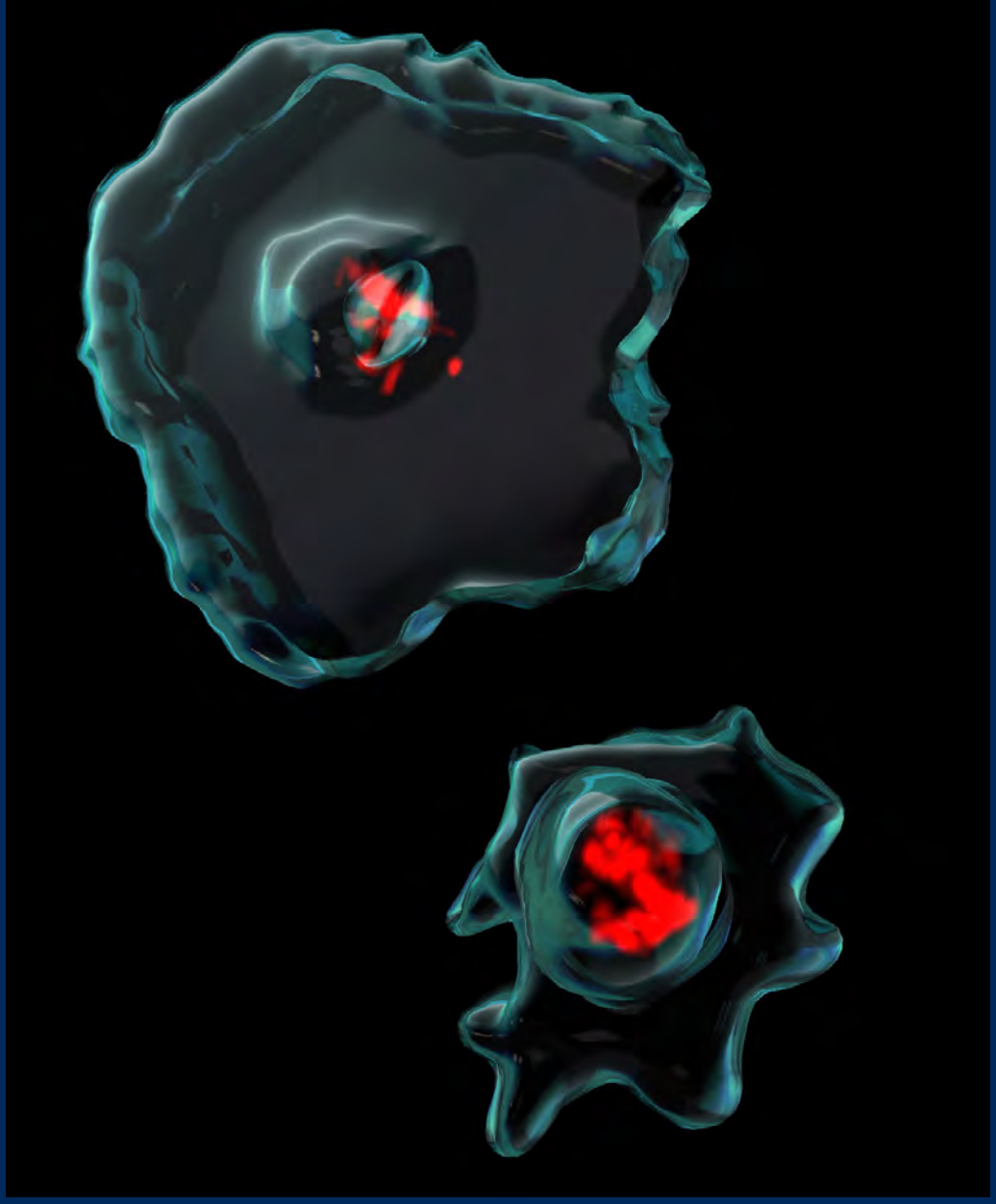

November 2025

Ludwig Link

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

Welcome

Unmesh Kher
Editorial Director

Somebody must have spiked the water at Ludwig labs. With what, we don't know. But whatever it is, Link staff would love to get their ink-stained hands on some.

Evidence? Exhibit #1 would be the gobsmacking deluge of arresting, transformative, surprising—and often medically promising—discovery that has poured out of Ludwig's Branches and Centers over the past few months. Even by Ludwig's extraordinary standards, it's been nothing short of astonishing.

Read on and you will see what I mean. You'll learn of a previously unrecognized physiological function of platelets (see cover), one that may be readily harnessed to improve prenatal screening and liquid biopsies for cancer. You'll discover how distinct immunologic subtypes of ovarian cancer are linked to DNA repair deficiency, how each distinctly evolves upon disease recurrence to resist therapy and potential interventions by which the resistance might be undone. Other research briefs relay findings from a pair of preclinical studies examining how diet and the microbiome affect responses to cancer therapy and illuminate the ways in which immature neutrophils suppress anti-tumor immune responses and immunotherapy in both primary tumors and bone metastases. And that's just a random sampling of the scientific delights in the pages that follow.

Aside from that, we have the usual *(usual!)* news of Ludwig researchers winning prestigious awards, a small feature introducing a new member of our community—the chemist and Nobel laureate David MacMillan, who joined Ludwig Princeton in June as a distinguished scholar—and frontline reporting from Endicott House in Massachusetts, where your intrepid reporters infiltrated Ludwig MIT's annual retreat and even returned home with pictures. Finally, we asked early career researchers from Ludwig Chicago, MSK and MIT to tell us a little about themselves and their work. We're sure you'll enjoy those interviews as much as we did.

Happy reading!

With warmest regards,

Unmesh Kher
Editorial Director

On the cover

These 3D renders of micrographs reveal the presence of DNA (red) inside human platelets (turquoise surface mask). Ludwig Oxford's Bethan Psaila, Lauren Murphy and colleagues showed that platelets mop up cell-free (cf) DNA from blood plasma—likely helping to prevent systemic inflammation—and release that DNA when they're activated. This suggests they deploy their cargo in a manner that prevents nonspecific inflammation yet elicits targeted inflammatory responses where they're needed. The researchers also found that platelets can carry a significant amount of rare cfDNA derived from tumor cells. They demonstrated that platelet DNA can be used in liquid biopsies to detect not only established cancers but also precancerous lesions in the colon.

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Image by Lauren Murphy

In this issue

Ludwig Lausanne's George Coukos named Fellow of the Academy of Immuno-Oncology

Our congratulations to Ludwig Lausanne Director George Coukos, who in August was named Fellow of the Academy of Immuno-Oncology of the Society for Immunotherapy of Cancer (SITC). The Academy of Immuno-Oncology was established to honor individuals who have helped build the field of cancer immunotherapy into what the SITC says is "the breakthrough cancer treatment it is today, bringing together the brightest minds in the field to inspire the next generation of immuno-oncologists." On its website, the Society lauds George for his discovery of spontaneous anti-tumor immunity in ovarian cancer, which it notes helped overturn the longstanding dogma that solid tumors are generally immunologically unresponsive. This work, it adds, "catalyzed global research into T cell responses in cancer." SITC also cites George's many other contributions to tumor immunology and immuno-oncology in the years since, including his exhaustive characterization of the ovarian tumor microenvironment (TME) and its various mechanisms of immune suppression. These include his discovery of the vascular endothelial barrier and elucidation of how that vasculature limits T cell infiltration. It notes that his lab has also described TME characteristics that support anti-tumor immunity and chemokines essential to T cell trafficking. These and other discoveries, it says, "have informed new therapeutic strategies now undergoing clinical testing" for the treatment of cancer.

G.Weber / CHUV

George Coukos

Ludwig Princeton's Vanha Nhat Pham named 2025 Ludwig Cancer Research-Jane Coffin Childs Fellow

Ludwig Princeton's Vanha Nhat Pham, a postdoctoral researcher in the laboratory of Branch Director Joshua Rabinowitz, was named the inaugural Ludwig Cancer Research-Jane Coffin Childs Fellow in July. Over the course of the three-year fellowship, Vanha will explore the roles molecular components of cell membranes known as phospholipids play in cellular physiology. With a few notable exceptions, phospholipids have traditionally been seen as interchangeable in their biological function—mainly the modulation of membrane structure and fluidity. There are, however, several hundred chemically distinct varieties of phospholipids in cells, inviting the question of what necessitates such diversity. There is some evidence that they might have more complex roles in cell biology than is generally presumed. For example, specific changes in the phospholipid profile of cell membranes accompany several diseases, including neurodegenerative disorders and cancer. Further, Vanha's own preliminary studies have uncovered variations in the distribution of different species of phospholipids across distinct regions of the brain. Vanha hypothesizes that, based on their chemical characteristics and locations within cells and tissues, phospholipids are likely to have varied roles in molecular communication that affect the fate and function of cells. She has proposed a series of studies employing cutting-edge technologies for large-scale molecular analysis—including many pioneered by Ludwig Princeton—to examine that idea.

Vanha Nhat Pham

Yang Shi

Ludwig Oxford's Yang Shi awarded 2025 Léopold Griffuel Prize for Fundamental Research

Our congratulations to Ludwig Oxford Member Yang Shi, who was recognized by the ARC Foundation for Cancer Research with the 2025 Léopold Griffuel Prize for Fundamental Research for his contributions to the field of cancer epigenetics. Established in 1970 by the Association pour la Recherche sur le Cancer (ARC), now known as the Fondation ARC pour la Recherche sur le Cancer, the Léopold Griffuel Prize is among the most prestigious international awards honoring discoveries that have significantly advanced our understanding of cancer biology and treatment. This year, the award for Fundamental Research was shared by two laureates: Yang and Giacomo Cavalli of the Institute of Human Genetics, Montpellier, for their work in epigenetics. Yang is renowned for his discovery of LSD1, the first identified histone demethylase, and many additional demethylases in subsequent work. These discoveries fundamentally changed our understanding of gene regulation, demonstrating that histone methylation—a critical epigenetic process once thought to be irreversible—is in fact dynamic and reversible. His subsequent work has provided important insights into the mechanism of action of demethylases and their roles in physiological and pathological processes, including cancer. It also opened new approaches to cancer therapy, revealing how chromatin-modifying enzymes might be harnessed to improve immune responses to tumors.

Crystal Mackall

Ludwig Stanford's Crystal Mackall honored for her contributions to cancer immunotherapy

Ludwig Stanford's Crystal Mackall was awarded the 2025 AACR-Cancer Research Institute Lloyd J. Old Award in Cancer Immunology and delivered an award lecture during the AACR annual meeting in Chicago in late April. The AACR honored Crystal for her many contributions to cancer immunotherapy, including enhancing CAR-T cell therapies, identifying mechanisms of resistance, developing treatment algorithms for cancer immunotherapy and leading pioneering clinical trials that have opened up opportunities to apply this powerful therapy to a wider range of cancers. The AACR made special mention of her "seminal discovery of the role of IL-7 in T-cell homeostasis and her unwavering dedication to translational research, leading to the establishment of novel immunotherapeutic strategies for pediatric cancer patients." Crystal's early work on T cell homeostasis, the AACR observed, established the scientific foundations for lymphodepletion as a key step in adoptive cell therapies. It also noted her pioneering contributions to the clinical development of CAR-T therapy, especially trials demonstrating the extraordinarily effective use of CD19-targeted CAR-T cells in pediatric patients with B cell acute lymphoblastic leukemia. The AACR also highlighted her work on extending the durability and applicability of CAR-T cell therapies—some of which Crystal presented in her award lecture—as being of singular importance to the field.

Ludwig Scientific Advisor Karen Vousden recognized for her contributions to basic cancer research

Ludwig Scientific Advisor Karen Vousden received the AACR-G.H.A. Clowes Award for Outstanding Basic Cancer Research and gave an award lecture at the 2025 AACR Annual meeting in late April. Karen was honored for her investigations of the biology of tumor suppressors and contributions to cancer metabolism. Karen's "research elucidated the regulation of p53 by MDM2, defined key metabolic dependencies in cancer cells, and revealed the impact of dietary interventions on tumor progression," the AACR noted in issuing the award. "Her insights into reactive oxygen species in tumor development and metastasis have informed therapeutic strategies." Karen is well known for her contributions to our understanding of how the tumor suppressor p53 is regulated in health and disease, and its role in cell metabolism. Her early work established that MDM2 is a ubiquitin ligase that tags p53 for degradation and described how the protein is inhibited to permit p53-mediated responses to cellular stress. Those studies laid the foundations for the development of cancer therapies targeting MDM2. Karen is also renowned for her characterization of HPV's role in cervical cancer and elucidation of how the oncoproteins it encodes drive carcinogenesis. In her award lecture, Karen discussed her lab's ongoing studies on the complex role of reactive oxygen species in cancer progression and metastasis.

