune-based treatment for melanoma and kidney cancer. And the work there extended into cellular therapies. I went into a laboratory there focused on developing more potent cells for these treatments and it turned out to be a great experience. I ended up being there for six years, basically in a postdoc type of position.

About five years into it, though, I lost my right eye to an ocular melanoma. It’s a rare kind of cancer. I had to stop operating as a surgeon because my depth perception was thrown off by monocular vision. I was, at that point, six



years in as a laboratory researcher, trying to make cells more potent. But on the clinical side, we were just starting to genetically engineer cells to be able to target specific antigens in the tumor. That engineering approach was really interesting, but the early trials targeted proteins that were expressed more on tumors but also on healthy tissues. In pretty much all cases they would cause horrendous toxicity.

Observing that, I was thinking, well, how am I going to make the cells stronger if everything's limited by this toxicity from targeting healthy tissues? And putting it all together, I decided, okay, I'm going to retrain in internal medicine and medical oncology, and become a medical oncologist. At this point, I was, I think, 40-ish, and had a one-year-old kid at home. I got a year of credit in internal medicine from my prior clinical training, so I started as a second-year resident, and did a medical oncology fellowship at the NCI. On the back end of that fellowship, I went into Steve Rosenberg's main lab group, and I said, "Steve, I want to do clinical trials to treat cancers that are caused by human papillomavirus." My rationale was that when HPV causes cancer, it does it primarily through two proteins, E6 and E7, and they continue to be present in the tumor cells as they divide. They're expressed by all of the cells in the tumor, as far as we know, and they're not expressed by any healthy cells, because they came from a virus. So to me, this was the place to do proof-of-concept studies, to develop cellular therapies for epithelial cancers that express these specific viral antigens, E6 and E7.

Tell us about that first clinical trial.

So the first trial I did was with an approach that we call TIL, or tumor infiltrating lymphocytes. For this, we grow the T cells out of a patient's tumor, test the cultures for reactivity against the E6 and E7 oncoproteins,

grow them up, and give them back to the patient. In that trial, we saw tumor responses in a little over a quarter of the patients. In some patients the tumors completely went away. Two patients with cervical cancer had no evidence of disease 10 years after treatment—very dramatic, because both had been told, "Get your affairs in order."

That was, to me, kind of a first-generation approach, because it requires surgery, takes a long time to grow the cells, and the cells target whatever they target. What I'd always wanted to do was an engineered approach. It took some time, but our team identified a T cell receptor that targets the E7 oncoprotein—which we then evaluated in an engineered cell therapy trial at the NCI. We saw some really dramatic tumor responses, but we didn't cure anyone, and we also came to understand some of the mechanisms of resistance.

And now, at Rutgers?

So with that in mind, I was recruited to Rutgers, where I set up the cell therapy program. One of the main trials is a phase 2 trial with that engineered E7 TCR approach. Based on what we learned about the mechanism of resistance in the first trial, we're selecting patients more likely to respond. Of the first 10 patients, six had tumor responses including two complete responses that were ongoing at 11 and 12 months after treatment.

We do have another active clinical trial going on. I had a patient—one of the TIL patients who had all their cancer go away—and when I studied the cells that we gave her, it turned out that the main targeting was actually not against HPV. Two-thirds of the cells that we gave her had the exact same receptor, targeting the exact same antigen—something called KK-LC-1, from a class of cancer antigens commonly targeted in oncology, called cancer germline antigens. It's actually

commonly expressed in cervical cancer, maybe in the range of 30% or 40% of the tumors, and surprisingly uniform when it occurs. So there's definitely a fraction of patients who have uniform expression of this target antigen in their tumors, and we have a phase one clinical trial targeting it that's active now.

Could these approaches be extended to other cancers as well?

Yes, absolutely. The KK-LC-1 TCR I mentioned is also being studied for KK-LC-1-positive gastric adenocarcinoma, lung adenocarcinoma, and triple-negative breast cancer, in addition to cervical cancer. The HPV-targeted approach also covers some territory, because throat cancers, the oropharynx region specifically, about 60 to 70% are caused by HPV—actually a growing group. And HPV can also be found in cervical and other genital cancers like vulvar and vaginal cancers and in men, penile and anal cancers. We've actually seen a few esophageal cancers too, probably an extension of the head and neck process. Yeah, I think there are a fair number of patients who could benefit.

Tell us a little about your collaborations with Ludwig Princeton.

One area where we're doing research, and have funding, is in studying the metabolic requirements of the T cells that we're generating for therapeutic use. This is in collaboration with Eileen White and Geoff Markowitz, who's actually the most central person at Rutgers working on this. This collaboration also intersects with other investigators, like [Ludwig Princeton Director] Josh Rabinowitz, and we are also participating in the newly funded Weill Cancer Hub East, a collaborative effort that includes investigators at Ludwig Princeton and Weill Cornell. It is a very exciting concept—to study



the T cell and host metabolic demands *in vivo* in humans, after we give them cell therapies.

Tell us a bit about your hobbies, family ...

I am married and my wife works in clinical development in the pharmaceutical industry, so we have interesting dinner conversations, crossover a lot. We have two teenage sons. I spend a lot of time with my family, and I like to run, and I do resistance training, sometimes with my kids.

Do you have any favorite music, a favorite book?

Well, so yeah, I do have favorite music, but I tend to listen to niche alternative, mostly rock, country, folk sort of bands that no one else has ever heard of. Sometimes I go to concerts with a friend of mine in Washington D.C. who has the same taste, and sometimes with my brother in New York. But usually it'll be at a venue that's in the range of a hundred to 2,000 people, not a bigger place with bigger, better-known bands. I love Sturgill Simpson for example. Another band I went to watch recently is called Brown Horses. I don't do a lot of recreational reading. Most of what I read is science and news, especially articles about technology, which I enjoy.

Christian with his patient Maria (right) and her sister during a clinical visit at the Jack & Sheryl Morris Cancer Center in New Brunswick, New Jersey. A participant in a clinical trial led by Christian, Maria remains cancer-free nearly two years after receiving an innovative T cell therapy for HPV-associated cancers.

LUDWIG LAUSANNE

Caroline Arber

Tell us a bit about yourself.

I'm from Switzerland. I grew up in Basel, a small town on the border with France and Germany, with my sister and my parents. When I was four years old, my dad received the Nobel Prize in Physiology or Medicine for the discovery of restriction enzymes. I had no idea what it meant, but I had the feeling that it was something very important. I was doing a painting class, and they gave me a big white piece of paper and said, "Just put something that makes you feel something important happened." I remember that I just drew one huge flower. My parents have hung this painting at their place, and it's kind of a memory of that important event. This experience certainly influenced my personal life and my professional development. We were often accompanying my dad to scientific meetings together with my mom, and we had the opportunity to meet renowned scientists. This was a very special and amazing experience for me.

