

Ludwig Link

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Welcome



Unmesh Kher
Editorial Director

It is with great pleasure that we bring you the Fall 2023 issue of Ludwig Link. This is not only because we get to showcase Ludwig research, and the talent behind it, but because it's a privilege to represent an organization with such an abundance of both.

That abundance accounts for a Research news section brimming with exquisite science. You'll discover in here, for example, that the ratio of two proteins expressed by certain tumor-associated immune cells can serve as a proxy for whether the tumor microenvironment tilts toward supporting cancer growth or activating anti-cancer immunity, evincing a surprising coordination of gene expression programs across cell types within tumors. You will learn that estrogen not only fuels cancers but can induce genomic rearrangements to initiate malignant transformation, that a class of otherwise humdrum blood pressure medications can induce potent anti-tumor immune responses—and a great deal more.

We also, sadly, share news of the death of Mike Waterfield, who was director of the former Ludwig Branch at University College London, whose work on PI3 kinase and its role in cancer led to the launch of Ludwig's first startup company. We offer our condolences to his family and friends and remember him with gratitude for his many contributions to cancer research.

Our Q&A in this issue is with Ludwig Oxford's Richard White, who spoke with us about his fascinating work with zebrafish and equally interesting life. And, of course, we also have the usual news of awards, promotions and honors earned by Ludwig researchers. In our "Ask a scientist" section, researchers from across the global Ludwig community share their insights on what we can do to help build public support for scientific research.

We hope you enjoy this issue of the Ludwig Link as much as we enjoyed preparing it.

Sincerely,

Unmesh Kher
Editorial Director

On the cover

Researchers led by Ludwig Lausanne's Mikaël Pittet reported in *Science* that tumor-associated macrophages (TAMs) that express high levels of CXCL9 (magenta) are poised to attack cancer cells, while those expressing high levels of the gene SPP1 (pale blue) are in a state supportive of tumor growth. Intriguingly, when the ratio of CXCL9 to SPP1 (or CS) is high in TAMs, gene expression programs in other cells in the tumor microenvironment indicate a similarly anti-tumor slant—and vice versa—across multiple types of tumors. Patients with high CS also tend to have better prognoses. CS could, with further assessment, prove to be a useful prognostic marker. Image by the Pittet lab.

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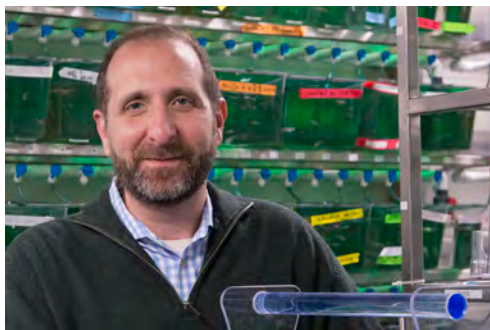
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Given the influence public opinion has on science funding and policy decisions, what can we—as individuals and as a community—do to build public support for scientific research?

Ludwig Oxford's Yang Shi elected to the U.K. Academy of Medical Sciences

Yang Shi, a Member of the Oxford Branch of the Ludwig Institute for Cancer Research, was elected in May to the U.K. Academy of Medical Sciences. Election as a Fellow is primarily reserved for scientists who, the Academy says, have made "exceptional contributions to the medical sciences, either in the form of original discovery or of sustained contributions to scholarship." Yang was recognized for his outsize contributions to epigenetics, which explores the chemical modifications made to DNA and its histone protein packaging in the cell's nucleus. These modifications help regulate the expression

of the genome and are broadly disordered in cancer. Most notably, Yang's discovery in 2004 of an enzyme, LSD1, that erases methyl marks from histones upended a 40-year-old dogma that considered histone methylation irreversible, challenging long-standing models of genomic regulation. His lab went on to identify several other histone demethylases and described their roles in an array of biological processes. Yang's findings are today being translated into new approaches to cancer therapy, including strategies to improve the efficacy of immunotherapy.



Yang Shi

Ludwig Lausanne's Douglas Hanahan elected Foreign Member of the Royal Society

In May, Ludwig Lausanne's Douglas Hanahan was elected a Foreign Member of the Royal Society, a storied fellowship of eminent scientists, engineers and technologists in the U.K. and Commonwealth whose mission is to "recognize, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity." In honoring Doug, the Royal Society recognized a body of work that has profoundly influenced cancer research and new approaches to cancer diagnosis and treatment. While still a young scientist at Cold Spring Harbor Laboratory in New York in the 1980s, Doug created one of the

first mouse models engineered to develop cancers in specific organs. He has since used his models to examine the stages of cancer progression, the role cancer genes play in that process and the immune system's interplay with the growing tumor. Doug is also noted for his authorship, with Ludwig MIT Co-director Robert Weinberg, of *The Hallmarks of Cancer*, which established an unprecedented conceptual framework for understanding the cellular and molecular underpinnings of cancer. He is the third scientist affiliated with the Ludwig Institute to be elected to the Royal Society, which counts among its Fellows and Foreign Members some 85 Nobel Laureates.



Douglas Hanahan

A new Leadership Fellow at Ludwig Oxford

Ludwig Cancer Research extended a warm welcome in August to Marketa Tomkova, who joined the Ludwig Oxford Branch as a Leadership Fellow. Marketa joins us from the University of California, Davis, where she was a postdoctoral researcher working jointly in the labs of David Segal and Fereydoon Hormozdiari. She is leading her first independent research program at Ludwig Oxford, focused on computational cancer genomics. After training in computer science, Marketa became interested in applying her expertise to important questions in biology and medicine. Marketa has secured funding from the Wellcome Trust and Cancer Research UK to investigate the role of DNA polymerase errors in mutational

processes and continue her development of sequencing-based tools for the detection of non-clonal mutations, mismatched base pairs and DNA damage in single molecules. Her work at Ludwig Oxford is at the interface of technological development, epigenomics and mutagenesis, and she will collaborate closely with other groups to develop computational methods to better analyze sequencing data and investigate the role of RNA modifications in cancer initiation and progression. Marketa will also apply cancer genomics, deep learning and interdisciplinary approaches to study how various DNA polymerases contribute to distinct mutational processes and develop methods to detect new drivers of cancer.

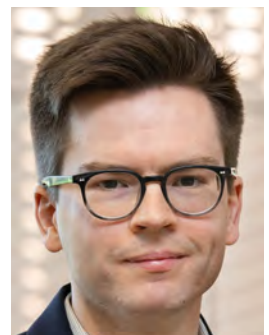


Marketa Tomkova

Ludwig Princeton's first faculty hire

Computational biologist Michael Skinnider joined Ludwig Princeton in September—the first faculty hire of the Branch. Mike joins the Branch as an assistant member. He has also been named assistant professor at Princeton University and holds a joint appointment with the Lewis-Sigler Institute for Integrative Genomics. Mike, who completed his MD-PhD at the University of British Columbia just this year, will use machine learning and other computational methods to explore the biology and chemistry of the countless small molecules found in the body that are generated by metabolic processes or introduced from the environment. He is particularly interested in developing methods to identify every one of

these molecules—known as the “dark matter of the metabolome”—and studying how they’re linked to the genetic background and the microbiome in ways that influence cancer risk, initiation and progression. These interests are an excellent fit for the Ludwig Princeton Branch, which focuses on cancer metabolism and its manipulation for cancer therapy. Mike received the International Birnstiel Award in 2022, the same year he was named to the “Forbes 30 Under 30” list for his development of algorithms that uncovered a novel antibiotic and, separately, others now used by police to identify “designer drugs”. Both awards, of course, recognize young researchers of exceptional promise.



Michael Skinnider



IN MEMORIAM

Michael Waterfield, 1941–2023


Mike Waterfield, former director of the Ludwig Institute for Cancer Research at University College London, died on May 11, 2023, at the age of 81. A preternaturally gifted scientist, Mike made seminal discoveries in the early 1980s on the regulation of cell growth and its relationship to cancer, showing—most notably—that the ErbB oncogene is the retroviral counterpart to the epidermal growth factor receptor. Later, as Director of Ludwig's UCL Branch, he authored an extensive body of research on PI3 kinase and its targeting for the treatment of cancer. Six cancer drugs aimed at the growth-regulating enzyme are today in use around the world. Mike earned his PhD at King's College and moved to the U.S. in 1967 for his postdoctoral studies, first at Harvard University and then at the California Institute of Technology, where his work contributed to dramatic advancements in protein sequencing technologies. He returned to the U.K. in 1972, recruited to the Imperial Cancer Research Fund Laboratories, which he left in 1986, when he established Ludwig's UCL Branch. His work on PI3K led to the launch of Ludwig's first startup company, Piramed, which the drug giant Roche acquired in 2008. That same year, Mike wound down his lab—and an exemplary life of science—to enjoy retirement. He is survived by his wife Sally and daughters, Lucy and Rosie.

Ludwig Oxford labs earned a Silver rating for sustainability

Ludwig Oxford was awarded a Silver certificate by the Laboratory Efficiency Assessment Framework (LEAF) for its adherence to practices that reduce the environmental impact of laboratory research. A program launched by University College London, LEAF allows administrators to identify and track sustainability targets tailored to the specific needs and structures of their laboratories. Its guidelines and standards were developed over two years and across 23 institutions around the U.K. and Ireland. Since its recommendations were created in collaboration with labs, they are not only environmentally friendly but amenable to safety standards as well. They can also deliver modest cost-savings, according to LEAF, which notes that labs are estimated to account for "2% of global plastic waste and use three to ten times more energy per square meter than a typical office." Ludwig Oxford's implementation of LEAF—which was led by Lab Manager Stan Ng and supported by students and staff across the Branch—was given the second highest rating issued by the program for steps it took to reduce carbon emissions and waste. This included such measures as reducing single-use plastics and ensuring that fume cupboard sashes remain closed when not in active use. Stan can recertify annually with LEAF to maintain Ludwig Oxford's Silver rating.

A chemical modification makes MITF switch genomic targets

The microphthalmia-associated transcription factor (MITF) is the master regulator of pigment cell, or melanocyte, development. As a lineage survival oncogene, it plays a crucial role in the skin cancer melanoma and its resistance to therapy. How MITF distinguishes between its seemingly incompatible differentiation and proliferation-associated targets in the genome has been a bit of a puzzle. Ludwig Oxford's Pakavarin Louphrasitthiphol, Colin Goding and colleagues discovered that the ability of MITF to bind DNA is inhibited by CBP/p300-mediated acetylation of its lysine residue 206, which preferentially directs MITF binding away from DNA elements involved in differentiation. This may explain why a mutation of that residue—K206Q—is associated with Waardenburg syndrome, a congenital disorder often characterized by defects in pigmentation of hair, skin and eyes. Reported in a September issue of *Nature Communications*, the findings also reveal that more than 40% of MITF molecules are tightly bound to DNA, with residence times of over 100 seconds—compared to just a handful of seconds for most transcription factors. This makes MITF comparable to transcriptional repressor CTCF and polycomb repressive complex 1 (PRC1) and suggests that it might play similar roles in the establishment and maintenance of chromatin organization specific to the melanocyte lineage.