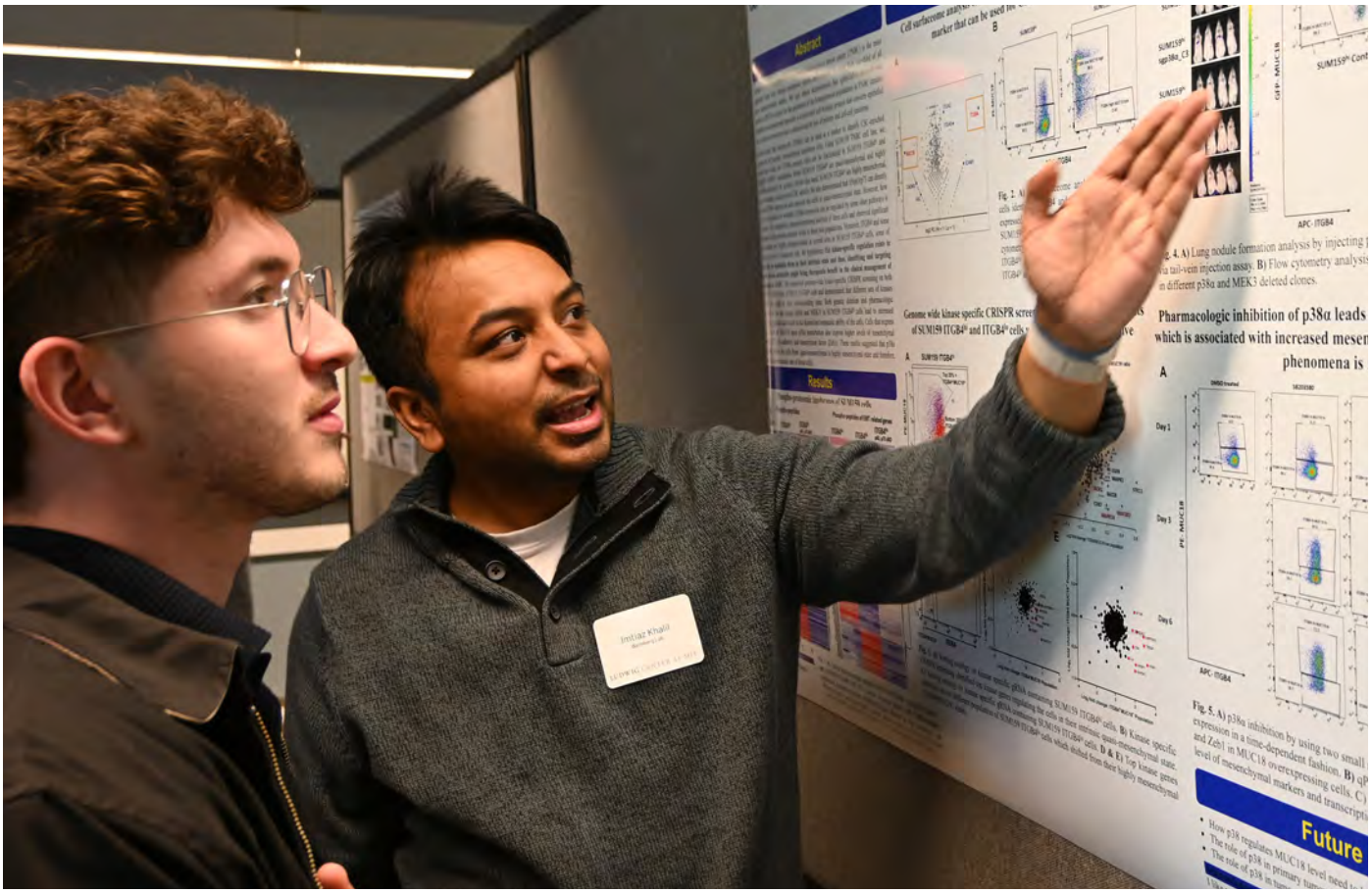
Karen Vousden

Ludwig Princeton's Michael Skinnider named a Searle Scholar

Our congratulations to Ludwig Princeton's Michael Skinnider, who in April became one of 15 exceptional early-career scientists to be named Searle Scholars of the Class of 2025. The Searle Scholars Program emphasizes support for notable young faculty in the biomedical sciences and chemistry who have recently been appointed as assistant professors on a tenure-track appointment and intend to pursue a career in academic research. Each Searle Scholar receives $300,000 in flexible funding over three years to support their research. This year, the Program—which favors high-risk, high-reward research across multiple scientific disciplines—considered applications from 194 nominees put forward by 145 universities and research institutions. Michael, whose proposal was titled, "Charting the unknown human metabolome with biochemical artificial intelligence," will apply his award to identify the many unidentified small molecule metabolites within the human body. Illuminating this so-called "dark matter" of the metabolome will clear a path to establishing the physiological origins, fates and roles of its constituent molecules and likely contribute to improving the diagnosis, prevention and treatment of cancer and many other diseases.

Michael Skinnider

Ludwig MIT's May retreat was one to remember



Photos by Unmesh Kher

Md Imtiaz Khalil, a postdoc in Robert Weinberg's lab, discussed his work exploring how kinase-mediated signaling regulates phenotypic plasticity in triple-negative breast cancer.

The 2025 Annual Retreat of the Ludwig Center at MIT, led by Ludwig MIT Co-directors Robert Weinberg and Tyler Jacks, was held in May on the gorgeous grounds of MIT's Endicott House. Ten Ludwig MIT trainees delivered 20-minute presentations on their research, with each talk followed by lively Q&As; another two dozen shared their work at a poster session following a sumptuous lunch and an opportunity, seized by many, to tour the surrounding woods and gardens. Graduate students won this year's cherished "Ludwig Buck", awarded by the directors and issued every year to the demographic—faculty, technicians, postdocs or graduate students—that asks the most questions.

The day ended with Bob Weinberg's closing remarks, which were, as always, memorable, though also bittersweet, as they were the last he will deliver at a Ludwig MIT retreat. After more than five decades as a renowned professor and scientist at MIT and nearly two as Director of the MIT Center, he will be closing his lab this year and shifting to emeritus status, one in which he will fortunately continue teaching. Needless to say, he will be very much missed, not only by the Ludwig community but across the world of cancer research, in which he remains a living legend.

Graduate students of Ludwig MIT show off the cherished Ludwig Buck (center), awarded to the group that asked the most questions at the retreat.

Robert Weinberg

Tyler Jacks

Jacob Kassama, a graduate student in the Tyler Jacks lab at Ludwig MIT, presented his studies probing how CD4+ T cell and cancer cell interactions in early tumorigenesis influence tumor progression.

Metabolic effects of mitochondrial defects in lung cancer

Eileen White

Respiration defects limit serine synthesis required for lung cancer growth and survival | *Nature Communications*, 2025 August 15

Mutations to mitochondrial (mt) DNA occur with variable frequency in cancer but their effects are not clearly understood. Researchers co-led by Ludwig Princeton's Eileen White reported in an August issue of *Nature Communications* their examination of the matter in mouse models of non-small cell lung cancer (NSCLC). The researchers introduced a proofreading mutant of DNA polymerase gamma (PolG^{D256A}) into the KP model of NSCLC, which closely mimics the human version of the cancer, to generate PGKP mice. Eileen and her colleagues found that mutations to mtDNA in PGKP mouse tumors caused an accumulation of defective mitochondria in NSCLC cells, reduced the proliferation and viability of those cells and were associated with better survival of the mice. Mitochondrial dysfunction, they found, causes defective respiration in NSCLC cells, making their metabolism highly dependent on glucose. Those defects also cause an accumulation of the coenzyme NADH in the cells, which compromises the biosynthesis of the amino acid serine, the antioxidant glutathione and nucleotides. Dietary serine/glycine depletion further suppressed tumor growth in mice and that suppression could be reversed in cell culture with glutathione supplementation. The findings show that mitochondrial health is essential to maintaining adequate serine synthesis, which in turn supports the anabolic metabolism and redox homeostasis required for NSCLC tumor growth.

People on the move

Renowned chemist David MacMillan has joined Ludwig Princeton

David MacMillan

We extend a warm welcome to David MacMillan, who joined our community in May as a distinguished scholar at Ludwig Princeton. David, who shared the 2021 Nobel Prize in Chemistry with Benjamin List for their independent development of an entirely novel type of chemical catalysis, is the James S. McDonnell Distinguished University Professor of Chemistry at Princeton University and founding director of the Princeton Catalysis Initiative. Catalysts had long been thought to fall into one of only two categories: metals and biological enzymes. In 2000, David upended that assumption with the development of asymmetric organocatalysis, in which catalysts are constructed from small organic molecules to which other environmentally benign elements—like oxygen, phosphorus and nitrogen—can be attached for distinct mechanistic purposes. Chemical reactions can generate products that are identical in every way except that they're mirror images of each other, with each having distinct chemical properties. David's catalysts could be fashioned to drive asymmetric chemical reactions that generate primarily one of those mirror images. The low cost and ease with which they can be designed to sequentially generate complex, symmetrically biased molecules has made them especially valuable to pharmaceutical manufacturers, as chirality is a key determinant of the biological activity of drug molecules. David is the third prominent scientist to be appointed by the Ludwig Institute's Board of Directors as a distinguished scholar.

A discovery of NO links to oxygen sensing

Researchers led by Ludwig Oxford's Thomas Keeley and Peter Ratcliffe reported in an August study in *PNAS* a previously unrecognized role of nitric oxide (NO) in cellular responses to oxygen sensing—one that involves the cysteine N-degron pathway for targeted protein degradation. This pathway helps mediate functional adaptations of cells to changing oxygen levels in the environment. It has also been shown to be a sensor of nitric oxide, though the mechanism by which that sensing occurs has been unclear. Its key component is 2-aminoethanethiol dioxygenase (ADO). The enzyme tags its target proteins—which include regulators of G-protein signaling—with oxygen, marking them for destruction. ADO activity rises when oxygen is abundant, permitting G-protein signaling, which modulates multiple cellular functions. It declines in hypoxic conditions, when a general slowdown in cellular processes is in order. Thomas, Peter and colleagues showed that NO regulates the stability of N-degron pathway substrates indirectly by regulating the availability of oxygen. It does this through the oxygen-dependent competitive inhibition of the core mitochondrial respiratory enzyme cytochrome C oxidase. This temporarily reduces mitochondrial oxygen consumption, increasing the oxygen available to ADO and allowing cells to fine-tune ADO-mediated protein degradation in hypoxic conditions. The researchers suggest that the mechanism helps link oxygen supply and mitochondrial respiration—and thus metabolism—to cellular responses to G-protein-coupled receptor activation.

Nitric oxide promotes cysteine N-degron proteolysis through control of oxygen availability
PNAS, 2025 August 19