After finishing high school, I was drawn into medicine because I felt that I needed to understand the human body, the different disease pathologies and how they were treated. Already during medical school, I was also attracted to translational research and interested in hematologic oncology. I liked the very strong lab component, which is important in the diagnostics of blood cancers but also for stem cell transplant and cell therapies. So I trained in internal medicine and hemato-oncology and complemented that with research experience at Stanford University. And after becoming a heme-onc and cell therapy specialist, I joined Baylor College of Medicine, where I really became passionate about immune cell engineering



and clinical trials with genetically engineered cells to treat malignancies and infections.

What are your main clinical and research interests?

My main clinical focus is on cellular therapies, and in particular immune effector cell therapies. So, in the routine clinical activity, I have established—together with key clinical colleagues—the CAR-T cell program in the Department of Clinical Oncology at CHUV for all available indications in hematologic oncology, in collaboration with pharmaceutical partners. And since 2024, I'm a co-director of our clinical cell therapy program. My research focus is also

Caroline's lab specializes in designing and engineering new receptors for chimeric antigen-receptor (CAR) or T cell receptor (TCR) based T cell therapies, with the aim of advancing such cell therapy products into first-in-human clinical trials. "My clinical focus and research focus are connected," she says.

on cell therapies. In my lab we engineer new receptors for CAR or T cell receptor (TCR) based T cell therapies, with a focus on future translation to first-in-human clinical trials. So my clinical focus and my research focus are connected. One example of a clinical trial where I have an important role is the T cell therapy for NY-ESO-1-positive sarcoma and for melanoma, where we know that a proportion of patients have high levels of NY-ESO-1 expression. It's a class I TCR directed against NY-ESO-1, and the TCR is expressed as a transgene in the patient's T cells, manufactured individually for each patient. It started last year, and our team has now treated four patients.

Whom have you collaborated with at Ludwig Lausanne?

I collaborated with Ping-Chih Ho on the impact of metabolic interventions on CAR-T cell therapies, to modulate the potency of the product, and we have tested that in preclinical models together. I've also worked with [former Ludwig Lausanne Director] George Coukos and [fellow Clinical Scholar] Bernhard Gentner in developing clinical trials with locally produced immune effector cells. For the NY-ESO-1 TCR study mentioned above, I'm the sponsor representative for the CHUV, as this is an academic investigator-initiated trial, and Bernhard is the clinical PI.

Tell us a little about your work on CAR-T cell design?

We have recently designed a new chimeric antigen receptor. We are finishing up the preclinical data package and are moving that into a first-in-human clinical trial for acute myeloid leukemia. We are targeting an antigen called CD70, and for that we used the natural ligand for the target. We first optimized the cell surface stability and signal transduction capacity of the CAR backbone. And then, in collaboration with a computational protein



design lab at EPFL, we optimized the interface of the ligand:receptor interaction to make it highly antigen-sensitive. So this CAR is actually able to detect very low levels of antigen, and that helps us with the heterogeneity that we find in these leukemias—some patients have high levels, some patients have low levels, and even within the patient we find different levels on different leukemia cells. So having a very sensitive CAR will help us to tackle a big proportion of these leukemic cells in the patient. We have obtained funding with philanthropic support to move this into a clinical trial. The trial could open in about a year from now.

Caroline, with her husband Patrick and their children Isabelle (right) and Adrian, in the Bernina region of the Alps. Summer hikes, and skiing in the winter, are among Caroline's favorite family activities.

What else are you doing in your lab?

We are also designing other chimeric receptors, not CARs, but receptors that can sense input from the tumor microenvironment. We think that for solid tumors, which are rich in soluble factors and cellular components that are immunosuppressive, we can use a second receptor to give the T cell an additional input and an advantage to overcome this immune suppression and reduce their exhaustion. So

Caroline, with members of her lab, celebrating Tiffany (Xingyun) Que's (front, left) defense of her PhD dissertation this summer.



now we are using basically two components on one T cell to cooperate and give it the capacity to better infiltrate solid tumors, overcome exhaustion signals and give it the signals to persist long-term.

What do you like most about working closely with patients?

I really like the personal interaction with people. We need to find solutions to go beyond the standard of care, and to really give patients options to participate in clinical trials that can potentially help them even when all standard treatments have been exhausted. That's one of the key driving motivations for me.

Which emerging technologies in your field excite you the most?

What I find extremely exciting are the *in vivo* gene modification tools that are now coming up for established targets of CAR-Ts. So now there's the option to create the CAR-T *in vivo*. And then other technologies that I think will help us to better choose our targets, our modulators, our drugs, are the 'omics tools—the single-cell and spatial 'omics that help us

to understand the microanatomy of tumors that we are trying to tackle and, together with artificial intelligence, to select potential combinations of treatments, combinatorial drug options based on molecular features. I think these technologies are very exciting.

Tell us a bit more about yourself—your hobbies, and how you spend your spare time.

I have two kids, and my husband and I love spending time with them. They are twelve and nine. We like to do outdoor activities with them, like hiking or skiing. Or we explore art exhibitions. And when I'm by myself, I play the violin. I also like to play chamber music with friends. I started playing when I was six, and I've been playing ever since. My kids play the piano, both of them, and my husband also plays the violin. So we can start playing together.

Do you have any favorite books or music?

I love to go to concerts and listen to chamber music, so again I'm more on the classical side. I really like the quartets of Beethoven. And for symphonies, I'm more into late 19th and early 20th century composers.

LUDWIG LAUSANNE

Bernhard Gentner

Tell us a bit about yourself. Where are you from, where were you raised?

I grew up in a very small village in the south of Germany. My father was an electrical engineer and a high school teacher. My mother was an administrative clerk, but she decided pretty early to use her time to raise me and my two brothers, which is a full-time job, as you can imagine. It was a wonderful childhood. We had a huge garden. My parents were just great—my mother was very caring, always there for me, and my father taught me that hard work, discipline, and performance can bring you forward in life. I think this was very important for how I approached university and also research afterwards. He also always encouraged me to go abroad and to learn about other environments and other systems, and this was very helpful. My childhood dream was to be a pilot, but my eyesight was unfortunately not good enough. As a second choice, I decided to become a doctor.

How did you get into gene therapy?