 **Acetylation reprograms MITF target selectivity and residence time** | *Nature Communications*, 2023 September 28



Pakavarin
Louphrasitthiphol




Colin Goding



Johanna Joyce

A searching analysis of TANs yields clues to improving brain tumor therapy

A team led by Ludwig Lausanne's Johanna Joyce and Roeltje Maas, a former MD-PhD student in her laboratory, detailed in a September paper in *Cell* the findings of an integrated, multifactorial analysis of neutrophils in more than 190 brain tumor samples from patients and experiments in mouse models of brain cancer. They reported multiple ways in which neutrophil phenotypes—or physical traits and functional states—differ from that of their counterparts in the circulation and in healthy brain tissues. Johanna, Roeltje and colleagues found that tumor-associated neutrophils (TANs) are more abundant in brain metastases from the lungs, breast and skin than in primary gliomas and tend to cluster around malformed blood vessels in tumors. TANs switch off gene expression programs that induce cell death while turning on genes that support cell survival—thus lengthening their lifespans. They churn out factors that stimulate the formation of blood vessels, become functionally suppressed—halting production of the reactive oxygen species they use to destroy cellular targets—and appear to actively suppress the types of T cells that target tumors. The researchers also identified specific cellular interactions and inflammatory factors in the microenvironment—TNF- α and ceruloplasmin—that are key to turning neutrophils into abettors of malignancy. The findings suggest new approaches to the treatment of both gliomas and brain metastases.

 **The local microenvironment drives activation of neutrophils in human brain tumors** | *Cell*, 2023 September 27



Sara Bobisse



Lana Kandalaft



Alexandre Harari



George Coukos

A duo of personalized therapies take on advanced ovarian cancer


Ludwig Lausanne's Sara Bobisse, Lana Kandalaft, Alexandre Harari and director George Coukos reported in *Nature Cancer* in September that combining adoptive T cell therapy with a personalized, dendritic cell cancer vaccine under development at the Branch can benefit patients with late-stage, drug-resistant ovarian cancer. The researchers analyzed responses to the combination therapy in patients who had previously participated in a clinical trial evaluating a regimen that included the vaccine. In this study—done, as before, in partnership with researchers at the University of Pennsylvania—those patients received an infusion of their own vaccine-primed, circulating T cells followed by multiple periodic doses of personalized vaccines. The combination vaccine-adoptive T cell therapy

(ACT), which was found to be generally safe, yielded control of the disease within three months in 12 of 17 patients. Though this was not a double-blind, placebo-controlled trial, the study recorded a median overall survival time of 14.2 months for patients who completed the regimen, compared to a median historical survival of six months or less for comparable patients receiving fourth- and fifth-line chemotherapy. The researchers also showed that T cells targeting the neoantigens were reinvigorated by the combination therapy and correlated with positive patient responses to the treatment. Further, DNA sequences encoding neoantigens targeted by the T cells were found at higher levels in circulating tumor DNA, suggesting a vaccine-directed attack against cancer cells.

 [A phase 1 trial of adoptive transfer of vaccine-primed autologous circulating T cells in ovarian cancer](#) | *Nature Cancer*, 2023 September 21

A simple metabolic tweak usefully transforms T cell identity

A study led by Ludwig Lausanne's Alison Jaccard, Ping-Chih Ho and their University of Lausanne colleagues Mathias Wenes and Pedro Romero uncovered an unexpected link between T cell metabolism, regulation of gene expression, persistence and functional efficacy that may be exploited using existing drugs to enhance cancer immunotherapy. The researchers reported in a September issue of *Nature* that CD8+ T cells, like cancer cells, employ reductive carboxylation to generate citrate—a metabolite required to make membranes—from the amino acid glutamine. But blocking this process genetically or with drugs known as IDH2 inhibitors does not compromise their effector function or proliferation. Rather, it turns them into functionally potent memory T cells. This, the researchers showed, is because it forces the T cells to activate compensatory metabolic pathways, altering the profile of metabolites in the cells and boosting some that inhibit the epigenetic enzyme KDM5. The resulting epigenetic changes open up access to genes in the T cells' chromosomes that define memory T cells, triggering their transformation. In the absence of IDH2 inhibition, those genes are kept under wraps, bolstering their typical terminally exhausted CD8+ T cell identity. The researchers demonstrated that chimeric antigen receptor (CAR) T cells cultured in the presence of IDH2 inhibitors show enhanced anti-tumor activity in mouse models of melanoma, leukemia and multiple myeloma.

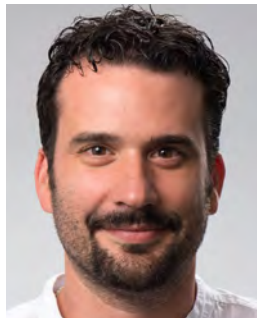
 **Reductive carboxylation epigenetically instructs T cell differentiation** | *Nature*, 2023 September 20



Alison Jaccard




Ping-Chih Ho



Grégory Verdeil

How T cell exhaustion differs between cancer and chronic viral infection

Persistent exposure to antigens renders T cells dysfunctional. The mechanisms regulating this "exhaustion" have been presumed to be common in infection and cancer. Ludwig Lausanne's Grégory Verdeil and colleagues showed in a September publication in *Nature Immunology* that this is not the case. They reported that the protein NFAT5 is highly expressed in exhausted T cells responding to both chronic infection and cancer—but only induces exhaustion in T cells in the tumor microenvironment. Grégory and his colleagues showed that overexpressing NFAT5 reduces tumor control in mouse models of cancer, while its deletion makes T cells resistant to exhaustion and improves tumor control in those models. The researchers found that the latter effect stems from an accumulation of CD8+ T cells that express relatively low levels of exhaustion-associated proteins PD-1 and TOX. A subgroup of these cells within tumors that play an important role in anti-tumor immune responses—precursor exhausted T cells—produces more of the immune factors IFN- γ and TNF, which are associated with T cell activation. The researchers also demonstrated that although NFAT5 level is high in exhausted T cells during chronic infection, it is not active in these cells and its activity is only triggered in the tumor microenvironment. Their discovery points to an approach to selectively boost anti-tumor T cell responses for cancer immunotherapy.

 **Activation of the transcription factor NFAT5 in the tumor microenvironment enforces CD8+ T cell exhaustion** | *Nature Immunology*, 2023 September 14


How oncogenic MYC disrupts the molecular clock—and much more—in cells

A study led by Ludwig Institute Scientific Director Chi Van Dang and colleagues at the University of Pennsylvania, the University of Rochester, The Wistar Institute and Johns Hopkins University described in an August paper in *PLOS Genetics* how the MYC oncogene interferes with the molecular clock in cells that governs their circadian rhythms. These are 24-hour rhythms that are woven into almost every aspect of cell biology—most notably metabolism and gene expression patterns—and are frequently disordered in cancer. Their disruption can, in fact, promote cancer initiation and progression. Using time-series RNA-sequencing and metabolomics in three distinct cancer cell lines, the researchers demonstrated that the heightened, oncogenic activation of

MYC, which is a master regulator of cell metabolism, disrupts over 85% of oscillating, clock-associated genes. The oncogene enhanced the synthesis of proteins in both mitochondria and the cytoplasm of cells, stepped up the biochemical programs that drive biosynthesis and inhibited the mechanisms that govern the cell's attachment to surfaces. It also altered the expression of proteins involved in importing nutrients, changed the balance of amino acids in cells and altered the times of day when the metabolism of amino acids and nucleic acids are at their peak. The findings suggest MYC-driven perturbations of the circadian clock release metabolic and biosynthetic processes from circadian control, potentially offering a metabolic advantage to cancer cells.



Chi Van Dang

 **MYC disrupts transcriptional and metabolic circadian oscillations in cancer and promotes enhanced biosynthesis**
PLOS Genetics, 2023
August 28


A high-res protein structure yields a blueprint for precision drug design

Researchers led by Ludwig Stanford's Christopher Garcia reported in an August publication in *Cell* the 3.4 Å resolution cryoelectron microscopy structure of the extracellular signaling complex of thrombopoietin (Tpo) with its receptor (TpoR)—an interaction essential to hematopoiesis, or the generation of the cellular components of blood. Tpo activation of TpoR is essential to hematopoietic stem cell maintenance as well as platelet production. Loss-of-function mutations in either cause thrombocytopenia—a dangerous deficiency of platelets—and bone marrow failure. Unrestrained TpoR signaling, on the other hand, drives slow-growing cancers known as

myeloproliferative neoplasms. The structure deduced by Chris and his colleagues explains how dimerization of TpoR activates its signaling and why certain mutations cause thrombocytopenia. While Tpo agonists that boost platelet production already exist, they bring with them a risk of excessive blood stem cell proliferation, bone marrow fibrosis and an increased incidence of thrombosis. Notably, Chris and his colleagues used their protein structure to design Tpo analogs ranging from antagonists to agonists of signaling that induce a spectrum of signaling activities inside the cell—including one that decouples blood stem cell proliferation and differentiation.




Christopher Garcia

 **Structure of the thrombopoietin-MPL receptor complex is a blueprint for biasing hematopoiesis** | *Cell*, 2023 August 25



Stefan Constantinescu

 **Modulation of human thrombopoietin receptor conformation uncouples JAK2 V617F-driven from cytokine-induced activation** | *Blood*, 2023 August 24


Functional analysis suggests new approach to treating subset of myeloproliferative neoplasms

Unfettered signaling by the thrombopoietin receptor (TpoR) plays a central role in the development of slow-growing cancers known as myeloproliferative neoplasms (MPNs). It can be caused by mutations of the intracellular proteins JAK2 and calreticulin or of TpoR itself, all of which activate TpoR, causing uncontrolled proliferation and differentiation of hematopoietic (blood forming) stem cells and blood progenitor cells. The V617F mutation of JAK2 is the most common driver of MPNs and drugs that target JAK2 are used for therapy, though they are not specific to the mutant protein. TpoR targeting, on the other hand, has so far been poorly explored despite its central role in MPN pathology. Researchers led by the

Ludwig Institute's Stefan Constantinescu reported in an August issue of *Blood* their characterization of human TpoR activation induced by JAK2 V617F. They found that human TpoR (hTpoR) adopts different dimeric conformations upon thrombopoietin-induced versus JAK2 V617F-mediated activation and described the one responsible for its activation in complex with JAK2 V617F. They also showed that modulation of hTpoR conformations by point mutations allows specific inhibition of JAK2 V617F-driven activation without affecting normal Tpo-induced signaling. This suggests the drug-mediated tweaking of hTpoR conformation is a viable therapeutic strategy for JAK2 V617F-positive MPNs.



