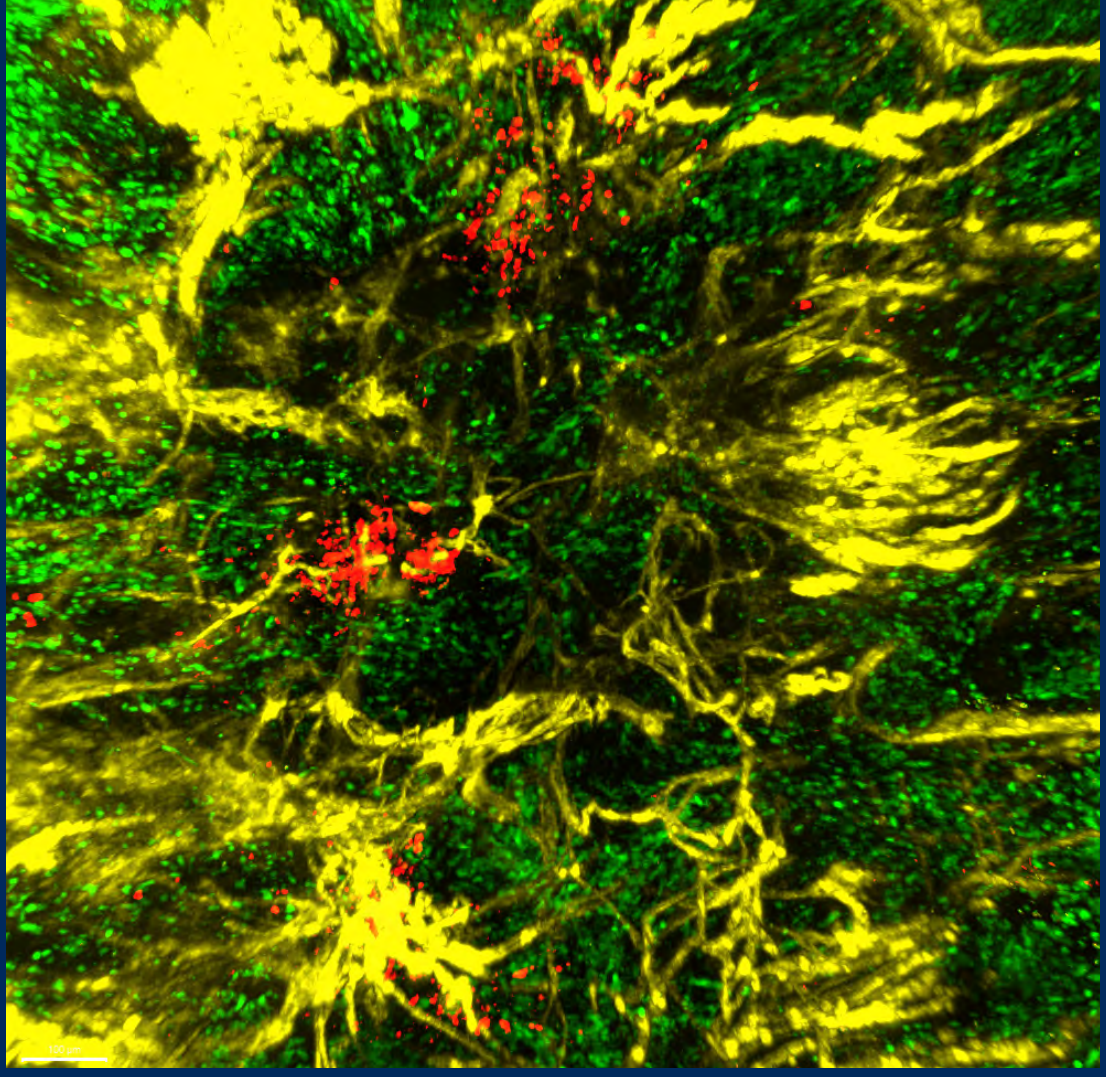


February 2023

Ludwig Link

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

Welcome

Rachel Reinhardt
Senior Vice President for Communications

Welcome to the winter 2023 issue of Ludwig Link!