This basically goes back to high school. We had a good biology teacher. He was very much up to date, because in 1995 he told us one day that a child with severe combined immunodeficiency, the so-called bubble boy, had been treated with gene therapy at the NIH. That was, for me, extremely inspiring—this idea that we can do gene therapy, we can correct genes. Then I went to medical school in Heidelberg—it's a major science hub in Europe. So I was immersed in that environment and got excited about doing research, not just clinical work. So I wanted to do an experimental doctoral thesis there, and as luck would have it, I stumbled across a gene therapy project. The goal was to develop



technologies to identify retroviral integration sites in repopulating stem cells exposed to an experimental gene therapy protocol. And I jumped onto this project, and worked almost three years full-time to develop the technology. And that's how I came into gene therapy during university. And I managed to do this in parallel with my medical studies.

And what made you pursue oncology?

My grandfather died from small cell lung



Bernhard with members of his laboratory in Lausanne. A hematologic oncologist, Bernhard has pioneered the genetic engineering of blood stem cells to cure monogenic diseases and that of myeloid progenitors to transform them into vehicles for innovative cancer immunotherapies.

cancer when I was little, and I was always very much scared to develop a cancer. Then I got exposed to oncology quite a lot in the last year of medical school in oncological surgery in Houston, Texas, at the MD Anderson Cancer Center, and in my first three years as a physician, when I worked in medical oncology for my residency in Erlangen, Germany. I have to say it was depressing for me, a frustrating experience, because this was before immunotherapy came in, so you basically couldn't cure these patients. You gave some chemotherapy, and then they relapsed. I thought, I don't want to work in medical oncology. But then I got very passionate about hematology because at least there was a fraction of patients you could cure in those days. And I also saw that most innovations—including targeted therapies and cellular immunotherapies—were pioneered in the setting of liquid cancers. So I pretty much shifted my focus and specialized in hematology and bone marrow transplantation in Milan, at the San Raffaele Institute.

What is your main clinical focus, and your connections and collaborations here?

My main focus is cellular therapy. I worked

many years on allogeneic hematopoietic stem cell transplantation—I was lucky to work in Milan, in a center that was at the forefront of alternative donor transplants, which taught me how to manage ultra-complex patients, some needing semi-intensive care that we administered ourselves on the floor. That was very enriching from a medical perspective, because we were doing the real doctor work, not just calling the consultant. But my real passion remained gene therapy. With industrial collaborations, we had the opportunity to bring treatments from the bench to the patient, and then even to the market. I understood that it doesn't finish with a phase one study where you get a nice paper. The real work starts afterwards, developing it into a drug, and I had the opportunity to see several programs in Milan successfully go this way. There's unfortunately a crisis right now with *ex vivo* gene therapy, because the industry feels it's not a good business model—it's a very expensive personalized treatment, paired with very high regulatory requirements, resulting in high costs. But I feel there's a lot of untapped potential in the new genetic engineering technologies. That's really where my passion lies.

What convinced you to move here and become affiliated with the branch?

I think professional growth was one of the drivers, and to get a little bit away from the rare disease indications. And an impressive infrastructure was in place here, thanks to [former Ludwig Lausanne Director] George Coukos, who did a fantastic job in setting all this up and creating this environment and infrastructure. It is unique in Europe, I would say. And I realized there is potential here to do translationally oriented team science, to develop cutting-edge new cell therapy approaches for cancer, in a center focused on cancer. I wanted to combine my clinical responsibilities with my research activities.

Tell us about the myeloid cell reprogramming work you're doing.

The idea is to reprogram the myeloid cell, because we know it's a key component of cancer ecosystems, often responsible for resistance to treatments and for cancer progression. There's a huge heterogeneity of different myeloid cell states. If you do treatments based on the mature myeloid cells, there will always be a way that the body, the cancer, will compensate for that function you block. So my vision is to go into the progenitor, or the stem cell, and influence the myeloid cells that will be recruited into the cancer. We're exploring different ways to influence the cancer ecosystem. One is delivery, generating specific transcriptional modules which release anti-cancer molecules, like cytokines and T cell engagers, locally within the tumor microenvironment. The other is reprogramming the myeloid cells. But you need to also work on the T cell side, combine it with some immunotherapy that enables the T cells to perform. So my lab is trying to find these synergistic combinations of myeloid-directed and T cell-directed approaches that would make a difference for selected cancers.

You recently reported the results of a Phase 1 clinical trial of Temferon, which uses hematopoietic stem/progenitor cell-derived macrophages for the targeted delivery of interferon- α 2 (IFN- α 2) to tumors (see page 11). Are you moving forward with that?

Absolutely. It was a very successful trial in my opinion, even though it's always hard to make any claims on survival when you do a phase 1 study without a control cohort. But the fact that we saw multiple patients that survived long-term, so beyond two years for this subset of glioblastoma (GBM), this is, let's say, noteworthy at least. And also, the two longest surviving patients developed a late response to the treatment, without any additional treatment. Together with the biological



data from this work, this clearly indicates that there is a possibility to reprogram this microenvironment in GBM. I definitely see the potential to bring this to the next level, with a new, improved construct and combination therapies to better engage the T cell compartment.

Any favorite music?

I like different kinds of music. On one hand, I like classical music very much. The older I get, the more I enjoy classical music because it's relaxing. But I also still like rock in general—what was “in” in the 1990s, like Guns N' Roses, that kind of stuff.

What's the best career advice you received?

I think the best advice is, work hard and smart. It's not sufficient to be a hard worker, because you are maybe not asking the right question, and maybe you're becoming inefficient. You have to also be very smart and have a clear plan for what you're doing. So I think you need both—work hard and smart.

Bernhard in the cockpit of a Douglas CD3-Dakota on display at the Aerospace Museum in Milan. “My childhood dream was to be a pilot, but my eyesight was unfortunately not good enough,” Bernhard says. “As a second choice, I decided to become a doctor.”