Karen Cichowski

 **Cotargeting a MYC/ eIF4A-survival axis improves the efficacy of KRAS inhibitors in lung cancer** | *Journal of Clinical Investigation*, 2023 August 15

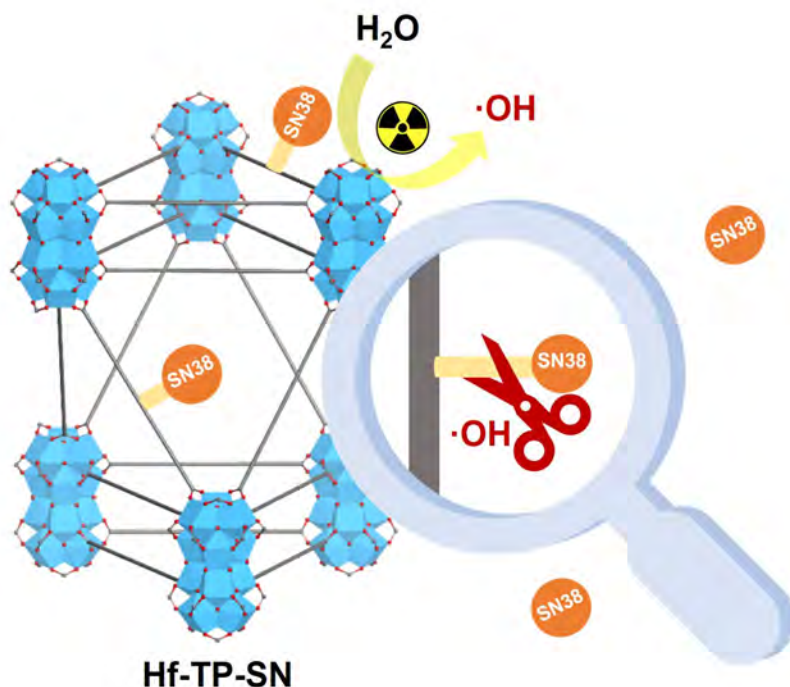
Co-targeting a cancer cell dependency may boost the efficacy of KRAS inhibitors

The eIF4F complex, which is involved in the translation of RNA transcripts into proteins, selectively enhances the expression of genes that promote tumor growth and is aberrantly activated by multiple cancer-driving signaling pathways in cells. Researchers led by Ludwig Harvard's Karen Cichowski reported in an August publication in the *Journal of Clinical Investigation* that an inhibitor of eIF4A, a key component of that complex, dramatically enhances the effects of KRAS inhibitors in non-small cell lung cancer (NSCLC). Activating mutations of KRAS occur in about a third of such cancers. Though drugs have been developed to target the most common KRAS mutation, G12C, they help fewer than half of NSCLC patients

and only do so temporarily. Karen and her team showed the combination of eIF4A and KRAS G12C inhibitors induces significant tumor regression in mouse models of NSCLC. This cooperativity, they found, is driven by the selective translational suppression of BCL-2 family proteins, which promote cancer cell survival. Further, overexpression of the MYC oncogene, common in cancer, confers sensitivity to the combination because it creates a dependency on eIF4A for expression of BCL-2 family proteins. The researchers also showed that eIF4A inhibition similarly cooperates with MEK inhibitors, suggesting an alternative strategy to treat lung cancers that harbor other kinds of activating KRAS mutations.

A targeted nanoparticle delivers a one-two punch to tumors


Nanoscale metal organic frameworks (nMOFs)—a versatile class of nanomaterials made by linking metal ions with organic molecules to create porous, crystalline structures—can be constructed to carry drugs and unload them into tumors in response to selected triggers. Ludwig Chicago's Wenbin Lin and colleagues reported in an August paper in the *Journal of the American Chemical Society* a heavy metal-based nMOF that both delivers a cancer drug and amplifies the effects of radiotherapy through the enhanced deposition of energy and generation of reactive oxygen species (ROS). The nMOF designed by Wenbin and his colleagues consists of a dozen atoms of the metal hafnium linked by organic molecules to which a prodrug of SN38 is covalently attached. Upon irradiation, the nMOF's electron-rich hafnium atoms serve as radiosensitizers, causing the generation of large quantities of hydroxyl radicals. Aside from killing cancer cells, these free radicals react with the nMOF to trigger the release of SN38—the active metabolite of the cancer drug irinotecan. This permits the targeted, synergistic treatment of tumors with radio- and chemotherapy and reduces the dosage of radiation required for effective treatment. Wenbin and his team showed that an intratumoral injection of nanoparticles followed by radiotherapy efficiently inhibits tumor growth in mouse models of colon and breast cancer.



Wenbin Lin

The nMOF designed by Ludwig Chicago's Wenbin Lin and colleagues consists of a dozen atoms of the metal hafnium linked by organic molecules to which a prodrug of SN38 is attached. Upon irradiation, the nMOF's electron-rich hafnium atoms generate a burst of hydroxyl radicals that, aside from killing cancer cells, trigger the release of SN38—the active metabolite of the cancer drug irinotecan.

Image courtesy the Lin lab

 **Nanoscale metal–organic framework with an X-ray triggerable prodrug for synergistic radiotherapy and chemotherapy** | *Journal of the American Chemical Society*, 2023 August 15

In the works: a better way to detect brain cancers



Chetan Bettegowda

The paucity of reliable, quantitative biomarkers for the diagnosis and monitoring of cancers of the central nervous system has long been a challenge in discerning nonmalignant lesions from malignant growths in the brain. Dangerous biopsies are the only definitive means of diagnosis for most such cancers. Researchers led by Ludwig Johns Hopkins' Chetan Bettegowda described in an August paper in *Cell Reports Medicine*—capped by an award-worthy pun in the headline—an analytic technique called Real-CSF (repetitive element aneuploidy sequencing in CSF) to detect cancers of the central nervous system by the evaluation of DNA in cerebrospinal fluid (CSF). The method, which involves the PCR amplification of short interspersed nuclear

elements (SINEs) using a single primer pair and evaluating the products by next-generation sequencing, assesses genome-wide copy-number alterations as well as focal amplifications of selected oncogenes. Applied to 280 CSF samples, the technique correctly identified 67% of 184 cancerous and 96% of 96 non-cancerous brain lesions using just 1 mL of each sample CSF to perform all assays. The gold standard today, cytology of CSF, has a sensitivity that ranges from 2% to 50%, depending on the type of cancer involved, and requires large amounts (10 mL) of CSF. Real-CSF plasma also proved to be more sensitive than cell-free DNA analysis in samples from the same patients.

 [Seq-ing the SINEs of central nervous system tumors in cerebrospinal fluid](#) | *Cell Reports Medicine*, 2023 August 15

Tracing the sources of cell-free DNA



Bert Vogelstein

Cell-free DNA is often elevated in the circulation of cancer patients, a phenomenon that has seeded a booming industry dedicated to the capture and analysis of the DNA shed by dead cancer cells for disease detection and the management of therapy. Yet the proportional contributions made by different cellular sources to this circulating DNA have long been unclear. To find out, a team of researchers led by Ludwig Johns Hopkins Director Bert Vogelstein assessed methylation patterns of cell-free (cf) DNA in 178 patients with cancers of the colon, pancreas, lung or ovary and 64 patients without cancer. Patterns of DNA

methylation, which regulate gene expression across the genome and so help determine the identity of any given cell, can serve as signatures of cell type and tissue of origin. Bert and his colleagues reported in an August issue of *Cancer Discovery* that the high levels of cfDNA in the blood of patients with cancer do not come from either dead cancer cells or from normal epithelial cells around tumors. Rather, immune cells, particularly neutrophils, are the leading contributors of cfDNA, accounting for some 76% of the total, irrespective of sample source. Based on these findings, the researchers suggested that cancers may have a systemic effect on cell turnover or DNA clearance.

 [The origin of highly elevated cell-free DNA in healthy individuals and patients with pancreatic, colorectal, lung, or ovarian cancer](#) | *Cancer Discovery*, 2023 August 11


How a neurotransmitter helps initiate melanoma

While the BRAF protein is mutated in about half of all melanomas, not all BRAF-mutant melanocytes become malignant. Researchers led by Ludwig Oxford's Richard White explored whether communication between mutant melanocytes and the surrounding microenvironment determines whether BRAF causes melanoma. Focusing on a type of cell in the microenvironment called a keratinocyte, they used zebrafish and human cells to study this problem. They discovered that the binding of the neurotransmitter GABA secreted by BRAF-mutated melanocytes to the GABA receptor on keratinocytes is essential to the initiation of melanoma and reported in an August paper in *Cancer Discovery* that this interaction occurs exclusively between keratinocytes

and melanocytes that are in direct contact with one another. GABA, which inhibits the electrical activity of neurons, had a similar effect on keratinocytes in culture. It also boosted their secretion of a protein, LIF, that promotes the cancer and increased the growth of those melanocytes. Genetic and pharmacological disruption of GABA production, which was found to be stepped up in melanoma cells, blocked cancer initiation in animal models. The study lends support to the hypothesis of oncogenic competence that Richard has been developing, which proposes that oncogenes can only drive cancers in particular cellular contexts. This work suggests interrupting GABA may be a way to prevent melanoma development in patients.



Richard White

 **GABA regulates electrical activity and tumor initiation in melanoma** | *Cancer Discovery*, 2023 August 9

The KRAS oncogene generates a stem cell to spawn an indolent lung cancer

Ludwig Stanford's Tushar Desai and colleagues identified in mouse models a new cell of origin for lung adenocarcinoma: the AT1 cell, which was not thought to be able to initiate lung cancers because it is not a stem cell. The AT1 cell, they showed, generates tumors that resemble lepidic cancer, a slow-growing malignancy that spreads along alveolar walls. Tushar's lab has previously shown that aggressive lung adenocarcinomas are initiated by transformed AT2 cells, which are stem cells. He and his colleagues found that oncogenic KRASG12D—which is known to drive aggressive lung cancers, among other malignancies—reprograms

AT1 cells into their parent AT2 stem cells. It is these reprogrammed cells that then go on to seed cancer. The tumors they form grow slowly, however, unlike the aggressive adenocarcinomas generated by AT2 cells. The latter are often driven by the signaling protein WNT. But in AT1-derived cancer, Tushar and his colleagues found, WNT activation has antitumor effects. This has significant implications for the personalization of lung cancer therapy, since the WNT pathway is considered a prime target for cancer therapies. In AT-1 derived cancers, however, its blockade might prove counterproductive.