Thomas Keeley

Peter Ratcliffe

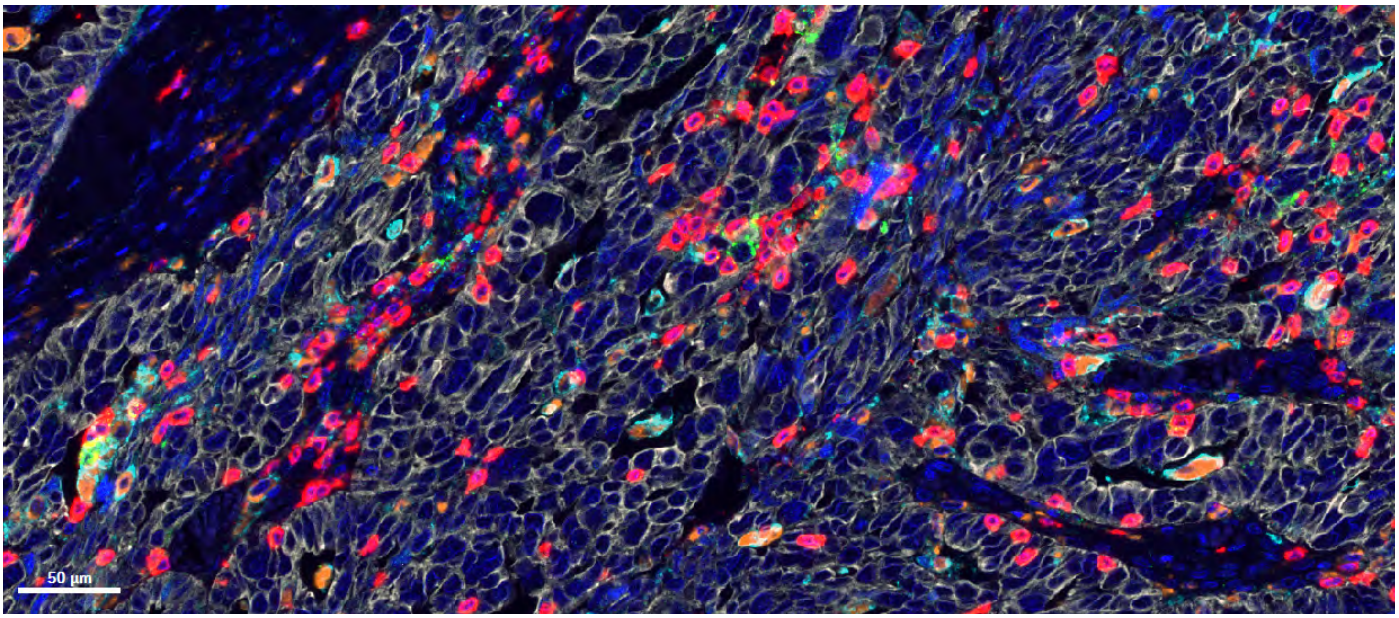
Ilja Shapiro

Michal Bassani-Sternberg

A better tool to explore the immunopeptidome

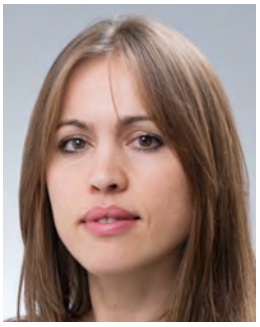
Only about 1% of somatic mutations seen in the genome sequences of cancer cells actually elicit anti-tumor T cell responses, as not all mutant proteins are processed and presented to the immune system by HLA molecules on the cellular surface. Mass spectrometry-based immunopeptidomics, which identifies cancer antigens isolated from tumor tissues that are actually presented to T cells, is thus a valuable tool for the identification of antigens for use in personalized immunotherapies. But methods employed in the clinic often entail a trade-off between capturing the global immunopeptidome—which can divulge valuable information about antigen presentation defects and help train machine learning models—and sensitivity for selected antigen targets. Researchers led by Ludwig Lausanne's Ilja Shapiro and Michal Bassani-Sternberg reported in an August publication in *Nature Communications* a new immunopeptidomics mass spectrometry acquisition method, NeoDiscMS, that overcomes this limitation. They showed using tumor cell lines and scarce patient samples that NeoDiscMS can enhance the speed and sensitivity of detecting antigenic targets without sacrificing information on the global diversity of the immunopeptidome. NeoDiscMS enhances the identification of peptides derived from tumor-associated antigens by up to 20% and improves confidence in detected neoantigens compared to the gold standard methods for such purposes. The NeoDiscMS module is included within NeoDisc—a start-to-finish computational pipeline for cancer vaccine design.

Sensitive neoantigen discovery by real-time mutanome-guided immunopeptidomics | *Nature Communications*, 2025 August 7



Eleonora Ghisoni

Purely inflamed ovarian cancer tissue visualized by multiplex immunofluorescence, with CD8+ T cells stained red; CD68 macrophages, orange; CD11c dendritic cell, cyan; CXCL9, expressed by macrophages, green; and cytokeratin, for tumor cell definition, pink. Purely inflamed tumors are enriched in T cell-dendritic cell and T cell-dendritic cell-macrophage niches, which they retain upon recurrence.



Denarda Dangaj Laniti

Eleonora Ghisoni

How recurrent ovarian cancers resist therapy

Researchers led by Ludwig Lausanne's Denarda Dangaj Laniti and Eleonora Ghisoni described in an August issue of *Cancer Cell* four immunologic subtypes of recurrent ovarian cancers, the relationship of each to DNA repair deficiency in the tumor and how each subtype evolves to resist therapy. The researchers found that tumors with DNA repair deficiencies, such as BRCA mutations, tend to be infiltrated with CD8+ T cells and respond better to chemotherapy. Networks of dendritic cells and T cells in these tumors, which support responses to immunotherapy, persist when the tumors recur. Such tumors resist chemotherapy and Olaparib, a standard therapy for BRCA-deficient ovarian cancer, by a mechanism involving COX/PGE2 signaling. Adding a COX inhibitor to standard therapy in these mice restored sensitivity to chemotherapy, extending survival significantly. That survival time doubled when immunotherapy was added to the regimen. DNA repair-proficient tumors, meanwhile, tend to be devoid of myeloid-T cell networks and recruit immunosuppressive macrophages to help them resist therapy. Denarda, Eleonora and colleagues show these macrophages express high levels of ApoE and Trem2, proteins involved in lipid metabolism. Targeting myeloid cells in such tumors with an antibody inhibitor of Trem2 improved responses to chemotherapy and delayed tumor recurrence in mouse models. The classification system developed in this study could also serve as a combined immunologic and genomic biomarker to guide ovarian cancer therapy.

Myeloid cell networks govern re-establishment of original immune landscapes in recurrent ovarian cancer
Cancer Cell, 2025 August 11

Boning up on neutrophils in cancer

Neutrophils are the body's frontline defense against pathogens. They are the most abundant type of immune cell in the human body, particularly in the bloodstream, where they make up about 50–70% of all circulating white blood cells. Like other innate immune cells, such as macrophages, they also play various roles in cancer, depending on their functional states. Their abundance in tumors has long been associated with poor patient prognosis. On the other hand, the cells can be key supporters of anti-tumor immunity. In a pair of studies published this summer, researchers co-led by Ludwig Weill Cornell Medicine's Taha Merghoub and Tao Shi with colleagues at Nanjing University in China detailed two distinct ways in which immature neutrophils suppress anti-tumor immune responses and immunotherapy in both primary tumors and metastatic bone lesions.

Taha Merghoub

Tao Shi

Tao, Taha and colleagues reported in an August publication in *Cancer Cell* that neutrophils in bone metastases, which are notoriously resistant to therapy, are reprogrammed into an immature state in which they suppress anti-tumor immunity. This is accomplished by a protein churned out by bone metastases, DKK1, that prompts functionally immature neutrophils to produce CHI3L3, which disrupts the activation and function of the CD8+ T effector cells. The elevated levels of DKK1 seen in mouse models were consistent with analyses of patient data and in serum samples obtained from gastric cancer patients with bone metastases. The researchers identified the biochemical signaling cascade activated by DKK1 that reprograms neutrophils. They also showed that DKK1 blockade—for which an antibody is currently in early clinical trials—restores the sensitivity of bone metastases to immunotherapy in mouse models, suggesting a combination with immune based therapies. Beyond that, CHI3L3 and the signature of gene expression it triggers could serve as biomarkers to identify patients with high neutrophil-mediated immune suppression and better tailor treatments to their tumors.

In the other study, reported in a July issue of *Cell Research,* Tao, Taha and colleagues identified separate precursors of neutrophils—specifically, myelocyte and metamyelocyte (MC & MM) stages of the developing immune cells—in human bone marrow that suppress anti-tumor immunity and drive cancer progression. These immature cells constitute the majority of neutrophils that infiltrate tumors across 17 types of cancer. The researchers showed that in mice with human immune systems, MC & MM are the majority of neutrophils in tumors. They also identified biomarkers to detect these cells in cancer patients and showed that their expression is associated with worse prognoses. The researchers preclinically demonstrated a strategy to trans-differentiate MC & MM-stage neutrophils into monocytic cells as a potential cancer therapy.

CHI3L3+ immature neutrophils inhibit anti-tumor immunity and impede immune checkpoint blockade therapy in bone metastases | *Cancer Cell*, 2025 August 7

Human myelocyte and metamyelocyte-stage neutrophils suppress tumor immunity and promote cancer progression | *Cell Research*, 2025 July 15

A malignant chain of metabolic chatter programs immunosuppression

Cancer-associated fibroblasts (CAFs) support cancer cell metabolism and have been shown to secrete multiple immune factors that can alter the function of immune cells like tumor-associated macrophages (TAMs) to enable tumor growth and survival. Researchers led by Ping-Chih Ho, Xiaoyun Li and Sofie Hedlund Møller of Ludwig Lausanne reported in a July issue of the *Journal of Experimental Medicine* that palmitic acid, a type of fat secreted by cancer cells, prompts fibroblasts in tumors to ramp up production of the amino acid glutamine. The amino acid switches tumor-associated macrophages (TAMs) into a functional state in which they promote cancer cell proliferation and suppress anti-tumor immune responses. The researchers found that palmitic acid provokes an inflammatory response when it binds its receptor on cancer-associated fibroblasts (CAFs), driving their expression of interleukin-6, which in turn induces heightened expression of glutamine synthetase (GS), an enzyme essential to glutamine production. The researchers showed that knocking out the GS gene in fibroblasts reprograms TAMs and restores anti-tumor immunity, impairing tumor growth in mouse models of melanoma. These findings support the targeting of GS in CAFs as a potential immunotherapy and nominate specific gene expression signatures in the cells as biomarkers for resistance to immunotherapy.

Tumor-instructed glutamine synthesis in cancer-associated fibroblasts promotes pro-tumor macrophages | *Journal of Experimental Medicine*, 2025 July 16

Ping-Chih Ho

Xiaoyun Li

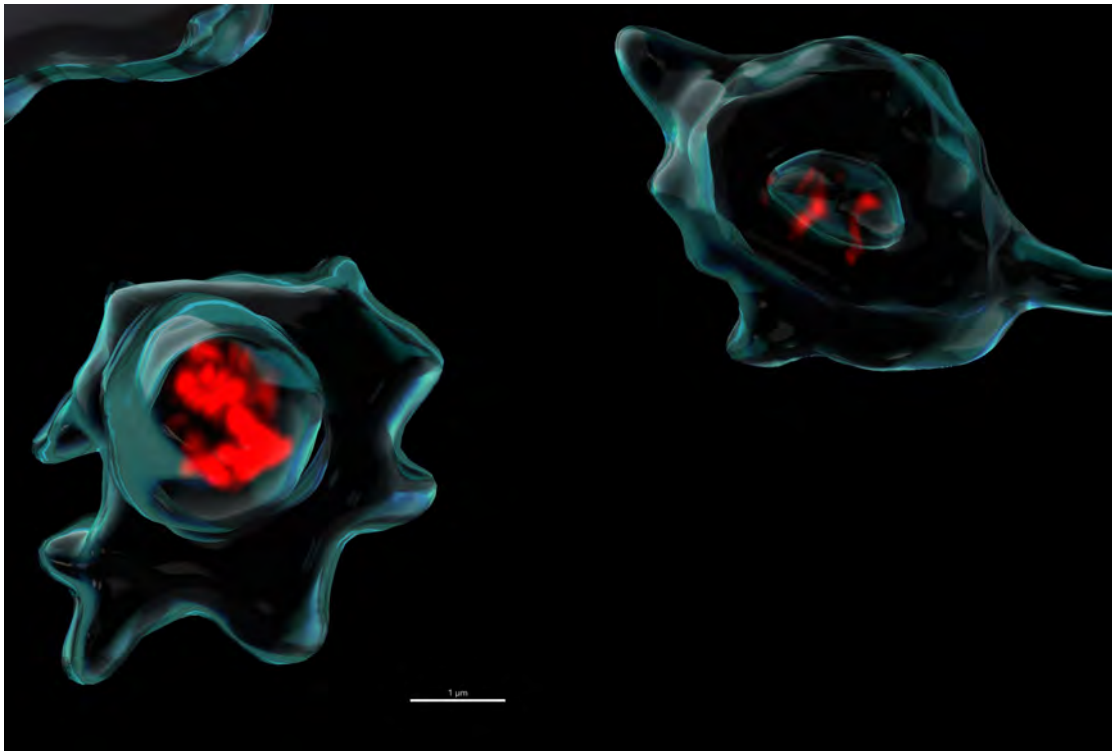
Sofie Hedlund Møller

Chuan He

Liquid biopsy of microbial RNA accurately detects colon cancer

Researchers co-led by Ludwig Chicago's Chuan He reported in a July *Nature Biotechnology* paper a method for profiling methylation patterns of cell-free (cf) RNA in plasma for the highly sensitive detection of colon cancer. One of the intrinsic limitations of cfDNA as a reporter of malignancy is that it is found at very low levels when cancers are in their earliest, and most manageable, stages of growth. This is less of a limitation with cfRNA. The method developed by Chuan and his colleagues, low-input multiple methylation sequencing, enables the detection and epigenetic analysis of diverse transfer RNAs and small noncoding RNAs derived from both the human genome and the microbiome. The researchers demonstrated that cfRNA derived from commensal gut bacteria is particularly useful for the detection of colon cancer by liquid biopsy. This is partly because inflammation around tumors remodels the local microbiome, and those changes are reflected in the altered patterns of chemical modifications seen in microbial cfRNA isolated from cancer patient plasma. Additionally, since bacteria turn over frequently, they release relatively large amounts of cfRNA into the bloodstream, greatly improving the sensitivity of detection. The researchers report that they could detect colorectal cancer in blood samples from patients with 95% accuracy even in the early stages of disease, when DNA-based liquid biopsies tend to miss the presence of tumors.