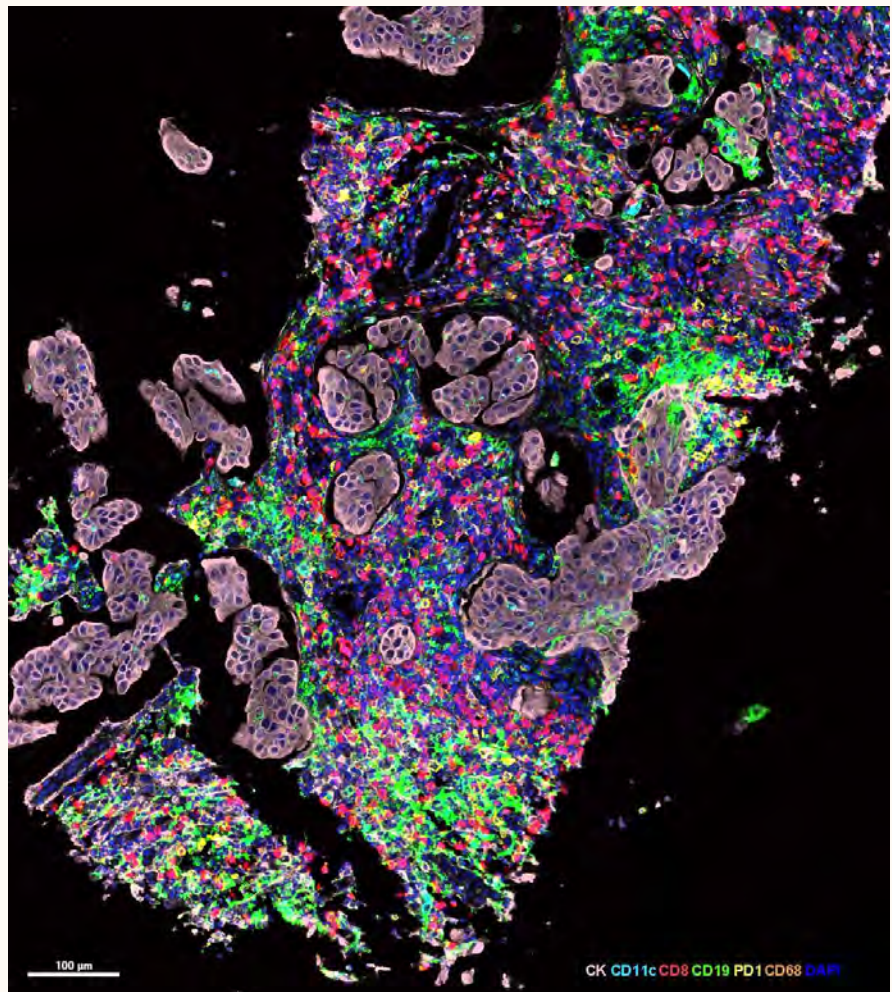
Image gallery

This image was shared by Ludwig Lausanne's Denarda Dangaj Laniti and Fernanda Herrera

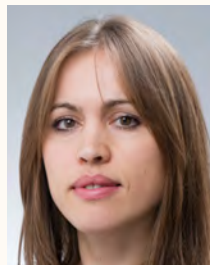
This image shows an ovarian cancer metastasis from a woman with high-grade ovarian cancer who experienced a durable complete response in the RACIN clinical trial after having recurrences following several lines of treatment. This image is from a biopsy collected ten days after low-dose radiotherapy, before anti-PD-1 checkpoint blockade had started, giving us a rare view of how radiation alone can begin to reshape the tumor microenvironment (see page 17).

The pale epithelial islands are cancer cells (pink). Surrounding them is a dense and colorful immune landscape, including CD8⁺ T cells (red), B cells (green), dendritic/myeloid cells (cyan) and other antigen-presenting cells, such as macrophages (orange). (PD-1 is stained yellow.) What makes the image powerful is the organization of these cells: immune cells are not simply present, they appear to be communicating, clustering and moving into tumor regions where anti-tumor responses can develop.

For us, this image tells the story of RACIN. The study was a genuine collaboration between Fernanda Herrera's expertise in radiation oncology and Denarda Dangaj Laniti's work in tumor immunology and the tumor microenvironment. Together with our clinical, pathology, computational and laboratory teams, we used paired patient biopsies and deep multi-omics to ask whether low-dose radiotherapy could help convert immune-excluded tumors into lesions more receptive to immunotherapy. This image reminds us why translational research matters: it connects patient care, mechanism and discovery in a single biopsy.