Tushar Desai

 **KRAS(G12D) drives lepidic adenocarcinoma through stem-cell reprogramming** | *Nature*, 2023 July 19



Mikaël Pittet

 **CXCL9:SPP1**
macrophage polarity
identifies a network
of cellular programs
that control human
cancers | *Science*,
2023 August 3


Gene expression is surprisingly coordinated across the tumor microenvironment

To examine how much the tumor microenvironment (TME) varies between tumors, researchers led by Ludwig Lausanne's Mikaël Pittet conducted an unbiased analysis of 52 primary and metastatic tumors from 51 patients with head and neck cancers, examining how global gene expression captured in individual cells but statistically analyzed across tumors as a whole corresponds to patient outcomes. They reported in an August paper in *Science* that patients with higher expression of the gene CXCL9 in their tumor-associated macrophages (TAMs) had far better clinical outcomes than those with higher expression of a gene named SPP1 by the immune cells.

TAMs expressing the former gene, they showed, are invariably poised to attack cancer cells, while those expressing SPP1 are in a state supportive of tumor growth. Most intriguing, however, was their discovery that when the ratio of CXCL9 to SPP1 is high in TAMs, gene expression programs in other TME cells indicate a similarly anti-tumor slant; a low ratio of the two (termed CS), on the other hand, invariably accompanies pro-tumor gene expression signatures across other cell types in the TME. With further validation in prospective studies, Mikaël and his colleagues noted, the CS ratio could prove to be an easily measured molecular marker of patient prognosis for the management of therapy.



Sean Pitroda

 **Integrated**
clinical-molecular
classification of
colorectal liver
metastases | *JAMA*
Oncology, 2023 July
20.

Molecular markers predict outcomes for patients with liver metastases of colorectal cancer

Researchers led by Ludwig Chicago's Sean Pitroda reported in *JAMA Oncology* in July a method to accurately predict which patients with limited metastases—or oligometastases—of colorectal cancer are likely to have a favorable outcome following surgical removal of tumors that spread to the liver. The findings could help improve the personalization of colorectal cancer therapy. The study built on previous research led by Sean and Ralph Weichselbaum, co-director of Ludwig Chicago, who in 2018 reported unique molecular patterns that identified patients with a subtype of colorectal liver metastases that was associated with robust 10-year survival rates after surgery. Both that and the most recent study were broadly

based on a hypothesis proposed in 1995 by Ralph and Samuel Hellman—a former board member of the Ludwig Institute for Cancer Research—that cancer metastases exist on a continuum and that those that are relatively limited could be cured with localized treatment. Sean and his colleagues devised an artificial intelligence neural network classifier that predicted the molecular subtype of the disease with 96% accuracy and validated this classifier on a cohort of 147 patients with limited liver metastases who were treated with chemotherapy and surgery in a randomized clinical trial in the U.K. Their classification, combined with clinical features like tumor size, predicted treatment outcomes in patients with high fidelity.

A novel mechanism for evolution of drug resistance in lung cancers

Researchers led by Ludwig Harvard's Aaron Hata and Hideko Isozaki explored the mechanisms that drive resistance to targeted therapies like tyrosine kinase inhibitors in lung cancer. They reported in *Nature* in July that, based on their analysis of drug-resistant cell lines and patient tumor samples, treatment with common targeted therapies induces expression of a cytidine deaminase enzyme, APOBEC3A (A3A), that drives sustained mutagenesis in drug-tolerant cancer cells that persist during therapy. The APOBEC family has been implicated in tumor evolution, but it was unclear how its members contribute to the phenomenon. Aaron, Hideko and colleagues showed that A3A activity not only induces mutations known to be involved in drug resistance—like those of the ALK gene—but also promotes double stranded breaks to DNA, causing genomic instability in persister cells. This accelerates their accumulation of mutations, fueling tumor evolution. In support of that hypothesis, deletion of A3A resulted in a reduction of mutations in persister cells and a delay in the development of drug resistance. Further, tumor samples from lung cancer patients who responded to therapy for relatively long periods before developing drug resistance harbored mutational signatures associated with APOBEC activity. The researchers suggest that suppression of A3A expression or activity could be a powerful strategy for delaying or overcoming lung cancer resistance to therapy.

 **Therapy-induced APOBEC3A drives evolution of persistent cancer cells** | *Nature*, 2023 July 5



Aaron Hata



Hideko Isozaki



Xin Lu

Tumor monocytes take a star turn in immunochemotherapy for esophageal cancer

Researchers led by Ludwig Oxford Director Xin Lu and alumnus Thomas Carroll reported in *Cancer Cell* in July that a relatively high number of monocytes in tumors is linked to better outcomes in esophageal cancer patients treated with a combination of chemotherapy and immunotherapy. Further, they found that combining measurements of tumor mutational burden along with monocyte content (TMC) better predicts treatment response than either measurement alone. The study also uncovered a novel T cell inflammation signature that could serve as a general indicator of potential responsiveness to immunotherapy. Xin, Thomas and their colleagues analyzed samples from a clinical trial launched in 2015 by Ludwig Oxford, in which 35 patients with inoperable esophageal adenocarcinoma received four weeks of immune checkpoint blockade therapy alone before undergoing 18 weeks of combination immunochemotherapy. The researchers performed single cell RNA sequencing (scRNA-seq) on 65,000 cells from a subset of the clinical trial patients to generate a detailed cellular atlas of all the cell types of the upper gastrointestinal tract. Biopsies from all patients underwent bulk RNA sequencing. The team used computational methods—deconvolution algorithms—to analyze both datasets to determine the proportion of different cell types in each biopsy. The researchers additionally confirmed that the link between high TMC and improved outcomes also holds for the most common forms of gastric cancer.

 **Tumor monocyte content predicts immunochemotherapy outcomes in esophageal adenocarcinoma** | *Cancer Cell*, 2023 July 10

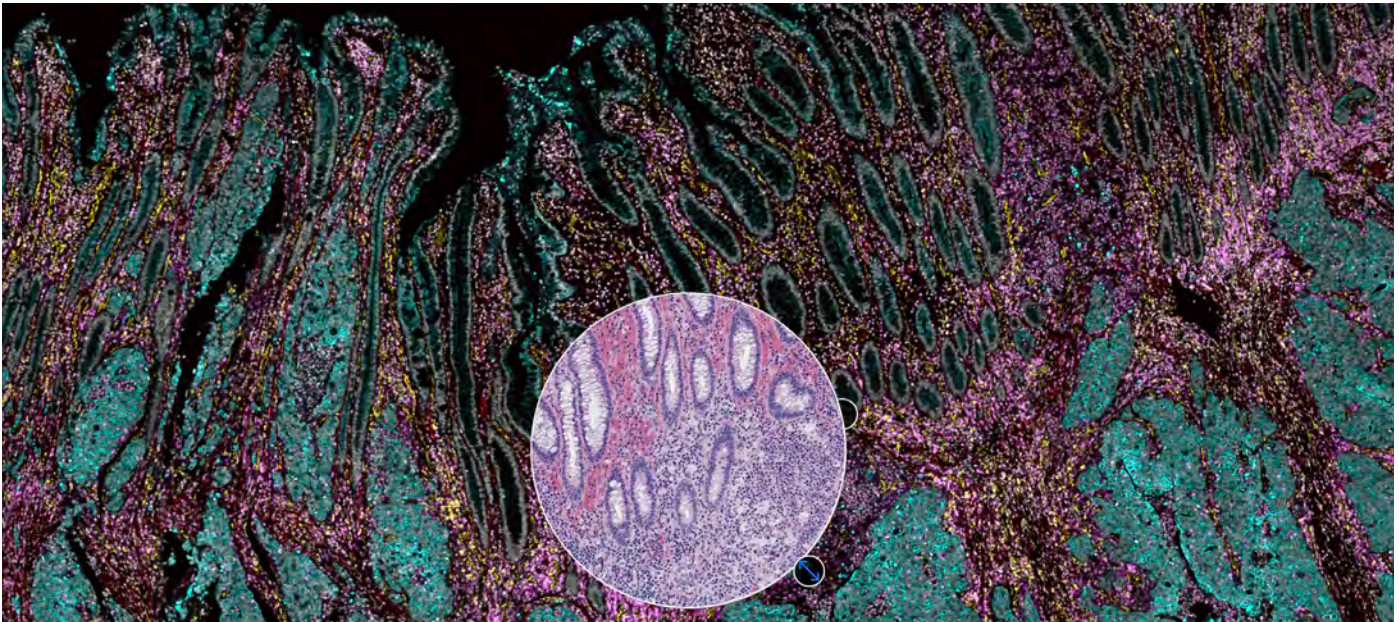


Image courtesy Santagata and Sorger labs

Image of a tumor border, showing normal colorectal mucosa (top center) with circular cross-sections of intestinal crypts, surrounded by tumor tissue (bright cyan). Blood vessels (yellow), DNA (white), immune cells (magenta) and smooth muscle (red) are visible too. The highlighted circle is the same tissue stained with conventional H&E, showing clusters of budding tumor cells adjacent to the normal mucosa.

Bridging the parallel worlds of multiplex imaging and H&E microscopy



Sandro Santagata



Peter Sorger



Jia-Ren Lin



Yu-An Chen

Researchers led by Ludwig Harvard's Sandro Santagata, Peter Sorger, Jia-Ren Lin and Yu-An Chen described in a June *Nature Cancer* paper a platform technology that enables integration of the methods used in surgical pathology—the examination of hematoxylin and eosin (H&E) stained slides—with emerging research methods in multiplexed tissue imaging for visualization of multiple molecular markers in individual cells. The new platform, Orion, allowed both human experts and artificial intelligence algorithms to identify cellular and molecular features that predict progression-free survival of colorectal cancer (CRC) patients. Analyzing cancer specimens from 40 CRC patients, the researchers sifted through some 15,000 combinations of biomarkers to identify those most tightly linked to patient prognosis. They then applied them to samples from an additional cohort of CRC patients whose outcomes were known. Their biomarkers accurately predicted—just a one in 20 chance of being wrong—the likelihood of poor prognosis. The approach revealed interesting relationships between the molecular markers, cell morphology and tumor topography. One such finding indicated that inflammation—or immune activity—at the rim of the tumor is of pathological significance, while another revealed the molecular basis of a tissue morphology associated with a likelihood of metastasis.