We hope you all had a happy holiday season and are ready, and refreshed, for the year ahead. If you're looking for some extra inspiration, our roundup of research news from Ludwig labs should help. You'll read in here about the creation and mechanistic analysis of a novel nanoparticle that triggers potent therapeutic immune responses in mouse models of multiple cancers and potentially powerful new uses of tumor aneuploidy as a marker for patient stratification. Another study reported here covers the identification of a single protein hyperexpressed by cancer cells across a broad range of malignancies that erects a multifaceted barrier to anti-tumor immune responses in mouse models—a discovery that has led to the launch of a new biotechnology company. There's also a brief on an intriguing examination of how high doses of vitamin C kill cancer cells. Its findings suggest novel dietary and pharmacologic approaches to enhancing the efficacy of some cancer therapies. And all this is just a sample of the fascinating science in this issue.

Our Q&A (page 20) is with our President and CEO Ed McDermott. We spoke with Ed about his formative experiences, how he was hired by the Ludwig Institute, how the organization evolved over the years and much more. We found the tidbits of Ludwig history he shared with us quite fascinating. We're betting you will too.

As always, we also have news of awards and honors won by Ludwig researchers (page 5) and of two new members appointed to the Board of the Ludwig Institute for Cancer Research (page 6). In our Ask a scientist section, Ludwig researchers weigh in on which aspect of tumor metabolism they consider most promising for the discovery of targets for cancer therapy or immunotherapy. See what they said on page 25.

Happy reading!

Sincerely,

Rachel Reinhardt

On the cover

A study co-led by Ludwig Lausanne's Johanna Joyce and alumnus Davide Croci devised a strategy to noninvasively and longitudinally track tumor-associated microglia and macrophages (TAMs) in brain and breast tumors in living mice using multispectral MRI. With further development, the method could be used to improve patient monitoring. This two-photon microscopy image shows TAMs that have taken up labeled nanoparticles (red), the tumor vasculature (yellow) and brain cancer cells (green).

STORY ON PAGE 10

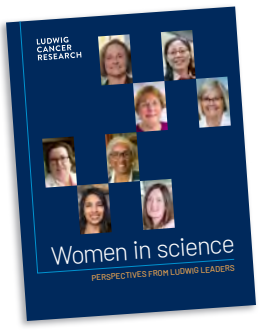
In this issue

When I joined, "the Ludwig Institute sat at the pinnacle of a pyramid, which was a vast commercial enterprise. … Mr. Ludwig's businesses were of unbelievable scale."

Q&A with EdMcDermott
page 20

FEATURED RESEARCH

Two recent studies described the use of aneuploidy as a marker for likely response to immunotherapy and, separately, to identify patients with metastatic non-small cell lung cancer who might benefit from combined immunotherapy and radiotherapy. **Page 7**



A special report profiles a handful of women leaders from across Ludwig Cancer Research, covering their lives, careers and views on gender-related issues.

Details on page 26

Ludwig MIT's Richard Hynes among winners of the 2022 Lasker Award for his seminal work on integrins

Ludwig MIT's Richard Hynes was named a winner of the Lasker Award for his discovery and subsequent research on integrins, a family of proteins that help cells adhere to each other and to the extracellular matrix and link the cell's external environment to its cytoskeleton and signaling circuitry. Richard shared the prestigious award with two other scientists, Erkki Ruoslahti and Timothy Springer, whose independent work on integrins converged with his to launch a field of research of enormous importance to our understanding of everything from embryonic development to immunology to cancer. Examining the differences between proteins around normal and malignant cells in the early 1970s, Richard and Erkki Ruoslahti independently identified fibronectin as a component of the extracellular matrix found in abundance around normal cells, but not cancer cells. Richard also found evidence that this protein somehow linked to the protein skeleton of cells and later identified the receptor responsible for that linkage, naming it "integrin." The three researchers, and several other scientists, went on to establish that integrins belong to a large family of proteins involved in countless biological processes involving cell adhesion, structure and motility. Richard's lab has since extensively explored the role of integrins in cancer metastasis. View Richard's acceptance remarks here.