Modifications of microbiome-derived cell-free RNA in plasma discriminates colorectal cancer samples *Nature Biotechnology*, 2025 July 8



Lauren Murphy

Platelets (turquoise surface mask) mop up cell-free (cf) DNA (red) from blood plasma, likely helping to prevent systemic inflammation. They also carry a significant amount of rare cfDNA derived from tumor cells and their inclusion in liquid biopsies could improve the sensitivity of such diagnostic tests.

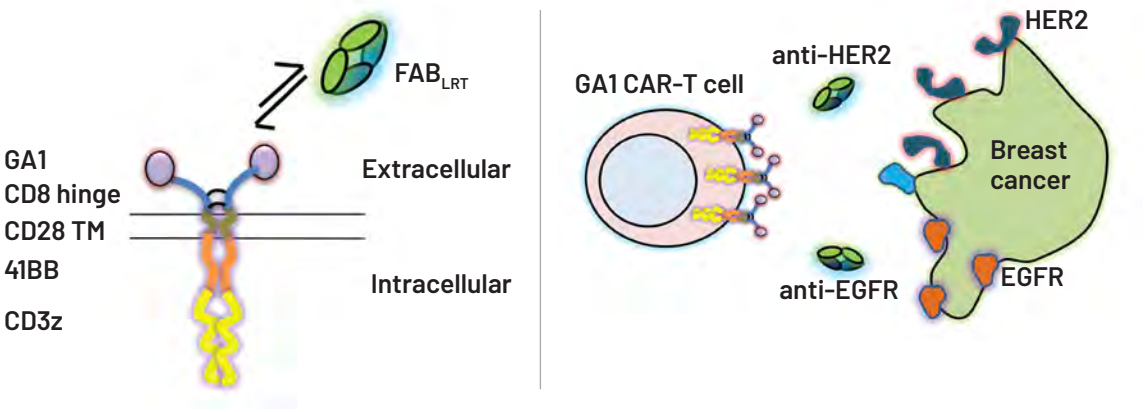
Yet another purpose for the humble platelet

Researchers led by Ludwig Oxford's Bethan Psaila and Lauren Murphy reported in a mid-August *Science* paper a previously unrecognized physiological function of platelets, one that may be readily harnessed for prenatal screening and liquid biopsies. The smallest cells in the body, platelets lack a nucleus. The researchers showed that these tiny cells mop up cell-free (cf) DNA from blood plasma, likely helping to prevent the systemic inflammation that such free-floating DNA could otherwise provoke. They also found that platelets release that DNA when they're activated, suggesting that they deploy their cargo in a manner that prevents nonspecific inflammation yet elicits targeted inflammatory responses where they're needed. To prove that they weren't just seeing residual DNA from megakaryocytes—nucleated cells from which platelets are derived—the researchers examined DNA from the platelets of pregnant women known to be carrying male fetuses. Using these platelets, they accurately predicted the sex of the baby in every sample they tested. Beyond that, platelets carry a significant amount of rare cfDNA derived from tumor cells, which means their inclusion in liquid biopsies—which largely only isolate cfDNA from plasma after cells have been discarded—could significantly improve the sensitivity of such diagnostics. Indeed, Beth, Lauren and their colleagues demonstrated that platelet DNA can be used to detect not only established cancers but also precancerous lesions in the colon.

Bethan Psaila

Lauren Murphy

Platelets sequester extracellular DNA, capturing tumor-derived and free fetal DNA | *Science*, 2025 August 14



The GA1 protein expressed on a T cell surface (left), which has high affinity for the antigen-targeting Fab$_{LRT}$. Both GA1 and antigen-binding affinities can be adjusted to tune the intensity of CAR-T cell responses. Different Fab$_{LRT}$ modules can be used to alter CAR-T cell targeting as needed (right). For example, GA1CAR T cells can target breast cancer cells using either an anti-HER2 or an anti-EGFR Fab$_{LRT}$.

A tunable, controllable and universal CAR for cancer therapy

A universal chimeric antigen receptor (CAR)–fragment antibody binder (FAB) split system for cancer immunotherapy
Science Advances, 2025 July 4

Researchers co-led by Ludwig Chicago's Ainhoa Arina reported in a July publication in *Science Advances* their design and preclinical evaluation of a modular chimeric antigen-receptor (CAR)-T cell construct that is not only universal, tunable and controllable, but can also be readily and repeatedly redirected to new antigenic targets. The extracellular portion of the CAR construct is an engineered G protein variant (GA1) that is activated by binding to an antibody fragment (Fab) that has two functions: antigen recognition via its variable domain and binding to the GA1 through its constant domain. The researchers, including Ludwig Chicago Co-director Ralph Weichselbaum, showed that both binding affinities can be adjusted to modulate the intensity of the CAR-T cell responses. Since the Fab and GA1CAR are delivered separately, the therapy can be switched off by the removal of the Fab, which can also be engineered to enable personalized antigen targeting and changed at any time to target alternative antigens as tumors evolve. The researchers demonstrated the efficacy of GA1CAR T cells and the ability to redirect them to new targets in mouse models of breast cancer. They also showed that the unloaded GA1CAR T cells can remain dormant in animals and be reactivated on demand with an appropriate Fab in case of tumor rebound.


Ainhoa Arina


Ralph Weichselbaum

How a mutant p53 engenders immunosuppression

Pancreatic ductal adenocarcinoma (PDAC) is highly resistant to most therapies, including immunotherapies. The cancer is characterized by activating KRAS mutations, seen in 90% of cases, and alterations to the tumor suppressor TP53 in some 70% of patients. Researchers led by Ludwig Harvard's Rakesh Jain and Phillip Sharp of MIT examined the impact of p53 missense mutations on the intrinsic gene expression of cancer cells and the tumor immune microenvironment (TME) in PDAC. They reported in a June paper in *Immunity* that a common oncogenic mutant, $p53^{R172H}$, establishes an immunosuppressive TME in PDAC, with fewer T cells and more myeloid-derived suppressor cells, which inhibit anti-tumor immunity. They also showed it impairs the efficacy of immune checkpoint inhibitors (ICIs) by regulating a distinct set of chemokines. Tumor-specific reduction of one of these cytokines, Cxcl1, which encodes a chemoattractant for neutrophils, promoted T cell infiltration and decreased tumor growth. The researchers show that $p53^{R172H}$ binds and occupies distal enhancers of Cxcl1, amplifying its expression and immunosuppressive function. Its occupancy of these enhancers and activation of Cxcl1 expression depends on the transcription factor NF-κB. The study shows that a common mutation in a tumor-suppressor transcription factor appropriates enhancers to stimulate chemokine expression and establish an immunosuppressive TME that diminishes ICI efficacy in PDAC.

Mutant p53 exploits enhancers to elevate immunosuppressive chemokine expression and impair immune checkpoint inhibitors in pancreatic cancer | *Immunity*, 2025 June 30

Rakesh Jain

Helen Carrasco Hope

Nicola Vannini

Overcoming the age-associated barriers to cancer immunotherapy

Research co-led by Ludwig Lausanne's Helen Carrasco Hope and Nicola Vannini reported in a May publication in *Nature Cancer* that the metabolic decline that accompanies aging promotes mitochondrial dysfunction and impairs the efficacy of CAR-T cell therapy. That dysfunction, they showed, stems from the age-related depletion of nicotinamide adenine dinucleotide (NAD+), a molecule of critical importance to energy production, metabolism and mitochondrial function. They found that CAR-T cells produced from the T cells of aged mice tend to lack "stemness", or the capacity to persist long-term *in vivo* and efficiently control tumor growth. These capabilities could be restored by NAD+-boosting compounds currently under clinical investigation for other conditions—which means that the strategy may be readily translated for clinical evaluation. Notably, parallel analyses of clinical datasets by the researchers confirmed that both chronological age and NAD^+-related gene expression correlate with outcomes of CAR-T therapy in patients. The findings underscore how fundamentally aging alters the function and metabolism of immune cells, ultimately compromising immunotherapy efficacy. The authors highlight the need to better model age in preclinical studies of immunotherapy, as three-quarters of patients eligible for such treatments are over 65 years old. Interventions that address age as a limiting factor of therapeutic response could improve outcomes for patients receiving immunotherapy.

Age-associated nicotinamide adenine dinucleotide decline drives CAR-T cell failure
Nature Cancer, 2025 May 20

A double take on diet and cancer therapy

Researchers led by Ludwig Princeton's Asael Roichman and Branch Director Joshua Rabinowitz reported this summer findings from a pair of studies in mice examining the influence of diet on cancer therapy. In the first, they explored how ketogenic diets, which are rich in fat and very low in carbohydrates, enhance the effects of cancer drugs in mice. That enhancement was thought to stem from the tendency of keto diets to lower insulin and blood sugar levels. They reported in a May paper in *Cell* that the enhanced efficacy conferred by keto diets to PI3K inhibitors has less to do with changes in carbs, fat, blood sugar or insulin than with the molecular complexity of the diet. The ketogenic food consumed by mice lacks the complex mix of phytochemicals that are present in standard chow. It turns out that gut microbes break down phytochemicals, namely soyasaponins derived from soybeans, into molecules that induce the expression of the detoxifying liver enzyme cytochrome P450. Elevated production of these enzymes in chow-fed mice drives the rapid clearance of PI3K inhibitors by a pharmacokinetic mechanism. The researchers also show that a high-carbohydrate but low-phytochemical diet—as well as antibiotics that suppress the gut microbiome—enhance PI3K inhibitor activity in the mice. These findings highlight interactions between diet and the microbiome as important factors in the efficacy of cancer therapies. They also open opportunities to develop new strategies for cancer therapy that take into account such factors as a patient's diet, microbiome composition and recent use of antibiotics, which alter the ecosystem of commensal bacteria.

The second study explored why a diverse microbiome and consumption of fiber-rich foods correlate with favorable immune checkpoint blockade (ICB) outcomes in the clinic. It has not been clear by what mechanism this occurs and, hence, what patients really need to eat to benefit. Asael, Josh and their colleagues, with equal contributions from the laboratories of Ludwig Princeton's Eileen White and Yibin Kang, investigated gut microbiome composition, metabolite levels and ICB responses in mice fed grain-based chow or purified diets with differing quantities of isolated fibers (cellulose and inulin). Their studies revealed that dietary fiber appears to have limited or inconsistent effects on ICB efficacy in mouse models. They reported in a June publication in *Cancer Research* that other dietary factors that correlate with fiber intake may underpin clinical correlations between fiber consumption and immunotherapy efficacy.

Asael Roichman

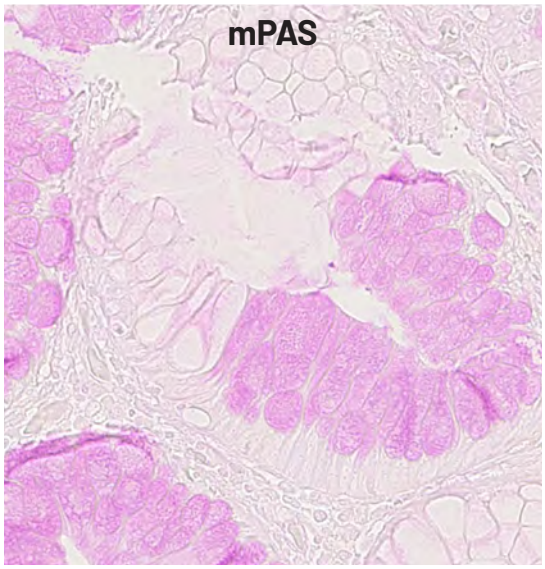
Joshua Rabinowitz

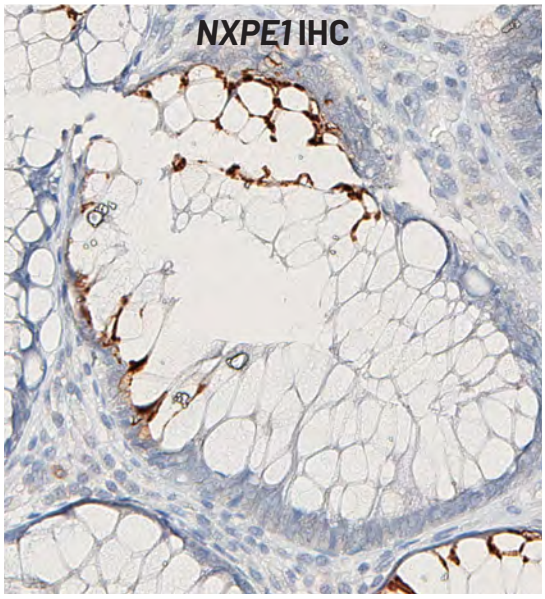
Eileen White

Yibin Kang

Microbiome metabolism of dietary phytochemicals controls the anticancer activity of PI3K inhibitors | *Cell*, 2025 May 19

Dietary Fiber Lacks a Consistent Effect on Immune Checkpoint Blockade Efficacy Across Diverse Murine Tumor Models *Cancer Research*, 2025 June 20





Nicolas Wyhs

The role of NXPE1 in mild periodic acid Schiff (mPAS) staining is exquisitely illustrated in these images. They capture a human colonic crypt generated by the extremely rare fusion of two stem cells with distinct genotypes for the NXPE1 gene. mPAS (top) stains one half of the crypt pink, due to a lack of modification to sialic acids, but fails to stain the other. This is because one half is NXPE1-positive, while the other is negative, as shown in the IHC-staining for the NXPE1-encoded protein (bottom).