[High-plex immunofluorescence imaging and traditional histology of the same tissue section for discovering image-based biomarkers](#) | *Nature Cancer*, 2023 June 22

Common blood pressure drugs stimulate anti-tumor immune responses

Researchers led by the Ludwig Institute's Benoit Van den Eynde and Jingjing Zhu reported in a June paper in *Nature* that existing anti-hypertensive drugs known as α 2-adrenergic receptor (α 2AR) agonists induce potent anti-tumor immune responses, even when they are used as monotherapies, in immunocompetent mouse models of multiple cancers. Those effects were absent in immunodeficient mouse models. They were also countered by compounds that block α 2AR and significantly amplified when the agonists were combined with immunotherapy. Jingjing, Benoit and colleagues showed that the anti-tumor effects of the α 2AR agonists depend on helper and killer T cells as well as macrophages, which can engulf pathogens and cancerous cells and stimulate protective T cell responses. Gene expression analysis of both cell types revealed signs of their functional activation in treated mice. Other studies established that the drugs act directly on macrophages, not cancer cells. Tumors treated with α 2AR agonists showed signs of an influx of T cells and a depletion of a class of immune cells, myeloid-derived suppressor cells, that frequently gather in tumors and inhibit antitumor immune responses. The effect of the drugs extended, notably, to cancer models that have long proved resistant to standard immunotherapies.

 **Tumour immune rejection triggered by activation of α 2-adrenergic receptors** | *Nature*, 2023 June 7



Benoit Van den Eynde



Jingjing Zhu



Alexandre Harari


Why neoantigen-specific T cells are better at targeting tumors

Researchers led by Ludwig Lausanne's Alexandre Harari reported in *Nature Communications* in June their exploration of why T cells that target neoantigens, which are generated by random mutations in cancer cells, are typically associated with better anti-tumor T cell responses. Alexandre and his colleagues profiled the biophysical and chemical properties of the T cell receptors (TCRs) of a large library of CD8+ T cells isolated from tumors and the blood stream of cancer patients, including those specific to cancer antigens, viral antigens and neoantigens. They discovered that neoantigen-targeting TCRs tend to have greater structural and functional avidity than those that target other types of cancer antigens; that is, they are both more sensitive in detecting and persistent in binding target antigens presented to them in complex with MHC molecules. T cells endowed with such TCRs tend to express a gene, CXCR3, associated with T cell homing and are far more likely to find and take up residence in tumors after adoptive cell therapy. The researchers also identified specific structural and chemical properties shared by high-avidity TCRs and applied these insights to develop and validate—using T cells isolated from tumors—a computational model to predict TCR avidity. Their findings provide a rational method for the selection of T cells to improve personalized immunotherapies.

 **Neoantigen-specific CD8 T cells with high structural avidity preferentially reside in and eliminate tumors** | *Nature Communications*, 2023 June 6



Constantine Mitsiades

 **Genome-scale functional genomics identify genes preferentially essential for multiple myeloma cells compared to other neoplasias** | *Nature Cancer*, 2023 May 26


Functional genomics approach finds scores of drug targets for multiple myeloma

Researchers led by Ludwig Harvard's Constantine Mitsiades used CRISPR genome editing to explore the distinct molecular dependencies of cells that give rise to the incurable plasma cell cancer multiple myeloma (MM) in the hope of finding targetable vulnerabilities that are specific to this cancer. They reported in a *Nature Cancer* paper in May their characterization of the molecular dependencies specific to the lineage of cells that gives rise to MM as compared to those of hundreds of non-MM cell lines. Constantine and his colleagues identified 116 genes—some known to be linked to the plasma cell cancer, many others not—that more significantly

support the fitness of MM cells than that of other cancers. Most are not among the top amplified, overexpressed or mutated in MM, and they include genes that encode proteins that regulate gene expression, such as transcription factors and chromatin modifiers, components of the endoplasmic reticulum—a cellular organelle involved in the processing and chemical modification of newly made proteins—regulators of cellular metabolism and signaling molecules. Their functional genomics approach, the authors noted, identified several potential drug targets that might not have been noticed via typical genomic, transcriptional or epigenetic profiling analyses.



Peter Park

 **ER α -associated translocations underlie oncogene amplifications in breast cancer** | *Nature*, 2023 May 17

Not just a fuel for growth: Estrogen drives oncogene amplifications in breast cancer

Researchers led by Ludwig Harvard's Peter Park and alumnus Jake June-Koo Lee reported in a May publication in *Nature* the molecular origins of certain types of breast cancer whose root genomic causes were a mystery. Their findings suggest that estrogen is not just a potential propellant of breast cancer growth, as was thought to be the general case, but may also serve as an initiator of malignant transformation in as many as a third of all breast malignancies. Through their analysis of 780 breast cancer genomes, Peter, Jake and colleagues discovered that the hormone's activation of its receptor (ER α) can lead to focal amplifications of oncogenes through a newly identified mechanism they call translocation-

bridge amplification. Their model holds that ER α binding to its target DNA sequences can induce DNA breaks, and that those breaks are sometimes repaired by the gluing together of two different chromosomes. The generation of these interchromosomal translocations triggers a cascade of events during cell division that—via the shattering of the abnormal chromosomes and the circularization of the resulting fragments into extrachromosomal DNAs—culminates in the focal amplification of oncogenes. The novel mechanism of genomic rearrangement they describe, and experimentally validate, explains the observed amplification of some key breast cancer oncogenes, including ERBB2 and CCND1.

Blocking an RNA-targeting protein could enhance responses to radiotherapy

A study co-led by Ludwig Chicago's Liangliang Wang, Hua Laura Liang, Chuan He and Director Ralph Weichselbaum showed that inhibiting a key protein expressed by immune cells that suppress antitumor immune responses may help overcome resistance to radiotherapy and boost antitumor immunity. The researchers reported in a May publication in *Cancer Cell* that ionizing radiation induces the expansion of myeloid derived suppressor cells (MDSCs) and their expression of YTHDF2 (or Y2) in both mouse models and cancer patients. Y2 expression in MDSCs, they showed, correlates with poor outcomes for patients and even seemed to promote metastasis of tumors at sites distant from the irradiation, a phenomenon that has been observed in patients undergoing radiotherapy. Its depletion or pharmacological inhibition, meanwhile, boosted the therapeutic effects of ionizing radiation in mouse models of cancer. The Ludwig Chicago team demonstrated that Y2 depletion enhances anti-tumor immunity induced by IR by altering the generation of MDSCs and their infiltration into tumors and inhibiting their immunosuppressive function. The expression of Y2, they found, relies on NF- κ B signaling and Y2 in turn activates NF- κ B by binding and degrading RNA transcripts encoding proteins that inhibit NF- κ B signaling, which activates Y2 transcription. The study also demonstrated that combining Y2 inhibition and RT with immunotherapy further improves outcomes. The strategy, notably, prevented progression of metastasis at distant sites.



Liangliang Wang



Hua Laura Liang



Chuan He




Ralph Weichselbaum

 **YTHDF2 inhibition potentiates radiotherapy antitumor efficacy** | *Cancer Cell*, 2023 May 25

Precursor cells of a rare leukemia tour the body to become malignant

Researchers led by Ludwig Harvard's Andrew Lane and Peter van Galen and a couple of colleagues at the Broad Institute of MIT and Harvard reported in a June publication in *Nature* their analysis of the development of a leukemia that typically presents as malignant cells isolated in the skin. Sophisticated genetic and single-cell gene-expression analysis revealed that the cancer—blastic plasmacytoid dendritic cell neoplasm (BPDCN)—stems from premalignant precursors of blood cells in the bone marrow. The researchers noted that the skin tumors of BPDCN tend to show up first in places that are exposed to sunlight and bear mutations associated with UV irradiation. The UV-damage to precursor cells, however, occurs prior to the acquisition of mutations that induce malignancy. Andrew, Peter and their colleagues also captured how the precursor cells of this cancer travel between tissues to develop into a full blown malignancy. Their model proposes that precursor bone marrow cells of the cancer first accumulate mutations but largely behave normally (known as clonal hematopoiesis). Next, at least one of those cells travels to the skin and acquires more mutations from UV light. This cell subsequently acquires additional mutations to transform into a leukemic cell. The researchers also show that mutations to the Tet2 gene—found in 80% of BPDCN patients—support cell survival following exposure to UV light.

 **Ultraviolet radiation shapes dendritic cell leukemia transformation in the skin** | *Nature*, 2023 June 7



Andrew Lane




Peter van Galen



Liron Bar-Peled


A cellular sensor of reactive oxygen species and its role in drug resistance

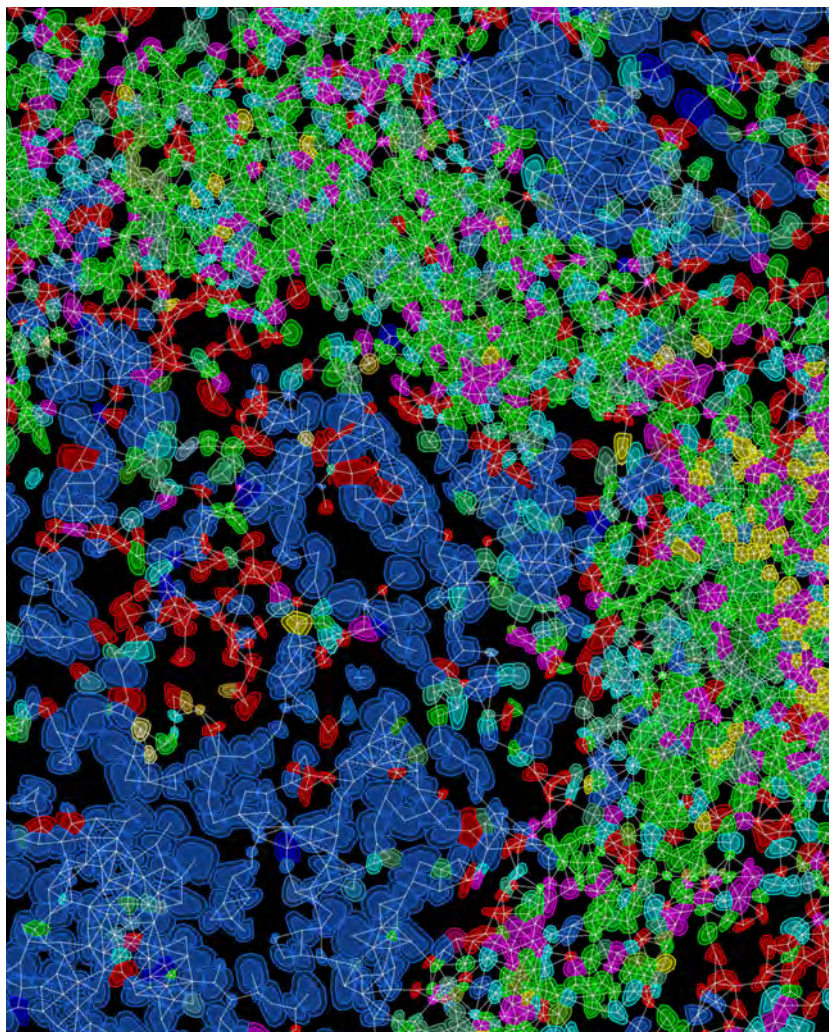
Many chemotherapies kill cancer cells by generating reactive oxygen species (ROS), but the proteins these unstable molecules modify, how those modifications affect cells and the roles the modified proteins play in sensitivity or resistance to therapy are not well understood. To address some of these unknowns, researchers led by Ludwig Harvard's Liron Bar-Peled explored the targets of 11 anticancer drugs using proteomics and CRISPR-based functional genomics methods. They reported in a May issue of *Cell* evidence of common mechanisms by which ROS-generating drugs target ribosomal proteins to regulate protein translation. Liron and his colleagues focused on a protein named CHK1, inhibitors of which are in clinical development, showing that it is a nuclear hydrogen peroxide (H₂O₂) sensor that dampens ROS indirectly through the regulation of mitochondrial translation. They found that H₂O₂ modifies a conserved cysteine within CHK1, causing a structural change that activates its enzymatic activity. Thus activated, CHK1 phosphorylates the mitochondrial single-stranded DNA-binding protein SSBP1, preventing its localization to mitochondria, which in turn leads to the reduction of H₂O₂ levels in the nucleus. They also showed that this druggable nucleus-to-mitochondria ROS-sensing pathway mediates resistance to platinum-based agents in ovarian cancer models and correlates with shorter time to platinum resistance in patients.