Richard Hynes

Yang Shi

Kornelia Polyak

Crystal Mackall

Three Ludwig researchers elected to the National Academy of Medicine

Ludwig Oxford's Yang Shi, Ludwig Harvard's Kornelia Polyak and Ludwig Stanford's Crystal Mackall were among 100 new members elected to the National Academy of Medicine (NAM) in mid-October. Membership in the Academy is among the highest honors in the biomedical field. Yang was recognized for his numerous contributions to epigenetic research, most notably his identification in 2004 of an enzyme, LSD1, that erases methyl marks from histones—a finding that disproved a 40 year-old model of epigenetics that presumed such methylation to be irreversible. His group went on to identify and characterize several other such enzymes over the years. The NAM noted that Yang's "elegant mechanistic discoveries" in epigenetics have revolutionized the field and had a "far-reaching impact on basic and translational research." Kornelia was honored for her work "documenting the clinical and functional relevance of intratumoral cellular heterogeneity" and for her creative use of new technologies and models to help establish the fundamental contributions of noncancerous cells to the biology of tumors. Crystal was recognized for pioneering immune therapies for pediatric cancers, for her many fundamental discoveries in human immunology and for translating those discoveries into "cutting-edge engineered cell therapies for cancer." We congratulate all three for this well-deserved recognition of their research and creativity.

Ludwig Lausanne's Michal Bassani-Sternberg recognized for her work on cancer antigens

Michal Bassani-Sternberg

Ludwig Lausanne's Michal Bassani-Sternberg has received the Swiss Bridge Award, one of two researchers to be so honored in 2022. The award this year focused on viral and bacterial infections associated with cancer, which account for some 15% of all cancers worldwide and exact a particularly heavy toll in developing countries. Michal and her team will apply the grant of 250,000 Swiss francs to explore the cancer antigens—and corresponding T cell receptors—of malignancies linked to Epstein-Barr virus, human papillomavirus and Merkel cell polyomavirus. These include cancers such as lymphoma, cervical cancer and an aggressive, if rare, type of skin malignancy known as Merkel cell carcinoma. Michal's lab has developed powerful proteogenomics and mass spectrometry-based methods along with computational systems to rapidly identify peptides likely to be presented by cancer cells and detected as antigens by T cells. Her methods are already being applied to advance personalized immunotherapies under development at Ludwig Lausanne. The ultimate aim of the Swiss Bridge-supported project is to translate the team's findings on viral antigens and T cell receptors to develop novel immunotherapies for the prevention and treatment of virus-driven cancers.

Two new members named to the Board of Directors of the Ludwig Institute for Cancer Research