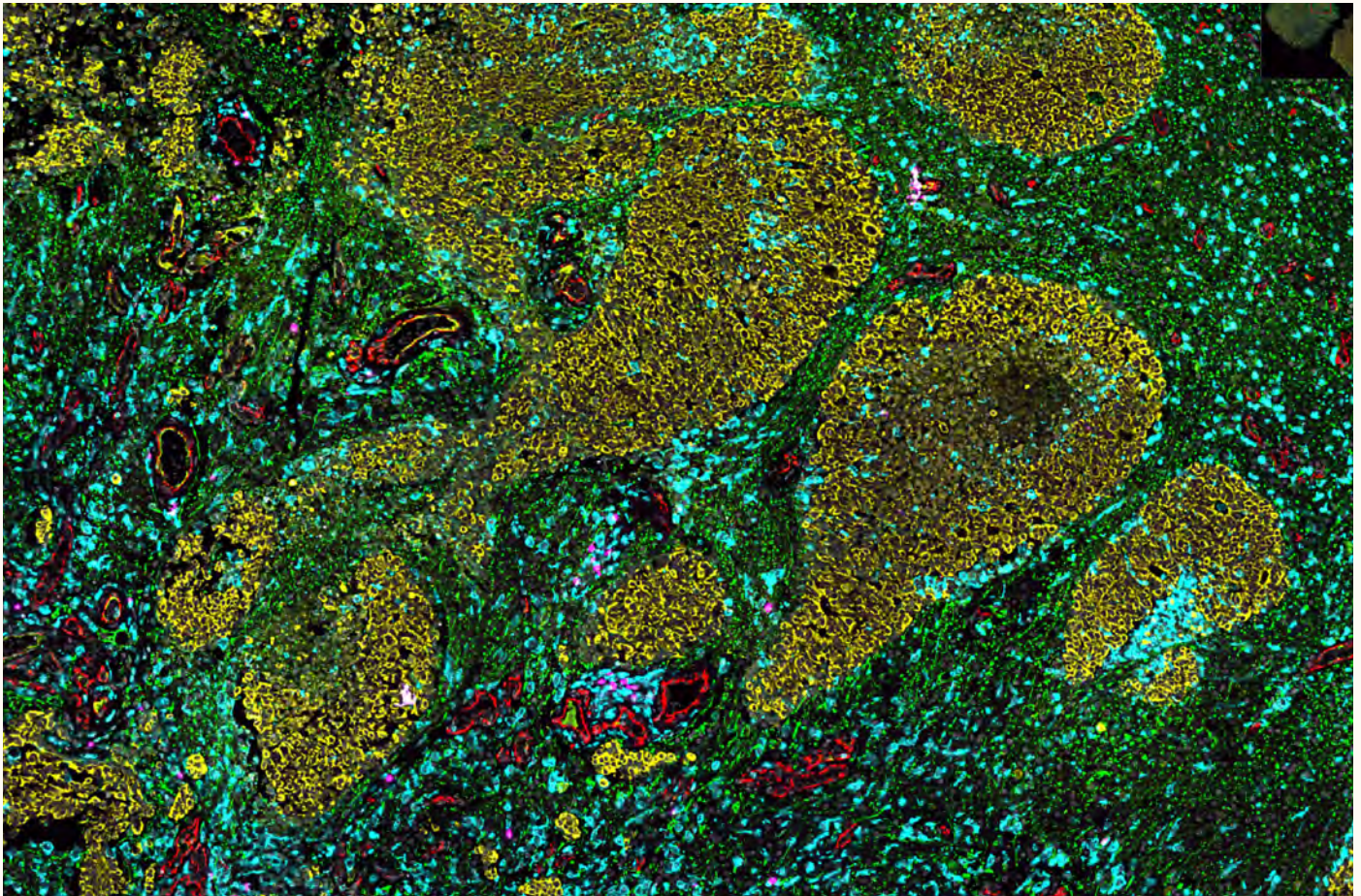
Dangaj Laniti lab



Denarda Dangaj Laniti



Fernanda Herrera



Jun Nishida

This image was shared by Ludwig Harvard's Kornelia Polyak and Jun Nishida

Our research aims to identify therapeutic targets of breast cancer brain metastases, with a special focus on the spatial heterogeneity of breast cancer brain metastasis and the interactions between the cancer cells and the brain microenvironment. This is a CODEX image of a breast cancer brain metastasis derived from an autopsy. The image shows a mass of invasive cancer cells (panCK+, yellow) surrounded by astrocytes (GFAP+, green) and myeloid cells (Iba1+, cyan). In these regions, very little T cell (CD3+, magenta) infiltration was observed. When seeing these images for the first time, we were amazed by the complexity and heterogeneity of the metastatic brain tumor microenvironment. The manuscript related to this image is currently under revision.