 **Systematic identification of anticancer drug targets reveals a nucleus-to-mitochondria ROS-sensing pathway** | *Cell*, 2023 May 15

Potently anti-tumor T cells gather in subset of lung-to-brain metastases

Among brain cancer patients, responses to checkpoint blockade immunotherapies are more commonly associated with brain metastases than with primary brain tumors, like gliomas. To explore the immunology underlying this variability, researchers led by Ludwig Lausanne's Johanna Joyce and former PhD student Vladimir Wischnewski conducted a comprehensive, integrated analysis on a single cell and bulk population level of circulating and tumor-infiltrating T cells from 84 individuals with primary brain tumors and brain metastases, and 44 others with primary lung and breast tumors. They reported in a *Nature Cancer* paper in May that a subgroup of patients with brain metastases (mostly from the lung), but not gliomas, had significant infiltration of potentially anti-cancer T cells in their tumors. Infiltrating T cells expressed CXCL13 and CD39, proteins that are associated with response to immunotherapy. These potentially reactive anti-tumor T cells accumulated in the brain tumors of these individuals in numbers comparable to those seen in primary lung malignancies. All other brain tumors, meanwhile, had low levels of these cells, similar to those seen in primary breast tumors. The findings show that T cell infiltration does occur in some brain metastases and suggest the phenomenon could be exploited for patient stratification in the management of therapy for brain cancers.

 **Phenotypic diversity of T cells in human primary and metastatic brain tumors revealed by multiomic interrogation** | *Nature Cancer*, 2023 May 22




Johanna Joyce

The image-based quantification above depicts the ability of potentially tumor-reactive T cells to infiltrate the tumor nests in brain metastasis, compared with other T cell populations that remain in perivascular niches.

Image by Paola Guerrero Aruffo, Vladimir Wischnewski and Johanna Joyce, University of Lausanne, Switzerland.



Tyler Jacks

 **A prime editor mouse to model a broad spectrum of somatic mutations in vivo** | *Nature Biotechnology*, 2023 May 11

A way to model virtually any mutation associated with cancer

Researchers co-led by Ludwig MIT Co-director Tyler Jacks described in a May issue of *Nature Biotechnology* a new method to construct genetically engineered mouse models that overcome a major limitation of previous approaches: that such models tend to capture just a small fraction of the genetic lesions that drive human cancer. Those that employ CRISPR-Cas9 can expand this fraction, but are limited by their reliance on error-prone DNA repair. Tyler and his colleagues showed that their approach, based on a more precise variation on CRISPR gene editing called “prime editing”, enables the accurate engineering of virtually any mutation in cell lines and organoids. It involves engineering mice to conditionally express

in every cell a reverse transcriptase fused to a DNA-snipping enzyme that nicks only a single strand of DNA. Expression of the fusion protein is induced by the injection of Cre recombinase into targeted tissues, while the addition of a guide RNA encoding a mutation of interest enables the precise replacement of any targeted DNA sequence. The researchers demonstrated this “somatic prime editing” *in vivo* using lipid nanoparticles, generating lung and pancreatic cancer models using viral delivery of prime editing guide RNAs or transplantation of prime-edited organoids. In testing their method, they showed how different types of somatic mutations in oncogenic KRAS generate distinct tumor phenotypes.



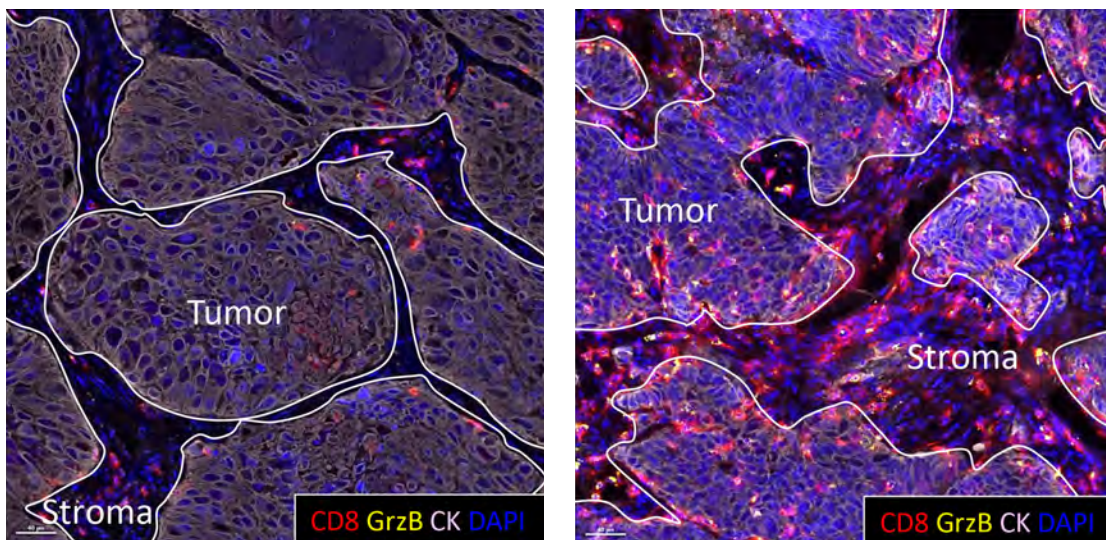
Alexander Rudensky

 **Conserved transcriptional connectivity of regulatory T cells in the tumor microenvironment informs new combination cancer therapy strategies** | *Nature Immunology*, 2023 May 1

Cells of the tumor microenvironment compensate for the loss of Tregs

The depletion of regulatory T cells from tumors has been shown in multiple studies using mouse models to suppress cancer growth, though most tumors progress following a brief hiatus. One possible explanation for this is that the loss of Treg cells—which not only prevent runaway immune responses but also participate in wound repair—induces compensatory responses in other noncancerous cells of the tumor microenvironment (TME). Examining this possibility, researchers co-led by Ludwig MSK Director Alexander Rudensky discovered that Tregs influence the gene expression programs of other cells, such as fibroblasts, macrophages and endothelial cells that line blood vessels, in the lung tumor

TME and in tissue inflamed by injury. They reported in a May paper in *Nature Immunology* that these effects are largely conserved in human lung tumors and showed how they might be exploited for the identification of potential combination immunotherapies. In a mouse model of lung cancer that replicates human cancers that are unresponsive to PD-1 checkpoint blockade, Treg depletion activated compensatory responses involving the upregulation of VEGF and CCR2 signaling-related genes. Alexander and his colleagues demonstrated that selectively depleting intratumoral Tregs while targeting VEGF overcomes the tumor’s resistance to PD-1 blockade and significantly extends survival of the mice.



Images by Stephanie Tissot

Multiplexed immunofluorescence images of non-inflamed and inflamed lung cancers, demonstrating the infiltration of CD3+CD8+ double-positive T-cells expressing GrzB within tumor and stroma niches.

Lung tumors that are poorly infiltrated with effector T cells express better antigens

Researchers led by Ludwig Lausanne's Michal Bassani-Sternberg examined how tumor heterogeneity, mutations and the antigen landscape are associated with immune infiltration in lung cancer. Tumors that are inflamed and infiltrated with CD8+ T cells are known to respond well to immunotherapy. What was less clear was whether these tumors express antigens substantially different from those expressed by their uninflamed counterparts. To find out, Michal and her colleagues integrated mass spectrometry-based immunopeptidomics with sophisticated genomics, spatial analysis of gene expression and imaging to analyze 61 tumor regions and adjacent nonmalignant

lung tissues from 8 patients with lung cancer. They reported in a May issue of *Nature Cancer* that lung tumors that are poorly infiltrated by CD3+CD8+ T cells—typical of those seen in nonsmokers—both express and present higher levels of tumor antigens computationally identified as being of high quality (i.e. those more likely to activate T cell responses) than the T cell-infiltrated tumors associated with smoking-related lung cancer. This most likely stems from immune editing, in which cancer cells expressing immune-stimulating antigens are eradicated over the course of tumor evolution. Their findings have implications for the design of personalized immunotherapies.



Michal Bassani-Sternberg

 **The immunopeptidome landscape associated with T cell infiltration, inflammation and immune editing in lung cancer** | *Nature Cancer*, 2023 May 1

Two technologies at the cutting edge of T cell engineering



Jesus Corria-Osorio



George Coukos





Melita Irving

Under conditions of chronic antigen stimulation, cytotoxic T cells that infiltrate tumors tend to enter a well defined dysfunctional state known as “exhaustion,” a typically inescapable fate that has posed a major challenge to the success of many types of immunotherapies. Researchers led by Ludwig Lausanne’s Jesus Corria-Osorio and Director George Coukos hypothesized that CD8+ T cells could be orthogonally engineered—that is, with cytokines that activate distinct but complementary functional immune axes—to avoid this fate. In an April *Nature Immunology* paper, they described their engineering of CD8+ T cells to secrete an interleukin (IL)-2 variant that binds the IL-2R $\beta\gamma$ receptor and the alarmin IL-33. The IL-2 variant, they hypothesized, would promote stem-like traits in the CD8+ T cells, while IL-33 would boost the ability of dendritic cells to prime the CD8+ T cells and further support their stemness. When adoptively transferred into mice, these engineered T cells acquired a novel, synthetic effector state that deviates from canonical exhaustion and displayed superior effector function, resistance to exhaustion and high levels of tumor engraftment without need for cytokine stimulation or other supporting measures.