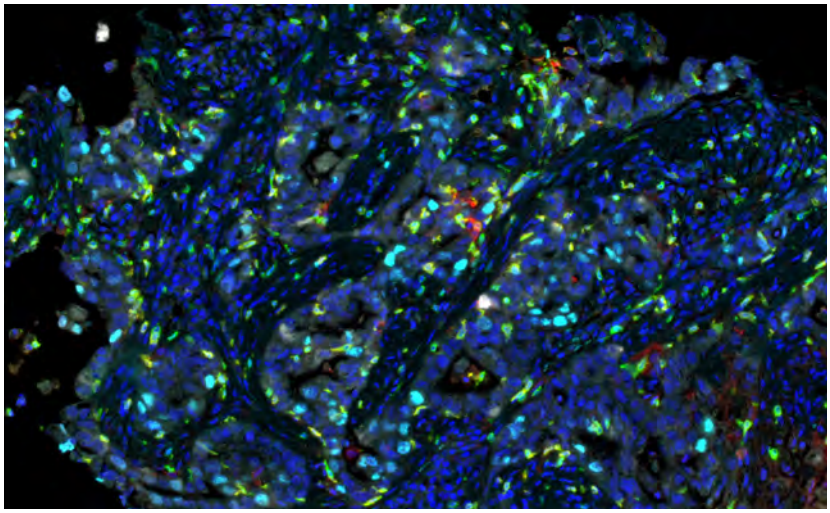
Jedd Wolchok

Nicolas Killen

In January 2023, Jedd Wolchok and Nicolas Killen joined the Board of Directors of the Ludwig Institute for Cancer Research and the LICR Fund, which manages the assets of the Institute. Jedd is currently Meyer Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine and co-director of the Ludwig Collaborative Laboratory at Weill Cornell Medicine, in New York. Nicolas is managing partner of the Geneva-based law firm Borel & Barbey. They replace Olivier Dunant, a partner at Borel & Barbey who joined the Board in 1998 and retired December 31, 2022; and Philip Pizzo, pediatric oncologist and David and Susan Heckerman Professor of Microbiology and Immunology, Emeritus, at Stanford University, who retired September 1, after eight years as a Board member. Nicolas, who has extensive experience in commercial and international tax law, received his initial law degree from Geneva University and earned an advanced degree in law (LLM) from Duke University. He joined Borel & Barbey in 1992 as an Associate, rising to Partner in 1999. A clinician-scientist and authority on cancer immunotherapy, Jedd has long been affiliated with Ludwig Cancer Research. He is a former Member of the Ludwig Institute, the former Lloyd J. Old/Virginia and Daniel K. Ludwig Chair in Clinical Investigation at Memorial Sloan Kettering Cancer Center (MSK) and former Director of the Ludwig Collaborative Laboratory at MSK.

Two studies find high therapeutic utility in measures of tumor aneuploidy

Ludwig Chicago's Sean Pitroda led two studies published in late November describing the potential use of aneuploidy—an abnormal numbers of chromosomes in cells—as a marker for likely response to immunotherapy and, separately, to identify patients with metastatic non-small cell lung cancer who might benefit from combined immunotherapy and radiotherapy. Tumors that have a high mutational burden (TMB) respond well to immune checkpoint blockade (ICB) therapy, but those with extensive aneuploidy in their cells tend to be poorly infiltrated by immune cells, suggesting they're less likely to respond to such treatments. The study reported in *Nature Genetics* examined whether aneuploidy scores of tumors could also be used, like TMB, to help predict which patients are most likely to respond to ICB. Sean and his colleagues analyzed data from more than 1600 patients with various types of cancer and found that high aneuploidy is indeed associated with worse survival after ICB. They also showed that its measurement complements that of TMB as a predictor of ICB response. This finding could aid the stratification of patients for immunotherapy. In the second study, Sean and his colleagues scrutinized how immunotherapy and radiotherapy (RT) interact in patients with lung cancer. The notion that RT can stimulate anti-tumor immune responses that can then be boosted by immunotherapy has been supported by animal studies. But the combination has largely proved ineffective in human trials. Sean and his team analyzed two cohorts of patients with advanced lung cancer who received ICB alone or either concurrent or sequential RT and ICB. They reported in *Nature Cancer* that local tumor irradiation alone does not stimulate anti-tumor immune responses in lung cancer patients; in fact, it has the opposite effect, and the subsequent addition of immunotherapy only helps because it reverses the apparent radiation-induced suppression of the immune response. They also discovered, however, that in patients whose tumors have a high level of aneuploidy, simultaneous administration of both RT and ICB was more effective at eliminating tumor cells and resulted in improved survival compared to sequential administration of the dual therapy. The effect was not observed in less aneuploid tumors. This finding supports the hypothesis that radiation and immunotherapy can interact positively—but only for a specific subset of patients.