Kornelia Polyak



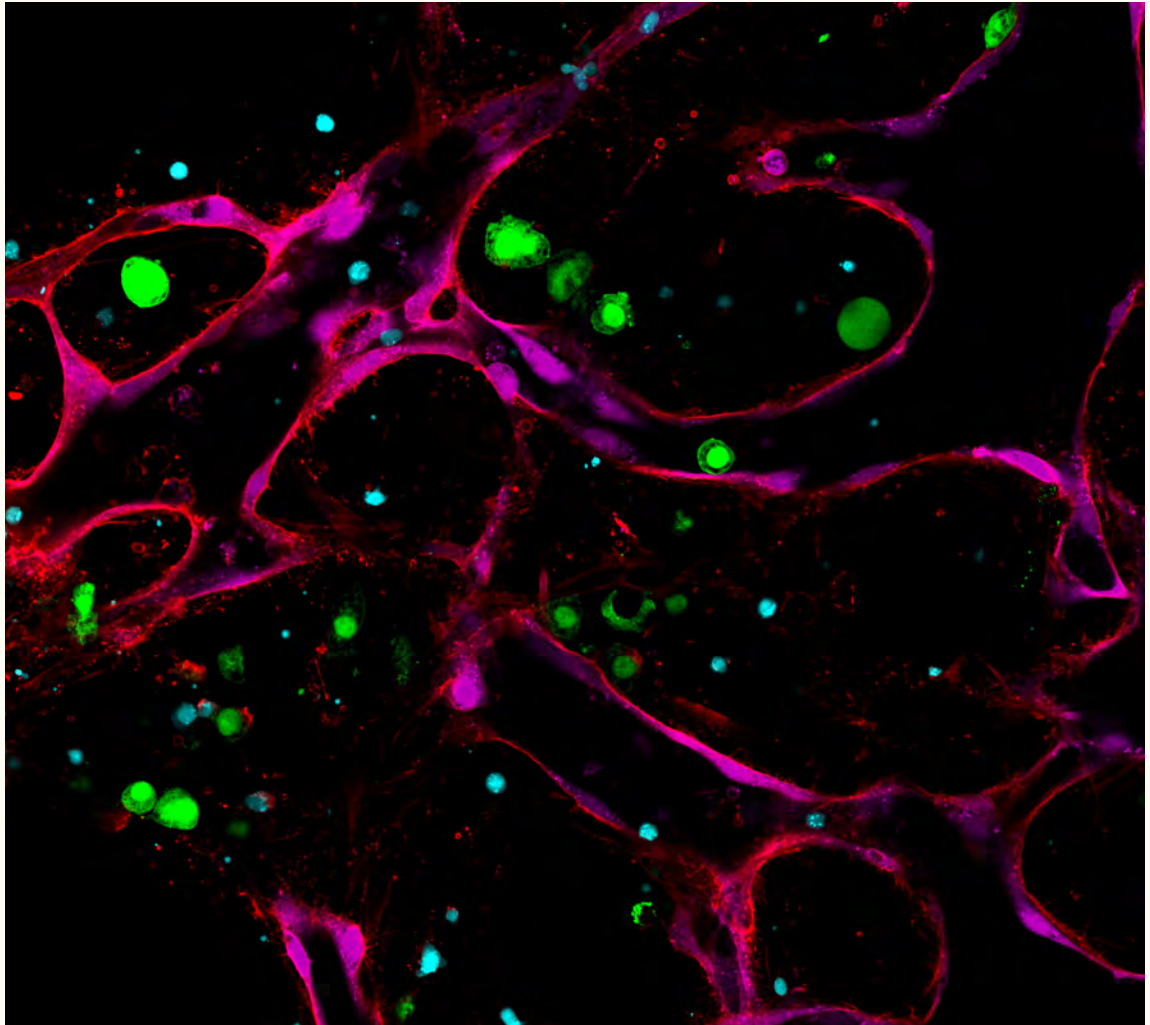
Jun Nishida



Leon Potgeter



Caroline Arber

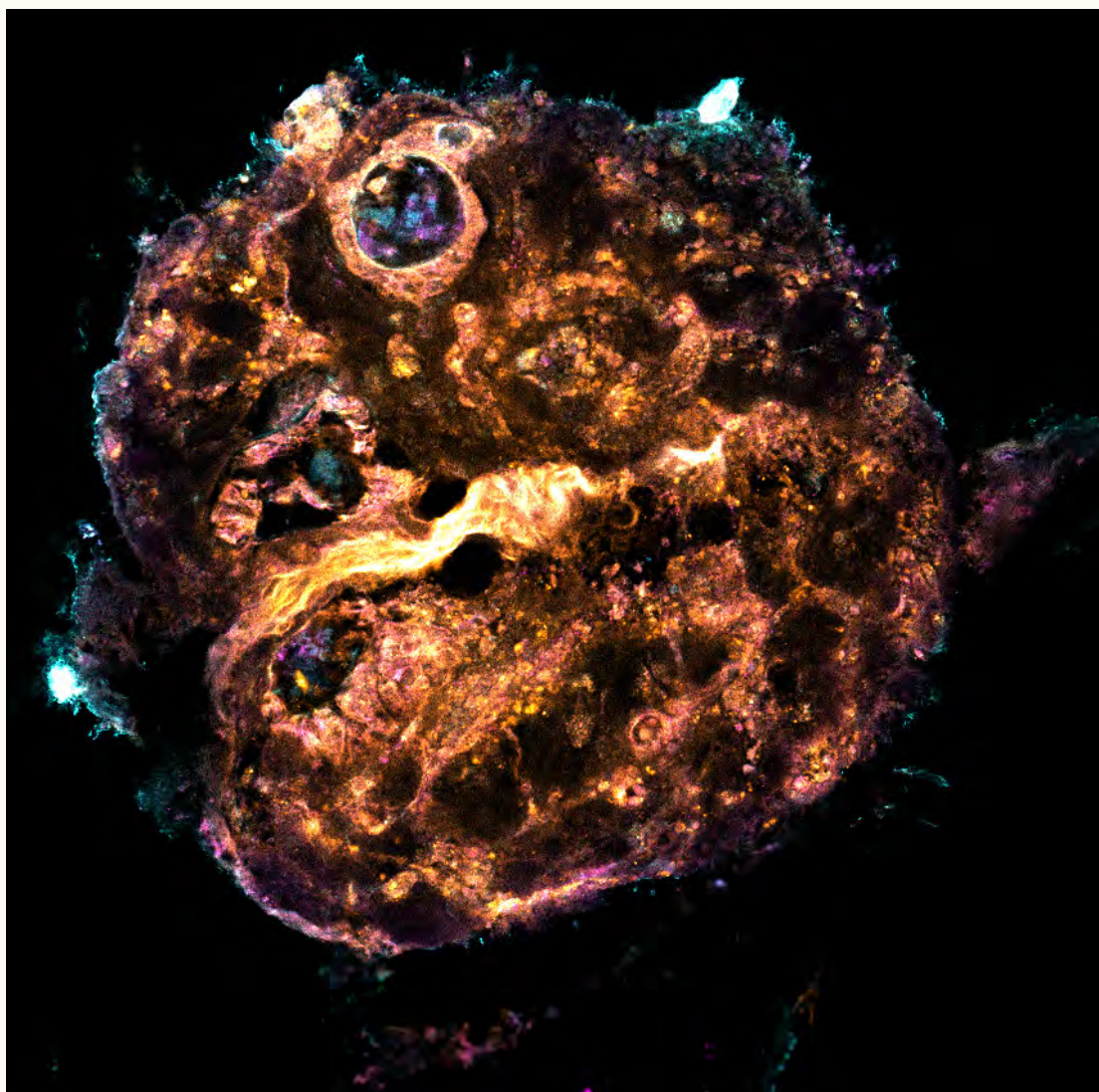


Leon Potgeter, Caroline Arber, Felix Bayerl

This image was shared by Ludwig Lausanne's Leon Potgeter and Caroline Arber

Multiple Myeloma (MM) is the second most common blood cancer. Chimeric antigen receptor (CAR)-T cell therapy has emerged as a potent treatment option for this type of cancer. However, the majority of CAR-T cell recipients eventually relapse. A major determinant of CAR-T cell efficacy is the immunosuppressive MM tumor microenvironment. This image shows a 3D *in vitro* MM-on-chip model that recapitulates hallmarks of the MM tumor microenvironment and is used here to investigate CAR-T cell responses against MM. MM cells (green), HUVECs—or human

endothelial cells isolated from umbilical cords (magenta)—and primary human bone marrow stromal cells (CD90 stain, red) are encapsulated in a fibrin hydrogel and self-assemble into a microvascularized network supported by pericytic bone marrow stromal cells. CAR-T cells (cyan) engage MM cells (lower-left quadrant) and can be seen trafficking through the system using the engineered microvasculature. We are hopeful that this platform will support the development of novel CAR-T cell therapies, specifically therapies aimed at modulating the interplay between CAR-T cells and the MM microenvironment.



Rhea Bhalla



Avery Buchanan

Rhea Bhalla and Avery Buchanan, Psaila lab, Khan lab

This image was shared by Ludwig Oxford's Rhea Bhalla and Avery Buchanan.

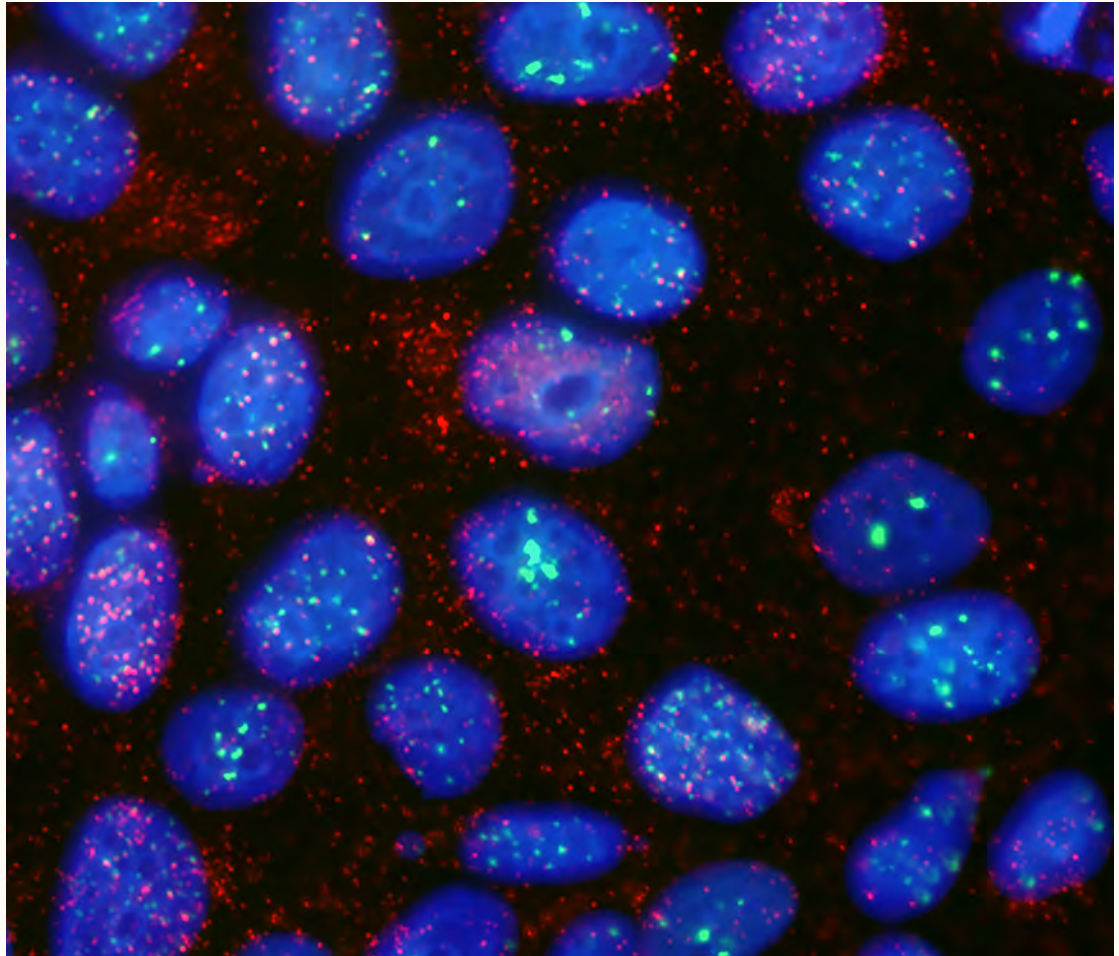
This image, which we find reminiscent of solar flares, captures a combined human bone and lympho-myeloid bone marrow organoid cultured in a rotationally and gravitationally driven, pump-free bio-compatible microfluidic device. The culture environment seeks to better replicate the bone marrow, supporting the development of a more representative *in vitro* tissue model. The fluidic forces and shear stress exerted on the organoid stimulate vascularization, with the aim of driving