A new gene behind an old workhorse of microscopy

Mild periodic acid Schiff staining (mPAS) has been used for over five decades to characterize sialoglycans (i.e. sialoglycoproteins and glycolipids) in tissue specimens, used for studies ranging from investigations of cell adhesion to immunology to cancer biology. These studies reveal striking variation in mPAS staining in human colorectal tissue but the cause of this variation was unknown. To find that cause, researchers led by Ludwig Johns Hopkins' Bum Seok Lee, Kenneth Kinzler and Nicolas Wyhs used haplotypes—stretches of DNA inherited intact from one parent—derived from whole genome sequencing to explore chromosomal regions associated with differences in mPAS staining. They reported in a May issue of *Nature Communications* that a haplotype on chromosome 11 is associated with such differences in colorectal tissue. The researchers found that NXPE1 is the gene within this haplotype responsible for the observed variations, and that altering a single nucleotide polymorphism in its promoter influences its expression and changes modified sialic acid levels. They also showed that the recombinant product of NXPE1 is able to acetylate oxygens on sialic acids in vitro and that this chemical modification disrupts the chemistry of mPAS staining, solving a 50-year old mystery of microscopy and pathology. The researchers present NXPE1 as a prototype of a new family of sialic acid O-acetylation-modifying enzymes and as the gene responsible for differences in colon mPAS staining.

NXPE1 alters the sialoglycome by acetylating sialic acids in the human colon | *Nature Communications*, 2025 May 27

Bum Seok Lee

Kenneth Kinzler

Nicolas Wyhs

Shattering revelation yields biomarker and drug target for BP-MPN

Chromothripsis is a massive genomic rearrangement event caused by the shattering and haphazard reassembly of chromosomal segments. A key mechanism for oncogene amplification and the loss of tumor suppressor genes, chromothripsis is pervasive in cancer and associated with poor prognosis. It contributes to 7% of acute myeloid leukemias (AMLs) unrelated to prior diagnoses of myeloproliferative neoplasms (MPNs), slow-growing blood cancers that can develop into AML. But its role in driving MPNs was not well understood. Charlotte Brierley, a clinician-scientist in the groups of Ludwig Oxford's Bethan Psaila and Adam Mead at the University of Oxford—all of whom led this study and participate in the collaborative MPN Program launched this year at the Oxford Branch—explored the phenomenon in a cohort of 64 patients with blast phase MPN (BP-MPN), an aggressive manifestation of the cancer. They reported in *Nature Genetics* in June a recurrent amplification of a region of chromosome 21q (chr. 21amp) in a quarter of the cohort. A third of these cases were driven by chromothripsis and had a particularly aggressive and treatment-resistant phenotype. The findings define chr. 21amp as a prognostic biomarker in BP-MPN. The researchers also identified *DYRK1A* as a potential therapeutic target. A serine-threonine kinase central to BP-MPN development, *DYRK1A* was the only gene that showed both increased expression and chromatin accessibility in the amplified region of chromothripsis-driven MPNs.

Chromothripsis-associated chromosome 21 amplification orchestrates transformation to blast-phase MPN through targetable overexpression of DYRK1A | *Nature Genetics*, 2025 June 9

Charlotte Brierley

Bethan Psaila

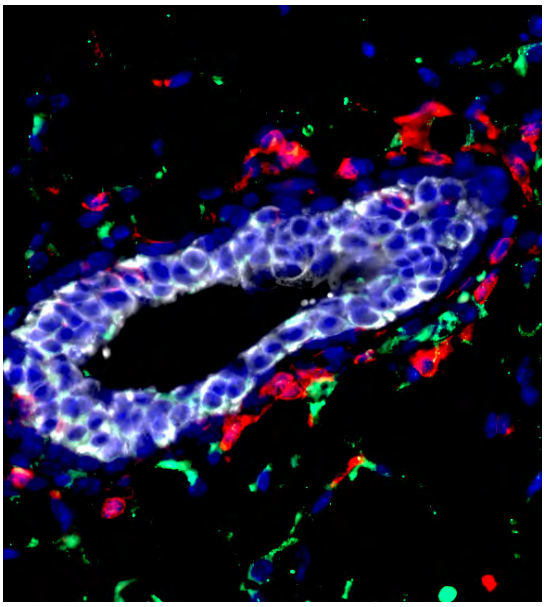
Adam Mead

Karen Adelman

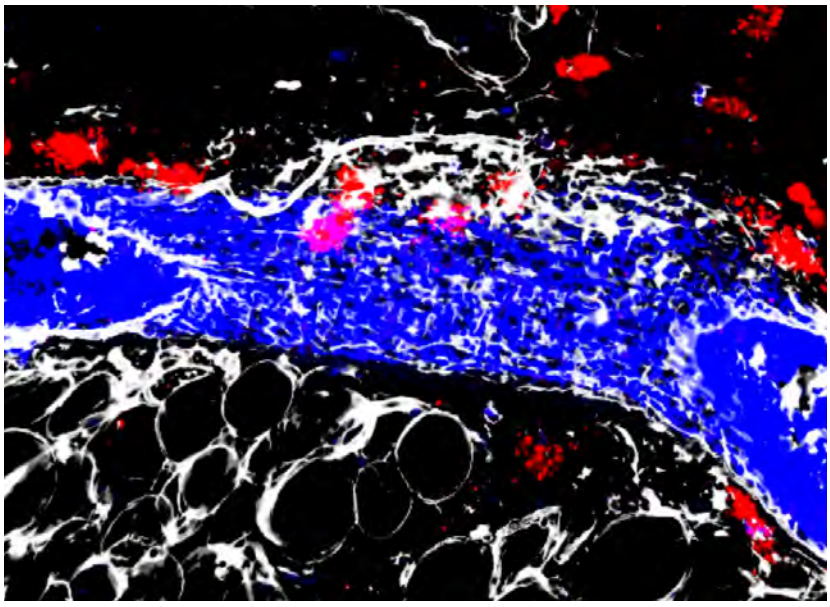
Integrator mutations trigger a persistent stress response to cause disease

Integrator (INT) is a large protein complex that targets RNA polymerase II (RNAPII), terminating gene transcription in its earliest stages to regulate gene expression, including that of stress-responsive genes. Mutations to INT components are associated with many diseases, including cancer and neurodevelopmental disorders, though how they contribute to pathology has been unclear. Researchers led by Ludwig Harvard's Karen Adelman reported in an April publication in *Cell* one possible mechanism for that. The loss of INT-mediated termination, they report, allows RNAPII to aberrantly escape into gene bodies, fully transcribing short genes but generating incomplete transcripts of longer ones. The researchers detail how this triggers the integrated stress response (ISR) in cells in two ways: by activating expression of short genes such as ATF3, a transcription factor that drives stress responses, and causing the generation of double-stranded (ds) RNAs. These dsRNAs, generated by the premature termination of transcription by immature RNAPII that escapes into gene bodies, are recognized by protein kinase R, which drives the activation of the transcription factor ATF4, a master regulator of ISR whose activation further sustains the stress response. Karen and her colleagues report that patient cells with INT mutations exhibit dsRNA accumulation and ISR activation, implicating chronic ISR in diseases caused by INT deficiency.

Integrator loss leads to dsRNA formation that triggers the integrated stress response | *Cell*, 2025 April 14



Mammary gland macrophages (red) expressing the receptor CXCR4 (green) that localize to the mammary epithelium (white), where they support branching morphogenesis and promote mammary tumorigenesis.

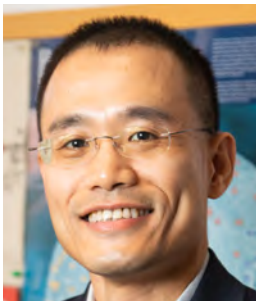


Eunmi Lee

Macrophages (red) infiltrating through the collagen-rich basement membrane (white) to contact the mammary epithelium (blue).

A niche role for ductal macrophages in breast cancer

To establish tumors, tumor initiating cells (TICs)—a.k.a. cancer stem cells—in the breast and elsewhere exploit many of the same intrinsic factors that regulate normal stem cells. But considerably less is known about the microenvironmental cells and extrinsic factors that regulate mammary stem cells (MaSCs) and TICs in the breast. In a May issue of *Nature Communications*, researchers led by Ludwig Princeton's Yibin Kang and Eunmi Lee identified ductal macrophages expressing the chemokine receptor CXCR4 as a key niche population in normal mammary ducts. They report that these CXCR4+ macrophages promote the regenerative activity of the mammary duct's contractile basal cells in response to the chemoattractant CXCL12 produced by its milk-producing luminal cells. The same CXCR4+ niche macrophages regulate the tumor-initiating activity of various breast cancer subtypes by enhancing cancer stem cell survival and tumor-forming capacity. They also nurture an immunosuppressive niche by expressing ALDH1a2, an enzyme whose product induces the differentiation of immunosuppressive regulatory T cells. The genetic depletion or pharmacological targeting of the CXCL12–CXCR4 signaling axis or ALDH1a2 inhibit tumor initiation, progression and metastasis by reducing the number and activity of TICs and Tregs while boosting the numbers of cytotoxic CD8+ T cells, which can kill cancer cells. Yibin, Eunmi and colleagues also show that a CXCR4+ niche macrophage gene signature correlates with poor prognosis in human breast cancer.



Yibin Kang

Eunmi Lee

CXCR4+ mammary gland macrophageal niche promotes tumor initiating cell activity and immune suppression during tumorigenesis | *Nature Communications*, 2025 May 25

Yuxuan Wang

Nickolas Papadopoulos

Bert Vogelstein

How early can a multi-cancer liquid biopsy detect disease?

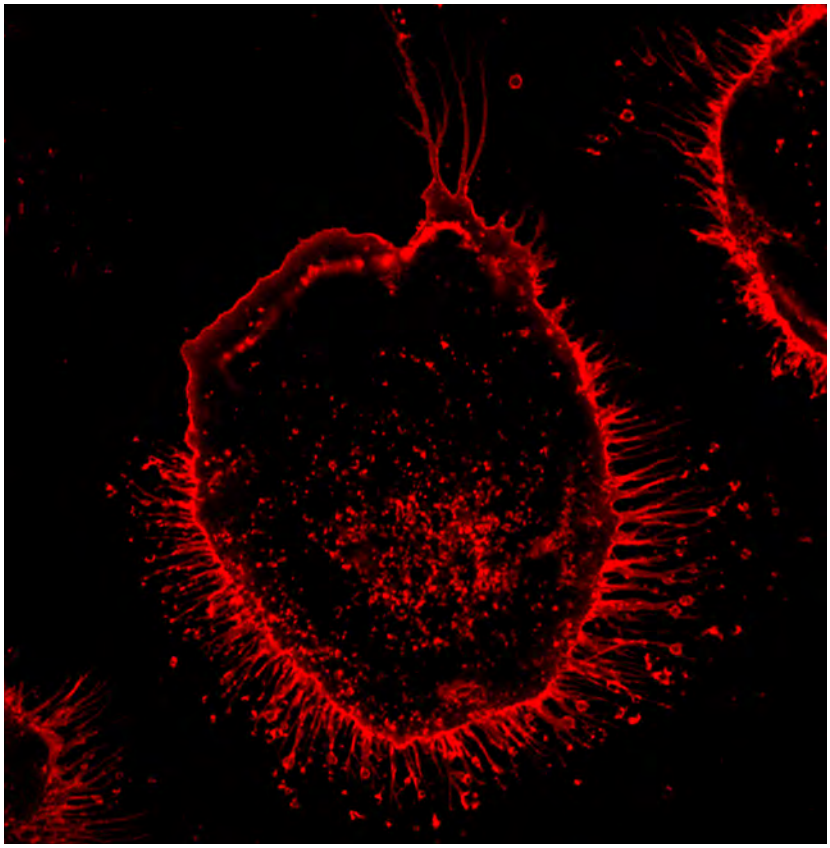
Cancers are easier to treat if they're detected at relatively early stages of their development. Liquid biopsies, which detect molecular markers of cancer in easily accessible body fluids, hold promise as routinely deployable tools for that purpose. But how early can such tests in fact detect malignancy? To answer that question, researchers led by Ludwig Johns Hopkins' Yuxuan Wang, Nickolas Papadopoulos and Co-director Bert Vogelstein with a Johns Hopkins colleague collected serial plasma samples from the Atherosclerosis Risk in Communities (ARIC) study, including 26 participants diagnosed with cancer and 26 matched controls. Eight of these participants scored positive with a multicancer early detection (MCED) test at a selected "index" time point and were diagnosed with cancer within 4 months of that blood draw. The researchers reported in a May issue of *Cancer Discovery* that in six of those eight participants, they were able to analyze plasma samples collected 3.1 to 3.5 years prior to diagnosis. In four, the same mutations detected by the MCED test were identified, but at about 8 to 80-fold lower levels relative to the levels at 4 months before diagnosis. The findings suggest circulating tumor DNA can be detected more than three years before cancer diagnosis and indicate how sensitive a liquid biopsy needs to be for that to happen.