The engineered cells induced regressions in mouse models of tumors that typically elude T cell targeting.

Another Ludwig Lausanne study, this one led by Melita Irving and George Coukos, reported in an April paper in *Nature Biomedical Engineering* the design, production and use of a lentiviral vector that enables the delivery of a variety of genes to human T cells to help them overcome barriers to T cell function in the tumor microenvironment. The vector, which encodes a constantly expressed receptor for a cancer antigen and a promoter that drives gene expression only after the T cell is activated, can be produced in accordance with good manufacturing practices. Melita, George and their colleagues, including Patrick Reichenbach and Greta Giordano Attianese, demonstrated its use by delivering a gene for interleukin-2 and a microRNA-based short hairpin RNA for the knockdown of the gene coding for hematopoietic progenitor kinase 1, a suppressor of T-cell-receptor signaling. They also showed that genes driven by the activation-dependent promoter are only expressed by T cells activated by contact with their target antigen in tumors.

 **Orthogonal cytokine engineering enables novel synthetic effector states escaping canonical exhaustion in tumor-rejecting CD8+ T cells** | *Nature Immunology*, 2023 April 20

 **A lentiviral vector for the production of T cells with an inducible transgene and a constitutively expressed tumour-targeting receptor** | *Nature Biomedical Engineering*, 2023 April 17


A DNA-barcoded nanotech for the detection, identification and staging of cancer

Researchers led by Ludwig MIT's Sangeeta Bhatia and alumnus Liangliang Hao devised and preclinically validated a multiplexed nanotech diagnostic that can not only detect malignant tumors but also discriminate between tumor types and states of disease progression through a simple urine test and could be dispensed at the point of care. The portable diagnostic employs synthetic biomarkers—DNA barcodes—each linked to distinct peptides known to be targets of specific proteases, which are themselves attached to nanoparticles (or nanobodies). When the peptides are cleaved by specific proteases in tumors, the DNA barcodes—chemically stabilized by phosphorothioate modifications, which are also used in RNA

vaccines—are secreted into urine. Once secreted, they can then be run through a test in which they're recognized by a programmable CRISPR-Cas nuclease, Cas12a, and read out as distinct fluorescent signals or as lines on a strip of paper. The particles can carry several barcodes capable of detecting multiple distinct proteases, dramatically boosting the sensitivity and information provided by the test. Reporting their work in a *Nature Nanotechnology* paper in April, Sangeeta, Liangliang and their colleagues showed that five DNA barcodes could distinguish primary from metastatic tumors in the lungs of mice and described a system for detecting up to 46 unique signals for highly sensitive, multiplexed cancer diagnostics.



Sangeeta Bhatia

 **CRISPR-Cas-amplified urinary biomarkers for multiplexed and portable cancer diagnostics** | *Nature Nanotechnology*, 2023 April 24


A polymorphism in a promoter explains a mystery of the blood

Mutations that accumulate in hematopoietic stem cells (HSCs) can, when they hit any of a variety of driver genes, boost the fitness of select cells so that their daughters come to dominate the bone marrow niches in which HSCs reside. This leads to a condition known as clonal hematopoiesis of indeterminate potential (CHIP), in which cells derived from such mutants ultimately predominate in the blood. These cells can be precursors for blood cancers—and have also been linked to a host of chronic diseases, including cardiovascular and liver disease—but the basis of their fitness advantage has long been a mystery. To solve that mystery, researchers led by Ludwig Stanford's Siddhartha Jaiswal developed PACER, a new method to infer

the expansion rate of clones from a single time point, and applied it to more than 5,000 samples from people with CHIP. They reported in an April paper in *Nature* their identification of a common inherited polymorphism in the TCL1A promoter that is associated with a slower expansion rate in clonal hematopoiesis overall. While normal HSCs did not express TCL1A, certain mutations led to aberrant expression of the gene and clonal expansion, but this was blocked by the protective polymorphism. The findings suggest that the fitness advantage of several commonly mutated driver genes in clonal hematopoiesis may be mediated by TCL1A activation and that TCL1A may be a viable target for the treatment of CHIP.



Siddhartha Jaiswal

 **Aberrant activation of TCL1A promotes stem cell expansion in clonal haematopoiesis** | *Nature*, 2023 April 12



RICHARD WHITE

The zebrafish maven

Ludwig Oxford's Richard White models cancer in fish that are easy to manipulate genetically and enable the clear visualization of individual cancer cells as they spread

Richard White joined Ludwig Oxford in October 2023, moving from New York's Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, where he had been an associate professor of cancer biology and genetics since 2012. A physician-scientist and authority on the use of zebrafish to model cancer, Richard has developed a nearly transparent model of the fish named casper that has proved very useful to his studies. His research interests revolve around two major themes: how cancer cells co-opt the genetic programs of embryonic development, and how their microenvironment influences

their fate. Richard's studies have established, for example, that migrating melanoma cells often move in clusters, interacting with each other and with fat cells to seed metastatic tumors. His work on the role of developmental programs in cancer has, meanwhile, pegged genes that help determine a cell's anatomical location as potentially novel targets for cancer therapy. Richard's contributions have not gone unnoticed: he received in August the Outstanding Research Award from the Society for Melanoma Research. Ludwig Link recently caught up with Richard to learn a little more about his life, his many fascinations and, of course, his science. Here's an excerpt of what turned out to be a very engaging conversation.

Tell us a bit about your background and family.

I grew up in Brooklyn, New York, and come from a slightly unusual background. A bunch of smart people in my family, but it's not a super educated family. I have two siblings, a brother, and a sister, and I was the oddball in the family. I was always pretty good at school and from a very early age knew exactly what I wanted to do, which was to become a doctor. My mom was a stay-at-home mom, but when I was around two or three, my dad, who worked for the U.S. Postal Service, developed what turned out to be lifelong mental illness, a psychotic disorder that made him violent. Eventually he was arrested and put in jail. He left the house when I was around 10 or 11 years old. That was pretty tough. So then, my mom had to go to work, because it's hard to raise three kids on public support. And she wound up working in an accounting department, rose through the ranks and did really well. She never went to college but just carried herself up and became a bookkeeper. I'm so proud of her.

Where did you go to college?

I was really focused on becoming a doctor,

"To be given the freedom to just wander, scientifically, for two years—that was the best gift. ... I began thinking about the strengths of the zebrafish, how we could use it to answer interesting questions in cancer. It seemed to me that the two interesting things were genetics and imaging."

so I joined the only six-year combined BS-MD program in the country at the time, at Rensselaer Polytechnic Institute and Albany Medical College in New York. I got to medical school when I was 19 and I really disliked it. It wasn't that I hated medicine. The reason, in retrospect, was that med school requires a lot of memorization but what I really enjoyed was the science part of medicine. I tried to quit four times and they told me, "No, that's not a good idea." But then I had a summer program with the person who became my PhD advisor, and I loved it, so I went back to the med school and said, "Okay, I won't quit if you let me join the MD-PhD program." There was a lot of controversy around that because they weren't sure if it was legal to do a combined BS-MD-PhD. But eventually they worked that out.

What did you study for your PhD and who was your advisor?

My advisor's name was Cathy Davison. What we studied was cell-cell communication: how endothelial cells interact with smooth

“DNA mutations occur all over the body but we, and now others, observed that it’s only the cells that adopt a configuration that turns on an embryonic gene expression program that eventually take off and become cancer. What that told us was that DNA mutations will never sufficiently explain why cancer cells act like they do.”

muscle cells, and how that mediates the pathogenesis of hypertension. There’s a direct line between that and what I do today, looking at how cell-cell communication governs nearly all aspects of physiology. Cathy was an amazing mentor. She gave me tons of freedom. What was a little bit frustrating was that the lab was small. It had three or four people and very little funding. This was because Albany wasn’t primarily a research medical school. My advisor told me, “You need to go to a bigger institution, a place that has lots of resources for research, so you can do the sort of stuff you want to do.”

Where did you do your medical residency?

I went to Yale for my residency. I totally blossomed at Yale. I did a very traditional residency track. I liked taking care of patients, and I felt I should learn how to be a good doctor. But I also met with lots of researchers and talked to them.

How did you start working on zebrafish?

I wanted to become an oncologist, so I decided to go to Harvard for my fellowship because it had an outstanding clinical cancer program but also world-class laboratories. My first year was at Dana-Farber Cancer Institute and Massachusetts General Hospital and I had remarkable clinical mentors. But there was no question I wanted to be a basic laboratory scientist. So I interviewed with 15 different labs and pretty much made up my mind where I wanted to go. And then changed it at the very last moment. A friend of mine said, “Oh, you should go talk to the zebrafish guy.” I was pretty confused why I would care about a fish. But I wound up meeting with Len Zon, who runs a big zebrafish lab at Harvard. It was such a fun conversation but I had almost no idea what he was talking about—why would we study fish cancer? And then, two days later, he emails me and he just says, “That was a great conversation. When are you starting?” And I was a bit taken aback because I had no idea what I would do. But he told me not to worry, we could just do interesting stuff. And I said, “I’m sold.”

The first two years were kind of a mess because I had no idea what I was doing. I didn’t have a background in genetics. I knew nothing about zebrafish, and he just let me wander in the woods for two years. He told me, “You’ll figure it out.” To be given the freedom to just wander, scientifically, for two years—that was the best gift he gave me. Len’s lab had just built the first melanoma model in zebrafish but I had no idea what to do with it. I began thinking about the strengths of the zebrafish, how we could use it to answer interesting questions in cancer. It seemed to me that the two interesting things were genetics and imaging. We could manipulate stuff in the fish and then we could image it. And so my work in the lab pretty much followed that logic—imaging and genetics.



Ludwig Oxford's Richard White has developed a nearly transparent zebrafish model, named casper, that has greatly facilitated imaging for his studies on cancer progression and metastasis.

Image by the White lab

What led to the development of casper?

I first turned my attention to the imaging side of things. Casper was pretty random, I've got to say. I'd become friends with a technician in the lab named Anna Sessa and we were on the T—the subway in Boston. There was a fish floating around Harvard called Roy Orbison that had these big black eyes and was sort of translucent. She said to me, "I wonder if we could make that fish transparent because then you could do cool imaging." We just started breeding this original fish with other fish and then, eventually, we came up with this fish called casper. And we thought, "Oh, that's clearly a pretty useful fish—it's not totally transparent, but it's pretty transparent." So now we had this fantastic tool for imaging, which we still use to this day. Nothing quite beats seeing things happen in real time.