enhanced functional maturation and tissue longevity. By prolonging survival *in vitro*, this system enables long-term experiments and provides an improved window for studying tissue recovery following drug therapy.

Fluorescent staining highlights key cellular components—with UAE1 in orange, CD34 in magenta and CD45 in cyan—revealing the spatial organization of stromal, progenitor and hematopoietic cells. The striking distribution of these markers highlights the complex architecture that emerges within the organoid under dynamic culture conditions.



Stephen Kron

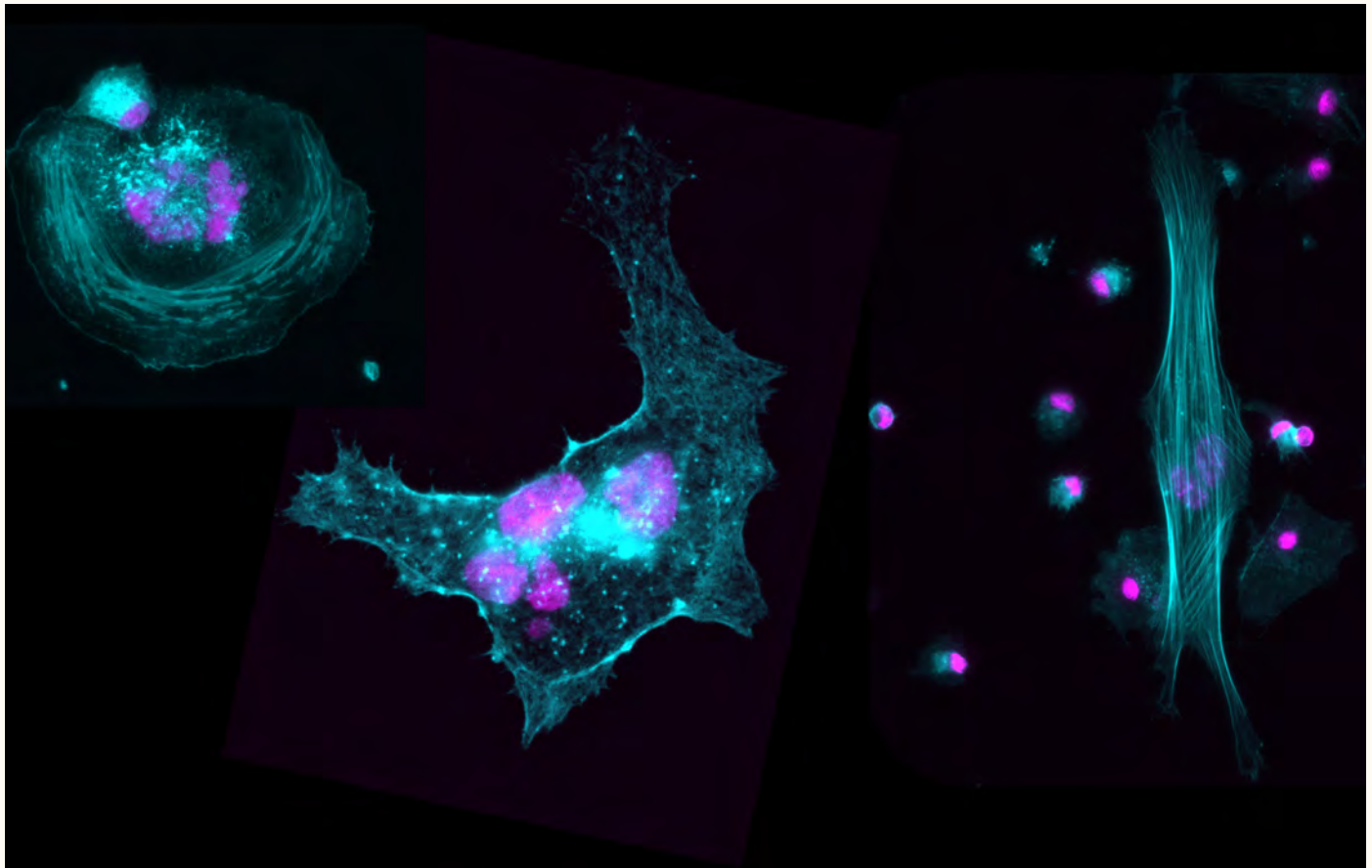


Stephen Kron

This image was shared by Ludwig Chicago's Stephen Kron.

This image shows MCF7 breast cancer cells 24 hours after irradiation in the presence of the PARP inhibitor veliparib. Nuclei are stained blue, 53BP1 DNA damage foci are green, and replication protein A (RPA) bound to resected single-stranded DNA is red. The most striking feature is the appearance of RPA-positive material outside the nucleus, representing complexes of RPA with resected single-stranded DNA that have accumulated in the cytosol. PARP inhibition is well known to delay repair of radiation-induced DNA double-strand breaks, but our results suggest that something more interesting is happening.