Detection of cancers three years prior to diagnosis using plasma cell-free DNA | *Cancer Discovery*, 2025 May 22

How macrophages paint cells for clearance

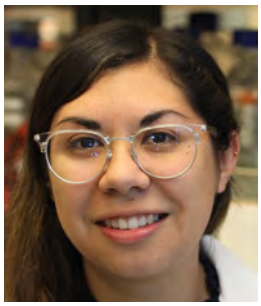
Recent studies have revealed that macrophages can transfer their own calreticulin (CALR) proteins to exposed asialoglycans on sick, unwanted or dying cells to direct their removal by phagocytosis, a process known as programmed cell removal (PrCR). Researchers co-led by Ludwig Stanford's Allison Banuelos and Irving Weissman explored the mechanisms by which CALR is processed, secreted and binds to its targets on cells. They reported in a May publication in *PNAS* that upon secretion by lipopolysaccharide-activated macrophages, CALR is cleaved—likely by cathepsins—at one end (the carboxy-terminal) and that this truncated CALR decorates the surface of target cells, serving as an "eat me" signal for macrophage phagocytosis. They also show that macrophages secrete neuraminidases, which clip off sialic acid residues on the cell surface and so prime their targets for binding by the cleaved CALR. A better understanding of these mechanisms of PrCR could inform the design of therapies to better recruit macrophages to the removal of cancerous and otherwise pathogenic cells. The authors note, however, that while their study describes how macrophages paint their targets for destruction, how they recognize which cells to target remains a mystery.

Macrophages release neuraminidase and cleaved calreticulin for programmed cell removal | *PNAS*, 2025 May 21

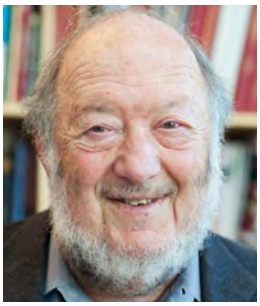


Allison Banuelos and William Kasberg

Macrophage activated by exposure to lipopolysaccharide, stained with the lectin phytohemagglutinin-L (PHA-L), which labels asialoglycans red on the macrophage surface. Macrophages can transfer their own calreticulin (CALR) proteins to exposed asialoglycans on sick, unwanted or dying cells to direct their removal by phagocytosis, a process known as programmed cell removal.



Allison Banuelos



Irving Weissman

New tumor suppressors for TNBC

Researchers led by Ludwig Princeton's Yibin Kang and alumnus Zheng Sun conducted a genome-wide CRISPR knockout screen in three-dimensional (3D) tumor spheroid and two-dimensional cell culture models to identify tumor suppressors that regulate triple-negative breast cancer (TNBC), the most aggressive and treatment-resistant subtype of breast cancers. They reported in a May issue of *Cancer Research* that chromatin remodeling SWI/SNF complex, which directly alters DNA accessibility to regulate gene expression, emerged as a potent growth suppressor in the tumor spheroid model, which mimicked tumor growth in vivo relatively well compared to 2D cell culture. SMARCA4, the ATPase subunit of this complex, was required for the expression of the Rho GTPase factor ARHGAP29. Its loss promoted spheroid growth—generating less compact spheroids in cultures—and enhanced primary tumor growth and metastasis across several mouse models of TNBC. The researchers showed that SMARCA4 increases DNA accessibility by directly binding the promoter for ARHGAP29, enhancing its expression. SMARCA4 deletion thus depresses ARHGAP29 expression and leads to hyperactive RHOA signaling—which disrupts cell adhesion. Zheng, Yibin and colleagues also showed that SMARCA4 loss enhances growth of primary tumors and promotes metastasis in several preclinical mouse models of TNBC. The findings establish SMARCA4 and SWI/SNF as tumor suppressors of TNBC.

SMARCA4 Inhibits Breast Cancer Progression and Metastasis through RHOA Suppression | *Cancer Research*, 2025 May 15

Yibin Kang

Ash Alizadeh

Maximilian Diehn

Detecting rarest of RNAs for liquid biopsies

A team led by Ludwig Stanford's Ash Alizadeh and Maximilian Diehn described in an April publication in *Nature* a method for the analysis of cell-free (cf) RNA for liquid biopsies named RARE-seq (for random priming and affinity capture of cell-free RNA fragments for enrichment analysis by sequencing). In developing RARE-seq, the researchers identified and addressed a previously unrecognized technical challenge of cfRNA-based liquid biopsy: platelet contamination, they found, is a major confounder of cfRNA analysis and developed a computational model to cut through that noise. By zooming in on the transcripts of some 5,000 genes not likely to be picked up in plasma, the researchers made their analysis 50-fold more sensitive in detecting tumor-derived cfRNA than the sequencing of whole transcriptomes (RNA-seq). Ash, Max and their colleagues evaluated RARE-seq's clinical utility using plasma samples from 369 individuals with disease and controls. They showed that its sensitivity in detecting non-small cell lung cancer (NSCLC) expression signatures increased with stage: 30% for stage I; 63% for stage II; 67% for stage III; and 83% in stage IV at 95% specificity. Further, RARE-seq could detect mutation-based mechanisms of resistance to tyrosine kinase inhibitors in patients with EGFR-mutant NSCLC. The researchers also demonstrated the use of RARE-seq for determining tissue of origin of various cancer types, assessing non-malignant pulmonary conditions and tracking dynamics of response to mRNA vaccines.

An ultrasensitive method for detection of cell-free RNA | *Nature*, 2025 April 16

Two new ways to target LSD1 for AML therapy

Acute myeloid leukemia (AML) stems from impaired differentiation of myeloid progenitor cells in the bone marrow. This results in the accumulation of immature precursor cells within the bone marrow and circulation, ultimately impairing hematopoiesis, or blood cell production, and other essential biological functions. One subtype of AML—acute promyelocytic leukemia (APL)—can be treated with a pair of drugs (all-trans retinoic acid and arsenic trioxide) that push cancerous precursors past the differentiation barrier. But there remains a pressing need to identify similar strategies for other AML subtypes. Inhibiting the epigenetic enzyme LSD1, which is highly expressed in AML cells, induces differentiation in AML stem cells. But LSD1 inhibitors have proved too toxic at the doses required to be viable for use as a monotherapy. Researchers co-led by Ludwig Oxford's Yang Shi and Amir Hosseini published a pair of papers this spring that addressed this issue in distinct ways.

Yang Shi

Amir Hosseini

In the first, led by Amir and Yang—along with colleagues in Finland and the U.S.—they reported in an April publication in *Nature* that an inhibitor of the GSK3α/β enzyme, a driver of the WNT signaling pathway, synergizes with low doses of an LSD1 inhibitor to drive AML precursor cell differentiation, inhibit cancer cell proliferation and extend the survival of mice engrafted with human AML cells. The combination rewires gene expression programs to suppress the stem cell-like traits of leukemic cells. It also induces a gene expression signature in leukemic cells similar to that seen in AML patients who live relatively longer with the cancer. The researchers showed that the combo selectively targets leukemic cells—not healthy hematopoietic ones—lowering the risk of toxicity in patients.

The second study took an entirely different tack to disrupt LSD1 activity in AML. LSD1's epigenetic function—reversing histone methylation at lysine residues—is only one aspect of its part in AML oncogenesis. The enzyme also serves as a scaffolding protein that stabilizes protein complexes on chromatin that are central to AML pathology. Researchers led by Amir, Yang and Jian Jin at the Icahn School of Medicine at Mount Sinai in New York, described a proteolysis-targeting chimera (PROTAC) degrader, MS9117, that binds LSD1 and targets it for ubiquitination—a chemical tag that ultimately marks it for destruction by the cell's protein-degrading machinery. They showed that MS9117, the first LSD1 inhibitor of this kind, effectively degrades LSD1 and suppresses the proliferation of AML cells in culture more effectively than pharmacological inhibitors of the enzyme. They also demonstrated that it sensitizes non-APL cells to treatment with all-trans retinoic acid.

Perturbing LSD1 and WNT rewires transcription to synergistically induce AML differentiation
Nature, 2025 April 16

Discovery of an LSD1 PROTAC degrader
PNAS, 2025 May 14


Ralph Weichselbaum


András Piffkó


Kaiting Yang


Sean Pitroda


Hua Laura Liang

How radiotherapy may promote metastases

Researchers led by Ludwig Chicago Co-director Ralph Weichselbaum reported in a *Nature* publication in May that high doses of radiation aimed at a single tumor can accelerate the growth of existing metastases elsewhere in the body. The study, to which Ludwig Chicago's András Piffkó, Kaiting Yang, Sean Pitroda and Hua Laura Liang contributed equally, analyzed samples from a clinical trial in which patients with various cancers received focused high-dose radiotherapy (stereotactic body radiotherapy, SBRT) combined with checkpoint blockade immunotherapy (pembrolizumab). Gene expression analysis revealed that SBRT induced the expression of the growth factor amphiregulin, and higher levels correlated with a size increase of preexisting metastatic sites. This effect was recapitulated in mouse models of metastatic lung and breast cancer. Elevated levels of amphiregulin were also found in the blood plasma of mice as well as patients enrolled in a trial evaluating SBRT and immunotherapy, and were associated with worse outcomes. Mechanistic experiments showed that amphiregulin reprograms EGFR-expressing myeloid cells into an immune-suppressive state and increases tumor expression of CD47, a "don't-eat-me" signal that prevents immune cells from engulfing cancer cells. Combining radiotherapy with antibodies that block amphiregulin and CD47 significantly improved control of metastases in mice.

Radiation-induced amphiregulin drives tumour metastasis | *Nature*, 2025 May 14

Krystyna Tesak

Phagocytosis of a cancer cell (top) by a macrophage (bottom), captured by high-resolution fluorescent microscopy. Stereotactic body radiotherapy (SBRT) aimed at a single tumor can accelerate the growth of distant metastases. SBRT induces the expression of growth factor amphiregulin, which reprograms EGFR-expressing myeloid cells into an immune-suppressive state and increases tumor expression of CD47, a "don't-eat-me" signal transmitted to macrophages. F-actin was visualized by phalloidin staining for this image.

How ascites fluid cripples natural killer cells

Produced copiously as ovarian tumors spread into the abdomen, ascites fluid is known to be immunosuppressive. But why it is so was not clear. Researchers led by Ludwig Princeton's Lydia Lynch reported in a May 9 publication in *Science Immunology* one significant reason this is the case: certain lipids found at high levels in ascites cripple natural killer (NK) cells, T cells and innate T cells. Lydia and her colleagues—including senior author Marcia Haigis of Ludwig Harvard—discovered that lymphocytes isolated from ovarian tumors and metastases produce very low levels of perforin and granzyme B, which kill target cells. Metabolic analyses and other studies revealed that while ascites is rich in nutrients, some of its fats cause lymphocyte dysfunction. NK cells, in particular, are so overwhelmed by the influx of polar lipids—especially phosphatidylcholine (36:1)—that they become incapable of handling, storing and processing fats. This undermines their ability to take up and use amino acids and glucose, which disrupts their cytotoxic machinery and production of stimulatory immune factors like IFNγ and TNFα. Depleting lipids from ascites restored the glucose uptake and cytotoxic function of NK cells. The researchers also identified a lipid transporter, SCARB1, behind the dysfunction. Blocking SCARB1 restores the cytotoxicity of NK cells in culture even when they're bathed in malignant ascites, suggesting a therapeutic strategy for further study.