So what are the most intriguing discoveries that you've made using zebrafish as cancer models?

After we made casper, I basically then turned to the genetics of the tumors. This interest started in Len's lab and then grew tremendously in my own lab at Sloan Kettering. The quality of my colleagues there pushed me to think about a more global view of what it means to be a cancer. It's not just genes, it is much beyond that.

There are probably three big buckets of discoveries we've made, and they're highly interrelated. The first was how, and why, cancers utilize developmental programs to get started. DNA mutations occur all over the body but we, and now others, observed that it's only the cells that adopt a configuration that turns on an embryonic gene expression program that eventually

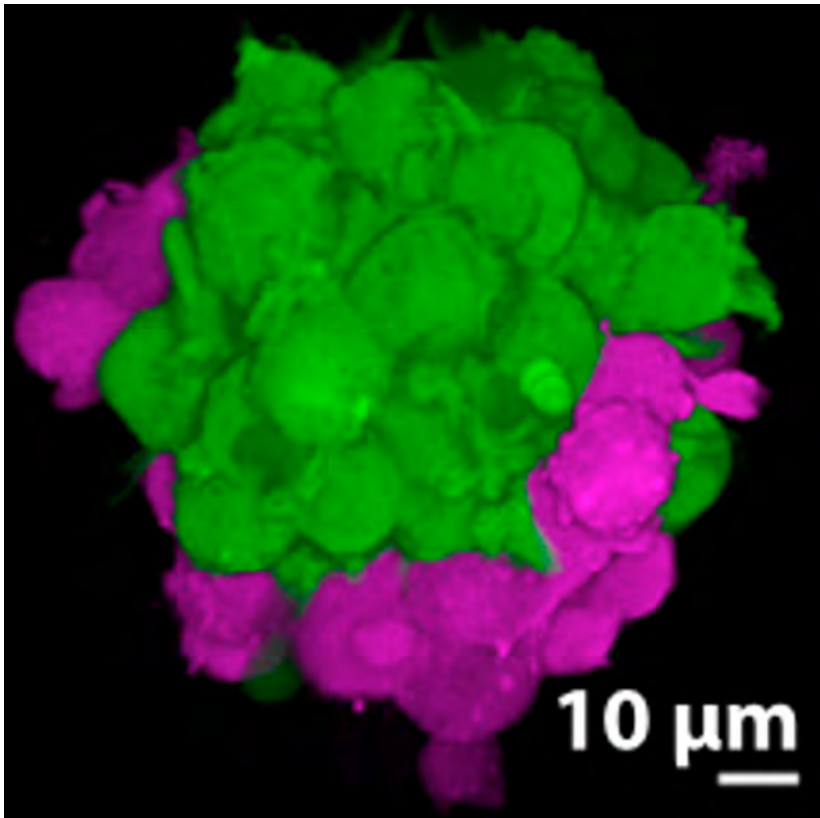


Image by the White lab

A cluster of cancer cells, with the green ones being more invasive, the red ones more proliferative. White's studies using the casper zebrafish revealed that such clusters metastasize more efficiently to distant organs, which implies that targeting the ways they stick together could help prevent metastasis.

take off and become cancer. What that told us was that DNA mutations will never sufficiently explain why cancer cells act like they do. You have to understand the epigenetic state of the cell because that's what turns on these embryonic programs, and that's as much a part of cancer as DNA mutations. So we developed this concept of *oncogenic competence*, where you get DNA mutations all the time but it's really the transcriptional state—especially these embryonic transcriptional states—that seem to be the special sauce that gives the cell its ability to form a cancer.

A second important finding was about anatomy. Some mutations can give you cancer in one part of the body but not in another. If the first concept was competence, this told us something about specificity. To explore this, we used a rare subtype of melanoma, called acral melanoma, which appears on the hands and feet. And these tumors turn out to have totally different mutations than melanomas in other parts of the body, and that's why they form where they do. So it's a very fundamental thing—that DNA mutations interact with where the cell is anatomically located in the body to cause cancer. And, again, that's governed by transcriptional and epigenetic programming. We call that concept *oncogenic specificity*. Competence is, can you become a cancer? Specificity is, why do certain mutations only cause cancer at certain anatomic sites?

And the third bucket?

The third one brings all of this together. If cancers only form from cells in certain places, under certain conditions, what brings that together is the surrounding cells—the local microenvironment that pushes a cell to become cancerous, or not cancerous. This led us into a whole series of studies looking at cell-cell interactions, how tumor cells in these different sites interact with their neighbors. In a way, that brought me full circle back to my PhD, where I worked on cell-cell communication, although in a totally different context. And that's been really exciting because I never fully appreciated how dominant the microenvironment could be—I grew up thinking about cancer as a cell autonomous thing, yet most evidence says it's a collection of cells acting in a coordinated manner. I think the real therapeutic opportunity in cancer is all the other stuff surrounding the cancer in these microenvironments.

Where is your research heading? Any new or emerging areas of interest?

We're developing a lot of tools to try and look in much more sophisticated ways at cell-cell communication. We're also trying to understand this very fundamental question of why certain genes that should be relatively ubiquitously expressed seem to exhibit extreme cell-type specificity. For example, many chromatin factors are expressed in pretty much every cell, or many, many types of cells, yet they have this extreme specificity, only exerting their effects in certain cells.

"We're developing a lot of tools to try and look in much more sophisticated ways at cell-cell communication. We're also trying to understand this very fundamental question of why certain genes that should be relatively ubiquitously expressed seem to exhibit extreme cell-type specificity."

What are your avocational interests?

When I was around 19, right around the time I started medical school, I started traveling a lot. It became this way of really seeing the world that even books couldn't provide. And so, I began traveling extensively. My partner Theresa and I met over a shared love of traveling. One day, she propositioned me and said, "Do you want to go to India? And I said, "Sure, that sounds fun." And we started dating shortly after that. I'm very happy to say that we've given this love of travel to our daughter Harper. It's just a way of thinking about the world, and I'd like to think she gets that. So we all travel together.

What country would you most like to visit?

I really want to go to Sri Lanka, which has an incredible history, and a lot of natural beauty. I've always wanted to explore Russia because my grandparents were born in Russia.

Any favorite music?

Oh, yeah. It's terrible. We gravitate more towards folk music, which is kind of funny—another shared love between my partner and me. We bonded over this very obscure folk band, and I was like, "Oh, my God, she's heard

of this band!" She had the same reaction. And we thought, "Well, clearly we should be together."

Who is your favorite author, and your favorite book, if you have one?

That's a tough one. The one that always pops into my head is Jose Saramago's *Blindness*. It's a perfect microcosm of, I think, what it means to be human. The other one is, *A Little Life* by Hanya Yanagihara. She does this amazing job of showing how that tiny little nucleus that is your world ultimately tells a bigger story about the things that everyone's going through.

The person I've read recurrently over the years is the Japanese author Murakami. He does an incredible job of showing how narrow the line is between reality and what might be considered fantasy, or magic, or something like that, and that it doesn't take much to cross that line.

Given the influence public opinion has on science funding and policy decisions, what can we—as individuals and as a community—do to **build public support** for scientific research?



EMMA HEATON
Ludwig Stanford

Clear, open communication is essential for efficient collaboration within the scientific community. Transparent dialogue is equally vital for connecting with the public. People can only engage with and support what they understand, so scientists must articulate our work clearly to diverse audiences. Emphasizing real-world applications makes research relatable, highlighting its impact on a personal level and fostering support. Finally, it's important to be honest about the limitations of our work to avoid the false elevation of public expectations and prevent future mistrust.



VINCENT ZOETE
Ludwig Lausanne

Doing more to explain our work to the public would help. My group is involved in many such activities. With support from the Leenaards Foundation, we built a website dedicated to Precision Medicine that explains its principles and, in collaboration with Canal 9, created several short videos on this topic as well. I have also given several presentations to the public at large during scientific fairs. More recently, Fanny Krebs, from my UNIL group, co-organized a "Pint of science" meeting in Lausanne, which was dedicated to precision medicine.

We need to engage the next generation to stimulate interest in science. Too few are choosing science as a career. From pre-school to high school, within 10 years these kids will be the next pair of hands that will make critical, perhaps lifesaving discoveries, undertake those clinical trials and possibly develop scientific policy.



JUANITA MERCHANT
*Scientific Advisory Committee,
Ludwig Institute
for Cancer
Research*

Perhaps—to paraphrase Carl Sagan—we can emphasize that we live in a society that is absolutely dependent on science and technology, and very few people understand science and technology. Failing to support scientists can threaten human wellbeing. Science is uncertain and scientific truths change in light of new evidence. You don't learn to be a scientist just by reading or listening, but essentially by doing scientific research.



SANTIAGO CARMONA
Ludwig Lausanne

Communication is key to garnering public support for funding scientific research. It is essential that researchers present their work in public forums including radio, television and social media in a way that can be understood by the average person. With respect to oncology, it is important for the public to understand that the treatments saving lives are thanks to research!



MELITA IRVING
Ludwig Lausanne

This is so important—especially with public investment in scientific research threatened in the US and other countries. Talk with your representatives and share with them the data that public withdrawal from scientific investment threatens national health and competitiveness. Tell them you want to see a budget that invests in the future. Join a group that advocates for public investment in research. Patient advocacy groups and research societies mount effective lobbying campaigns to increase government investment in scientific research. Find one that speaks to you and help out.



ALEXANDER
MUIR
Ludwig Chicago



EILEEN WHITE
Ludwig Princeton

I think the best way to build public support for scientific research is to communicate to the public what we do and why it is important to them and to society overall. I think it is underappreciated that cancer is a common disease that afflicts one in two men and one in three women, which means everyone will face it personally either themselves or with a family member. Finding better treatments and cures through research touches everyone.



FRANCESCO
BOCCELLATO
Ludwig Oxford

Enroll skilled content creators to produce original, engaging and scientifically accurate content for social media, including videos, reels, stories to explain and promote Ludwig research, making complex topics accessible. Highlight real-world applications, showcase behind-the-scenes work, and interact with the community to build trust and enthusiasm around our scientific endeavors.

To garner public support for cancer research, we need to convey the challenge, significance and impact of our work in languages that are accessible to the public. By fostering understanding and showcasing real-world benefits, we can ensure strong public support for innovative cancer research that will be the foundation for future therapeutic breakthroughs.



YIBIN KANG
Ludwig Princeton

The key to cultivating public support for scientific research is communication, but young scientists are not trained for this. Communicating science should play a part in educating every generation of young scientists; at Ludwig Oxford we have started a pilot program with secondary school students to achieve this.



ROMAULD BINET
Ludwig Oxford

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