As previously reported, loss of PARP activity can promote excessive DNA end resection, or hyper-resection, producing persistent single-stranded DNA that may exceed the cell's capacity for productive homologous recombination. What surprised us was how much of this RPA-coated DNA appeared in the cytosol, where it can engage the cGAS/STING innate immune pathway. This provides a potential mechanistic link between radiosensitization and anti-tumor immunity. PARP inhibition may not simply make DNA breaks formed in irradiated tumor cells harder to repair; it may also help convert unrepaired DNA damage into an inflammatory signal that makes the treated tumor more visible to the immune system.



Natalie Jooss

This image was shared by Ludwig Oxford's Natalie Jooss.

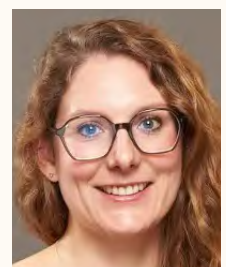
I am a postdoc in Beth Psaila's group at Ludwig Oxford, where I investigate blood cancers known as myeloproliferative neoplasms (MPNs). My research focuses on the role of the novel biomarker Galectin-1 and its underlying mechanisms in disease progression within the bone marrow niche as well as its effects on circulating platelets.

This image comes from our investigations into how changes in the bone marrow microenvironment affect megakaryocytes (Mks), the precursors of platelets.

Mks, generated here from induced pluripotent stem cells (iPSCs), are

remarkable cells. As they mature, they become much larger than most other cells and often develop polyploid nuclei, making them particularly impressive to observe under a microscope. Here, fluorescence microscopy reveals the cells' cytoskeleton in cyan and their nuclei in magenta. What struck me most was the diversity of the cells. Although they originated from the same iPSC line each developed its own distinctive shape.

That element of surprise is one of the things I find most exciting about science. Microscopy allows us to visualize a world that is normally completely hidden from us, and experiments intended to answer scientific questions can unexpectedly reveal just how intricate and beautiful biology can be.



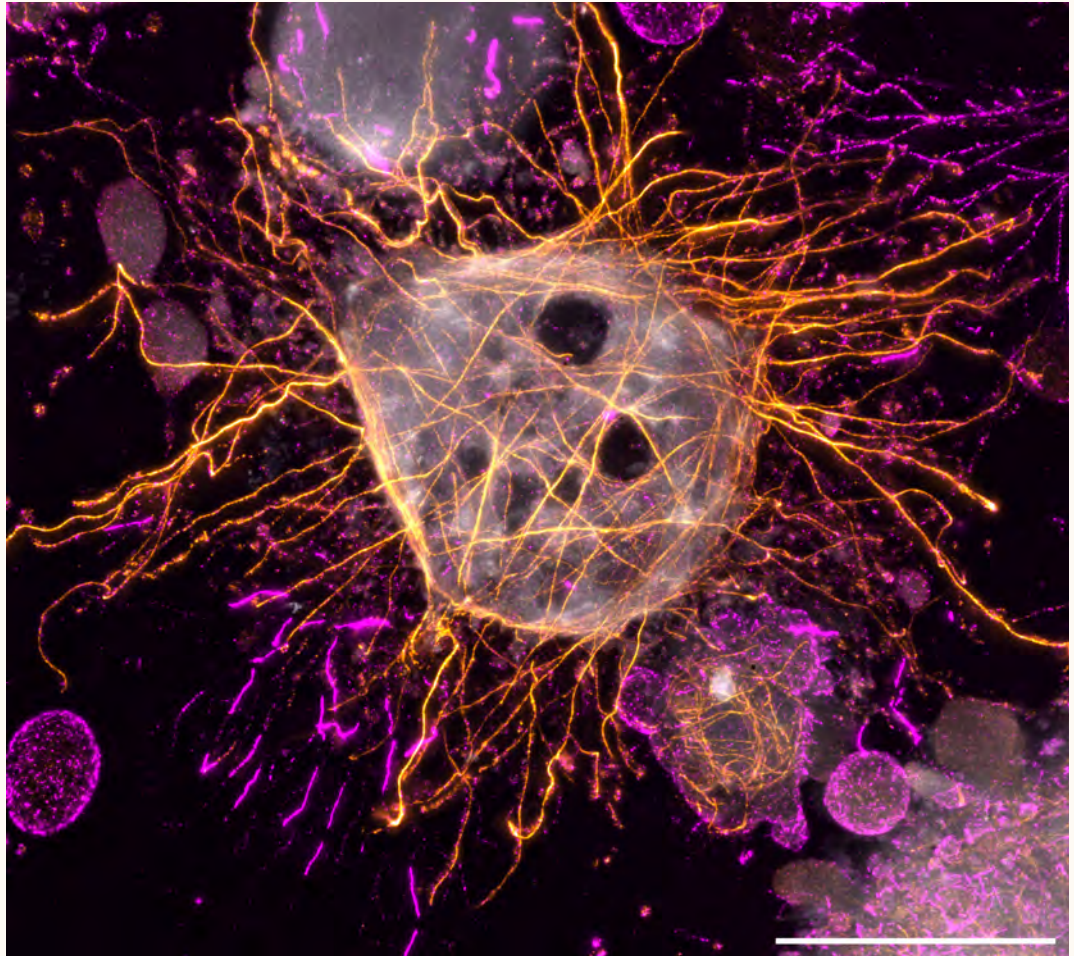
Natalie Jooss



Benita Wolf



Camilla Jandus



Benita Wolf, UNIL/CHUV (cells: Jandus lab)

This image was shared by Benita Wolf (Department of Oncology, UNIL/CHUV), in collaboration with Ludwig Lausanne's Camilla Jandus.

My group studies how cytotoxic T cells engage and kill tumor cells at the nanoscale. To do this, we adapted cryo-expansion microscopy (cryo-ExM) for T cell biology: cells are frozen at -180°C , embedded in a swellable hydrogel and physically enlarged, so that structures well below the diffraction limit become resolvable on a conventional confocal microscope. The technique is particularly suited to visualizing the immunological synapse.

Displayed here is a dying human melanoma cell (GEFI) after co-culture with cytotoxic CD4+ T cells, labeled for actin (magenta) and tubulin (orange), with an NHS-ester

counterstain of primary amines (gray). Scale bar: 10 μm (corrected for the expansion factor). The cells were provided by Camilla Jandus's lab; sample preparation, cryo-ExM and imaging were done in my lab.

As it happens, this image never made it into our study, because there is no bona fide immunological synapse in it, which is what we were looking for. But we keep coming back to it. What surprises us is the microtubule cytoskeleton in this dying cell: the way the microtubules still organize around the nucleus at a point when the plasma membrane has already lost its integrity. Cell death is usually described as a collapse, and here something is very clearly still organized. Whether that organization means anything, or whether it is simply what a cytoskeleton looks like on the way down, is a question we can't answer from a single image.



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