Uptake of lipids from ascites drives NK cell metabolic dysfunction in ovarian cancer | *Science Immunology*, 2025 May 9

Lydia Lynch

Marcia Haigis

Ping-Chih Ho

Yi-Ru Yu

Targeting a fat transporter to restore anti-tumor immunity

Researchers led by Ludwig Lausanne's Ping-Chih Ho and Yi-Ru Yu—along with Sheue-Fen Tzeng and Chin-Hsien Tsai, former postdocs in the Ho lab who now lead their own labs at Taipei Medical University in Taiwan—identified in an April publication in *Cancer Discovery* a specific mode of fat uptake by immune cells within tumors that serves as a metabolic checkpoint against anti-cancer immune responses. They also reported their preclinical development and assessment of a humanized antibody to dismantle that barrier for cancer immunotherapy. This antibody, PLT012, binds and blocks the activity of CD36, a transporter of lipids that is expressed by immune cells in acidic and fat-enriched tumor microenvironments. The influx of fat enabled by CD36 induces dysfunction in CD8+ T cells while bolstering the activity of immunosuppressive cells such as myeloid-derived suppressor cells and regulatory T cells. PLT012 undermines this metabolic checkpoint to restore anti-tumor immunity in mouse models of hepatocellular carcinoma (HCC) as well as in models of liver metastases of colon cancer. Ping-Chih, Yi-Ru and colleagues showed the antibody reshapes the immune landscape of tumors isolated from HCC patients, suggesting it is likely to replicate its effects in humans. Studies in monkeys and mice suggested it has an excellent safety profile.

PLT012, a Humanized CD36-Blocking Antibody, Is Effective for Unleashing Antitumor Immunity Against Liver Cancer and Liver Metastasis | *Cancer Discovery*, 2025 April 28

A model to predict lung cancer chemoradiotherapy outcomes

Ash Alizadeh

Maximilian Diehn

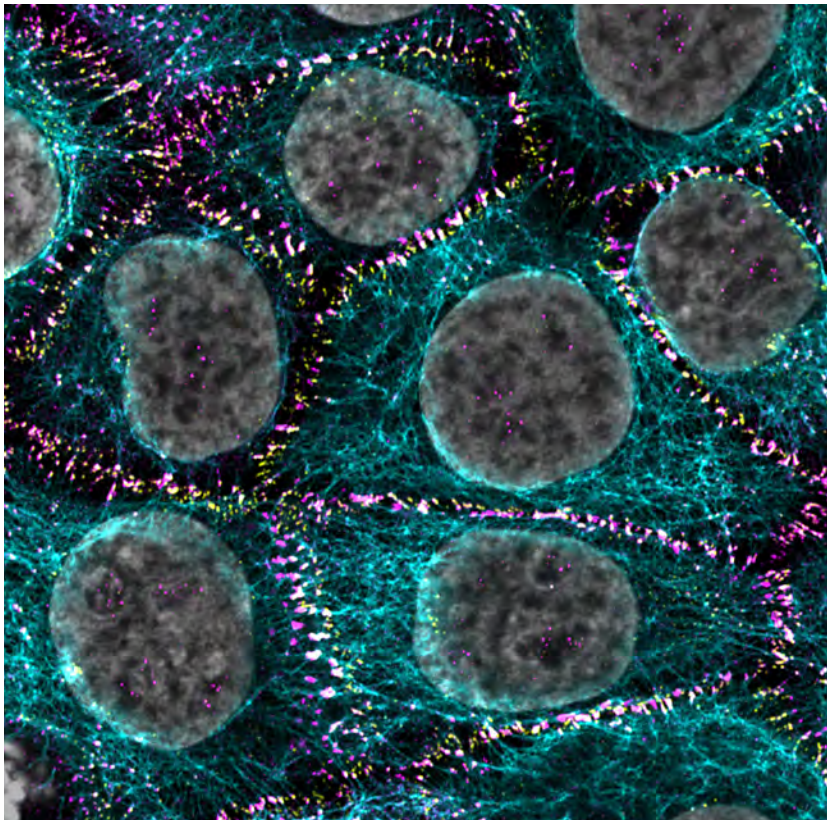
Measurements of ctDNA that reflect minimal residual disease following chemoradiotherapy (CRT) for non-small cell lung cancer (NSCLC) are highly predictive of ultimate patient outcomes. But biomarkers that offer such predictions during treatment could help clinicians adapt therapy to improve outcomes for their patients. Researchers co-led by Ludwig Stanford's Ash Alizadeh and Maximilian Diehn reported in an April publication in *Cancer Discovery* their development and validation of a dynamic risk model for this purpose. This model, termed Continuous Individualized Risk Index, was developed to address chemoradiotherapy (CRT)outcomes for locoregional lung tumors (CIRI-LCRT). Built on the analysis of 418 NSCLC patients undergoing such therapy, their model accurately predicted ultimate progression-free survival outcomes. The researchers showed that mid-CRT concentrations of circulating tumor (ct) DNA in patients strongly predict disease progression. They then integrated additional pre-CRT risk factors, including pre-treatment tumor histology and features from radiomic techniques—the use of image processing and statistical analysis to discern quantitative tumor features like shape and texture—with mid-CRT ctDNA measurements to develop a combined model, CIRI-LCRT, that improves outcome prediction. The researchers argue that tumor features, radiomics, and mid-CRT ctDNA analysis are complementary and, taken together, can accurately identify the risk of progression in patients. They are hopeful that this novel model will enable the fine-tuning or personalization of therapeutic strategies—for instance, changing systemic therapy—to improve treatment outcomes.

Integrating ctDNA Analysis and Radiomics for Dynamic Risk Assessment in Localized Lung Cancer
Cancer Discovery, 2025 April 29

Mutations in noncancerous cells fuel melanomas

The cellular and molecular microenvironment plays a critical role in malignant transformation. Researchers led by Ludwig Oxford's Richard White and Trey Ideker of the University of California San Diego reported in an April publication in *Nature Genetics* that mutations in noncancerous cells can drive melanoma. Scouring The Cancer Genome Atlas for mutations in genes encoding the components of desmosomes—transmembrane protein complexes that help establish adhesive contacts between cells—the researchers discovered that while several tumor types sport such mutations, the cancer type that most frequently harbors them is cutaneous melanoma. Desmosome mutations are seen in 71% of these tumors compared to about 40% in other tumor types. They found that in primary melanomas, but not in their metastases, these mutations lead to a decline in desmosome gene expression. Immunofluorescence and spatial transcriptomics studies indicated that the decreases in expression occur in keratinocytes in the tumor microenvironment rather than in the melanoma cells themselves. Keratinocytes account for 90% of the cells in the outer layer of skin and are among the cells incipient melanomas interact with most frequently. Richard, Trey and their colleagues found that knockdown of desmosome genes in keratinocytes boosted the proliferation of adjacent melanoma cells in keratinocyte and melanoma co-cultures, as did media preconditioned with desmosome-deficient keratinocytes. This adds to growing evidence that mutations in nontumor cells can contribute to neoplastic transformation, especially during tumor initiation.

Desmosome mutations impact the tumor microenvironment to promote melanoma proliferation | *Nature Genetics*, 2025 April 16



Mohita Tagore

A monoculture of keratinocytes (cyan and gray) linked by desmosomes (green and purple). Mutations in desmosome genes, seen in 70% of cutaneous melanoma tumors, occur in keratinocytes and inhibit their expression. Desmosome deficiency in keratinocytes boosts the proliferation of adjacent melanoma cells in culture, adding to evidence that mutations in nontumor cells can contribute to neoplastic transformation.

Richard White

LUDWIG'S EARLY-CAREER RESEARCHERS

Preparing for a future in science

Trainees at three Ludwig Centers set aside a little time to tell us about their lives, current research and avocational interests. Here are some excerpts of those engaging conversations.

Ágnes Bilecz

Visiting Pathology Scholar, Ludwig Chicago

Ernst Lengyel laboratory

Daniel Kim

MD-PhD candidate, Ludwig MIT

Sangeeta Bhatia laboratory

Clemens Hinterleitner

Postdoctoral research fellow, Ludwig MSK

Scott Lowe laboratory

Daniel Kim

MD-PhD candidate, Ludwig MIT

Tell us a bit about yourself and your life.

I was born in Memphis, Tennessee, but mostly grew up around the Boston area, in Lexington. My parents were from South Korea. They immigrated here to pursue graduate degrees. I have a brother, and a sister and two nieces who live in Seattle.

I'm currently an MD/PhD student at the Harvard-MIT MD/PhD program—a sixth year student overall. For the PhD, I am in the medical engineering and medical physics program at MIT. I'm also a second-year Emerson Harris program fellow at MIT, studying piano with Mi-Eun Kim. I'm a resident tutor in Adams House at Harvard, where I also help out in the arts and community endeavors.

Before going to college, my dream was to become a musician, a classical pianist. So I studied pretty seriously and went to New England Conservatory Preparatory School, which is a version of the conservatory for pre-college students. Did the competitions and the concerts and all that stuff. But due to a couple of factors, I decided not to go into music as a career. The summer before senior year I was doing three or four competitions and I was really stressed out. I developed some ulcers and I was like, OK, this is probably not the most sustainable career for me, getting stress ulcers at 16 or 17, which was tough because I really loved music.

Through college I played a lot of music and I didn't just do classical piano. I went into sound production for friends who were in the theater world. I played in some pit orchestras, explored other genres of music, and now I am coming back to classical music because this program is really cool. It tapped me into the MIT music community.

I am approaching the end of the PhD part of my training, and I'll return then for two years of medical school to complete most of my rotations. My plan is to also apply for a physician-scientist training program.

How did you find your way to scientific research?

I was really interested in a lot of different subjects in high school and in the early days of college. But I guess the most maybe significant experience was that I spent my freshman year summer in the Fernando

Camargo lab at the Boston Children's Hospital. The lab studies hematopoiesis but also models solid tumors, and I really loved learning about that field. In the early days of training, mentorship is the most important thing. Michael Dill, who was a postdoc in the laboratory and is now a professor at Heidelberg University, was my mentor. He showed me the excitement of science and how it's an art, in a way. I think he really helped me find those two sides. I was like, oh, this is great. I guess I'll go into that.

What does the Emerson Harris Fellowship entail?

It's actually quite involved, and it has made me better as a musician, which is really nice. It involves private studies, lessons every week. You also have a weekly seminar with other fellows, two hours on Mondays. People basically perform. There are instructors also there and, together, we critique the performance. It culminates, at the end of the academic year, with an hour-long solo recital. In addition, there's a lot of opportunities such as playing in masterclasses. I got tapped to play at some MIT based events ... playing for student composers, performances and all that stuff.

Who's your favorite composer?

It really depends on the mood, I think. I think, in general, I gravitate towards the heavy Russian hitters. So like Rachmaninoff and Scriabin and Prokofiev. They try to stare into the sun. That's what they try to do with their music, and they encompass a lot of human emotion too.

Back to the science, what are you working on now?

I'm aiming to develop non-invasive diagnostics for early detection and monitoring of diseases, currently focusing on cancer and infectious disease. I approach

this goal with two main focuses. One is developing breath biopsy tests to leverage volatile molecular signatures in breath for detection of disease. And the second is advancing blood biopsy tests. For breath, we're designing novel nanoparticle sensors that release synthetic volatile molecules instead of the ones you sort of produce in your own breath. So you would take them in and, upon interacting with disease associated proteases, they would release those volatiles, and then you can collect and detect them to monitor disease.

And then for blood, we're using different nanoparticles, such as liposomes, to transiently delay clearance of specific analytes in blood like extracellular vesicles and cell-free RNA. Nanoscale analytes are cleared mainly through the reticular endothelial system organs such as the liver, the spleen and vasculature. Usually, this is very good. You don't want unnecessary debris to build up in our circulation. But it can take away some informative analytes. So we're envisioning a way to transiently stop clearance that is not detrimental in the long run. That's where these nanoparticles come into play, what we call priming agents. Our lab and others published a seminal paper last year showing that administering these nanoparticle priming agents can slow clearance of key cellular agents in those organs—so for this window of time, you're getting buildup of the analytes. In that window, if you sample the blood, you can extract more information from the same amount of liquid biopsy.

What interests you most about this work?

I think for me, the most fascinating thing is that in early detection there are two main questions: what do we want to detect and how do we want to sense what we want to detect? The first question relies on deep understanding of biology. It's very important for clinical relevance. The latter, the "how do we sense?", is much more about advancing technology, which is principally driven by studies in physical sciences and engineering. Here we're thinking about both at the same time, we can find ourselves innovating on the technology that we use to detect certain biology, and other times we are discovering more in the biology that enables us or shows us a new use case for new technology. And so for someone with a pretty broad but disparate training, it's really rewarding to be in such an

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interdisciplinary space where I can see things connect, and my life feels coherent.

Do you have a favorite book?

Depends on the mood. I actually try to read quite a bit. And mainly I try to read fiction because I read a lot of nonfiction in my work and I enjoy trying to switch it up. So I'm enjoying this book called *The Hours* right now by Michael Cunningham. It's sort of this retelling of Virginia Woolf and her character. But I think the most impactful book that I've really read in the past year was this book called *Martyr!* by Kaveh Akbar. It's this book about a young poet who's going through a lot of tough situations and finds a way to reconcile their past and kind of find meaning in life. The reason I like it so much is because it's more common and straightforward to write a book where despair is the point.

Any hobbies?

I would just say I enjoy running. I used to hate running. Maybe it's like Stockholm syndrome. But I really like running and Boston's such a beautiful running city to run in, and it's very safe. And I really like cooking as well. Recently, I've also more often tapped back and connected with my mom to learn her recipes, which she learned from her mother and her sisters and brothers back in Korea.

What global issue concerns you the most?

It seems like there's new ones every day [laugh]. But I think, in general, one that maybe might encompass a lot of them is the spread of misinformation on social media and news outlets, particularly when aided by generative AI. And the reason why I think it concerns me the most is because it basically touches on a lot of different global issues and it actually affects people's actions in those issues.

How important has mentorship been to you?

I've been told good mentorship is the most critical thing for success and mentorship, I think, comes in many different forms. It comes in the scientific form, but it also comes in the cheerleading form. It comes in the "what's possible" kind of inspiring form. And it comes in the "dealing with hardship" form. Great mentors encompass all or many of those roles. Peers can be great mentors too. I've found that people are wiser in other things than I am. I've been taught a lot, in a way, by the students I advise.

Ágnes Bilecz

Visiting Pathology Scholar,
Ludwig Chicago

Tell us a bit about yourself.

I was born and raised in Hungary, and I also completed all my studies in Hungary. I was born in a small town called Balassagyarmat. It's my party trick to teach people how to pronounce it, which is close to impossible for non-Hungarians. It's near the northern border of Hungary, close to Slovakia. When I was growing up, it had like, 20,000 inhabitants, so it was very small. It has, I think, eight different schools because kids from the entire region come there to study for elementary school and then high school, so there are a lot of youth there.

My mom was a teacher and my father also moved to this town to be a teacher there. It was an important part of my upbringing, that they were educators. They were very involved with the community. Everyone knew them. They were the teachers for half the city. My dad was part of the local government while he was teaching philosophy in my town. Then he taught political sciences and world history in nearby colleges. And my mom was a musician. She played the cello and later became a music and Hungarian language teacher. So she always had these theater groups for kids as an after-school activity. She also started a video and film club for kids.

So studying and learning about things was always connected to my parents. They were always very curious, and I noticed it more and more in myself—that if you didn't know something, it wasn't a problem, ever. It was always 'oh, I haven't thought about this, let's learn about it. Let's go there.' I see this mindset in myself and my brother, who became a scientist. He studied particle physics. It's something I really don't understand but it's fascinating when he talks

about it. I think curiosity is a family value that we share.

Tell us about your training.

I studied medicine in Budapest, at Semmelweis University, and I also did my PhD there. I studied mesothelioma and prognostic and predictive factors in mesothelioma. I knew early on that I wanted to be involved in patient care, and pathology looked like a great opportunity. I completed my training in pathology in Budapest, did my residency there and then applied for a Fulbright scholarship, and was the most surprised that I got it. I was so happy I could come here. It was my mom's mindset: it looks hard, let's do it. And that's how I joined the pathology department at UChicago. First, to learn about gynecologic pathology because this is a huge center and this is what I developed an interest in during residency, especially ovarian cancer. It's often challenging from a diagnostic standpoint. It also has a lot of molecular implications that I have always been interested in. How can we figure out better treatment options based on the molecular characteristics of a tumor? And then I met Ernst Lengyel, who had just started an ovarian cancer transcriptomics and spatial proteomics project, which turned out to be a good fit for my molecular biology and pathology training.

How long have you been in Chicago?

This is my fourth year. It's a lovely city. I think it's lovely in the winter, actually. In Hungary, we don't really have snow anymore. And I'm always so happy when it snows, especially when there is a warning that I'm not supposed to go outside. I can tell my lashes are freezing, but I'm outside jumping around in the snow. You have to enjoy it. I also enjoy the proximity to the lake and the nature here as much as the people.

Tell us about your work? What about it fascinates you the most?

We work on gynecologic malignancies in the lab. The common denominator is improving patient outcomes, finding new therapeutic targets, repurposing drugs or finding new indications for drugs, early detection of cancers and prognostics. Everything is really about improving patient care.

I work on one project that is about the metabolism of clear cell ovarian cancer,

which is a special subtype. Early-stage patients have a good prognosis, but once it spreads, it's very resistant to therapy. So we are trying to understand what metabolic pathways are important for the cancer cells, what the weak points are.

So that's one thing that I'm working on. And I learned a lot about metabolism in general, methods like mass spectrometry from the core facility here and also a lot of *in vitro* work that's relatively new to me. But I have all my amazing colleagues who I can talk to. Another big part of my work is in projects that use spatial technologies.

I think one that I find fascinating, and I learned a lot from, is the study that was recently published by *Nature*. My amazing colleague, Janna Heide, the first author of the study, observed that when tumors express NNMT, there is less immune cell infiltration in those tumors. And the CD8+ T cells that infiltrate the tumor are less activated and less capable of killing tumor cells. She made this observation in mouse tumors, but the big question was: is this relevant for humans? For this, we performed a big spatial transcriptomics experiment and we showed that yes, when cancer-associated fibroblasts express a lot of this protein NNMT, tumors in human ovarian cancer patients also show less activation of CD8+T cells.

It's also one of the great examples that give you hope because our lab has been working with the National Center for Advancing Translational Science at the NIH, who provide drug development expertise to labs. Our lab pitched this project to them and they developed a really good inhibitor for this protein. In preclinical models, the inhibitor slowed down tumor growth and it actually reversed this immunosuppressive phenotype that we observed. Now we have a group of people working on developing it further

and bringing it to the clinic for early-phase clinical trials.

So what fascinates me? It's this, like, wow, things actually work out and we do actually connect back to patient care. I think about that a lot.

What are your hobbies?

I'm a bit of a shy person. I think I just spend a lot of time with my friends outside of work. And I do spend a lot of time with my cats, teaching them tricks, making them happy, and just generally trying to be a good cat owner to entertain them. Apart from that, I like making art. I think I was attracted to pathology because it's very much like art: very colorful and very visual and I love it. And I am making art, trying to learn to paint with different media like watercolors or drawing

"We are discovering these new targets and developing these new tests and I worry: how is it going to be accessible to as many people as possible? How do you make people aware of what you found? Just the diagnostic tests that are required to get into a clinical trial can be challenging. How do we really connect the community that we are serving to these fascinating new discoveries?"

pictures of the city. I'm not saying I'm good at it, but I really, really like colors and visual art.

And you said you like being outdoors?

Yes, to this day I don't know how to drive. I keep saying that I'm learning, but I'm not making much progress, so I have to walk and bike around Chicago. Growing up in that small town, my family never owned cars. We always went everywhere by bike. I think the largest cargo I ever biked somewhere was like 80 pounds. And I don't like working out. But I have to be fit enough to explore as much as I can. I have to work out for this specific reason. And I have so many plans to explore the US, the national parks.

Any favorite music or favorite books? Favorite authors?

I really like this one book. I keep gifting it to all my friends. *The Fox Was Ever the Hunter*, it's written by Herta Muller, who received a Nobel Prize. She is eastern European. She was born in Romania, but the German speaking minority in Romania. And it's a very central Eastern European story. It's about being surveilled by the Romanian secret police. Yes, it's a sad story. But community actually is the most important thing is what I bring home from it. And it's just a very poetic prose.

What issues concern you the most?

We are discovering these new targets and developing these new tests and I worry: how is it going to be accessible to as many people as possible? How do you make people aware of what you found? Just the diagnostic tests that are required to get into a clinical trial can be challenging. How do we really connect the community that we are serving to these fascinating new discoveries? I really do hope that more and more people will have access to this high quality of diagnostics and care that we are working towards. Another thing is access to science. A lot of really talented, smart people just don't get into science because they don't have access to education, or they just don't know that they could do it. I think it needs representation. Access to healthcare and access to education are things that really concern me.

Clemens Hinterleitner

Postdoctoral research fellow, Ludwig MSK

Tell us a bit about yourself.

I'm currently a postdoc in Scott Lowe's lab here at MSK. I grew up in Mainz, a mid-sized town near Frankfurt in Germany. It's a pretty classic German city with a lot of history. I studied medicine at Johannes Gutenberg University in Mainz, and then moved to Tübingen to begin my specialization in hematology and oncology.

What brought you to scientific research?

I've always been curious about how things work. My mom likes to remind me that as a child I would constantly ask questions about the world around me. I was especially fascinated by the idea that different animals can communicate and even collaborate despite not sharing the same 'language.' Looking back, that curiosity about how different systems interact and synergize has been a guiding theme throughout my scientific life.

I was always really interested in biology, and I also loved physics, even though, if I'm honest, my math skills probably weren't strong enough to make a career in it. So I ended up focusing on biological questions. I applied for university and got selected for medical school in my hometown.

During med school, I joined a research lab and studied cell death mechanisms and novel treatment options in leukemia. It was the first time I worked with cells directly, learned how to culture them and analyze their behavior. That experience really shaped me and made me realize I wanted to become a hematologist and oncologist. What's unique about that particular field is how closely treatment innovations are tied to scientific discovery.

After completing my specialization in southern Germany, I decided I wanted to

return to research and focus on translational questions arising from the clinic. In 2021, I joined Scott Lowe's lab at MSK. What I really like about our lab, aside from how collaborative and fun it is, is that we work right at the intersection of basic biology and translational cancer research.

How long have you been in the US at MSK?

I started my postdoc here at MSK in November 2021. I think I was literally on the first plane from Germany to New York after the travel ban. I'd actually never been to New York before, so it was quite an adventure. It's an incredible city, and the institute is truly outstanding. One of the things I really enjoy here is how interactive the center is and how easy it is to start amazing collaborations. I also really value the close connection between the research labs and the hospital. As much as I love asking fundamental biological questions, it's a big advantage to be able to test and validate findings from mouse models in a human context.

What does your current research aim to tackle?

In my current project I study a cellular program called senescence. When cells in our body get damaged, for example during inflammation, many of them die. But some manage to survive by entering senescence. These cells stop dividing to protect themselves from further stress and damage, but at the same time, they become remarkably active in communicating with their environment. They start secreting cytokines and extracellular vesicles, effectively becoming orchestrators of their own tissue environment.

What's fascinating, and also controversial, is that this same program can have very different outcomes. On one hand, senescent cells can promote wound healing. On the other, they can drive chronic inflammation, aging, and fibrosis. So one process can be both beneficial and harmful and we still don't fully understand why.

We identified a subset of senescent cells that accumulate in fibrotic tissues and the pro-fibrotic, immunosuppressive tumor microenvironment of liver and lung tumors. We found that these cells actually help tumor cells to evade the immune system. Working with Dan Heller's group here at MSK, we designed nanoparticles that can deliver drugs specifically to these cells and either eliminate them or to block their

communication. By targeting these cells, we can not only reduce fibrosis but also reprogram the immunosuppressive tumor microenvironment. Our treatment enables T cells to re-enter the tumor and attack the cancer cells. Ultimately, this treatment helps to enhance the effectiveness of immunotherapy in liver and lung cancer.

Any hobbies outside of work?

Besides the lab, I like to work out and spend time with my friends in New York. The city is full of things to discover every day. Also, as a good German, I love to discover new microbreweries. And honestly, if it's a rainy afternoon, I also like to watch documentaries.

Do you have a favorite brewery?

I like Fifth Hammer and Rockaway Brewery in Long Island City. They also have live music there on summer weekends.

Your favorite music?

I was thinking about this. I grew up with Metallica, Red Hot Chili Peppers and Green Day. These are the bands I grew up with and it never changed.

Favorite author or favorite book, if you have one.

I really like Stephen Hawkings' *The Universe in a Nutshell*. It gives unique new perspectives.

"I also really value the close connection between the research labs and the hospital. As much as I love asking fundamental biological questions, it's a big advantage to be able to test and validate findings from mouse models in a human context."