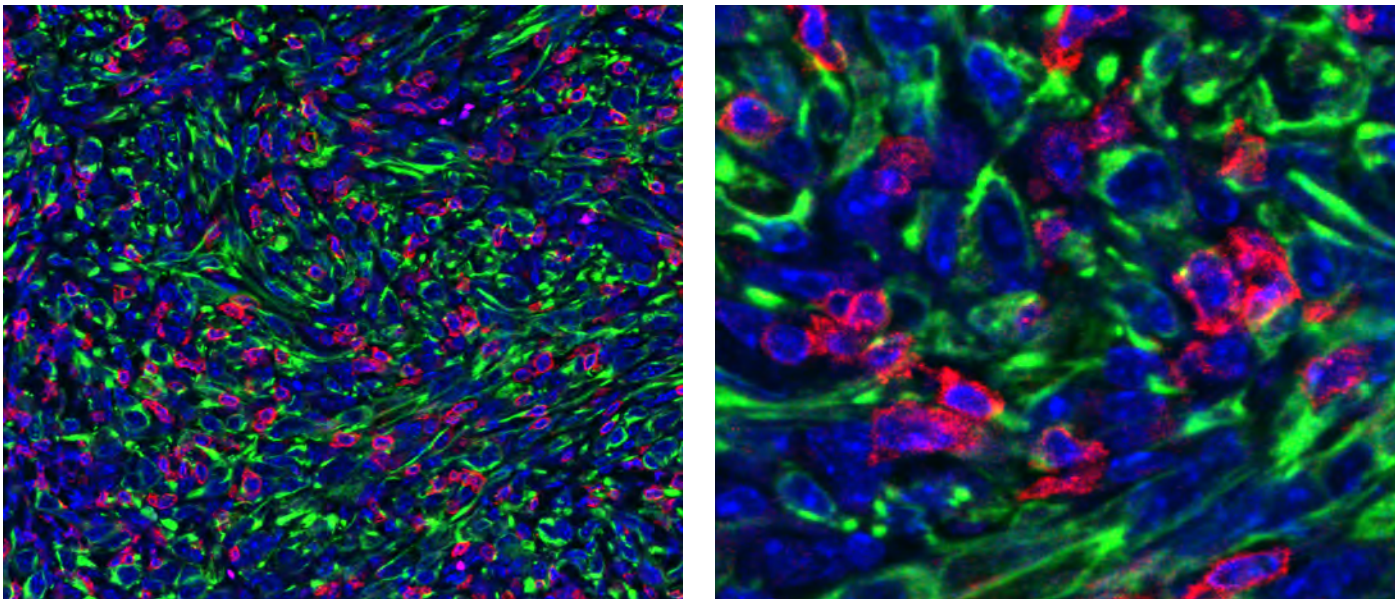


Multiplexed immunofluorescence image, using multiple markers on immune and cancer cells, of sample from a lung tumor treated with radio- and immunotherapy.

Sean Pitroda

Tumor aneuploidy predicts survival following immuno-therapy across multiple cancers | *Nature Genetics,* 2022 November 28

Highly aneuploid non-small cell lung cancer shows enhanced responsiveness to concurrent radiation and immune checkpoint blockade | *Nature Cancer,* 2022 November 28



Tumor with FMRP-deficient cancer cells (green) being infiltrated and attacked by killer (CD8) T cells (purple) — at low magnification, left, and high magnification, right.

Douglas Hanahan

Aberrant hyperexpression of the RNA binding protein FMRP in tumors mediates immune evasion | *Science*, 2022 November 17

A single protein erects a multifaceted barrier to anti-tumor immunity in mouse models

A study led by Ludwig Lausanne's Douglas Hanahan, alumni Qiqun Zeng and Sadegh Saghafinia, and graduate student Agnieszka Chryplewicz revealed a single protein hyperexpressed by cancer cells across a broad range of malignancies that erects a multifaceted barrier to anti-tumor immune responses in mouse models. It also captured a signature of gene expression induced by the protein, FMRP, that encompasses 156 distinct genes and predicts poor patient survival. A protein primarily expressed in neurons, FMRP has been extensively studied as a factor whose loss of expression during embryogenesis is associated with the neuro-developmental disorder fragile X syndrome. The researchers generated models of pancreatic, colon, melanoma and breast tumors lacking the gene for FMRP using immunocompetent and immunocompromised mice and compared them to corresponding tumors that retained the gene. Their studies using these models, reported in November in *Science*, showed that the gene-expression program regulated by FMRP in cancer cells promotes the induction of regulatory T cells—which suppress cytotoxic T cells—and reprograms macrophages into a functional state in which they support the growth and survival of cancer cells. The loss of FMRP in cancer cells not only reversed these effects but also induced their secretion of factors that support vigorous antitumor immune responses mediated by cytotoxic T cells and macrophages. The researchers have co-founded a company, Opna Bio, that is developing cancer drugs based on these findings.

Functional screen identifies enhancer elements associated with cancer cell fitness and proliferation

Research consortia have in recent years identified millions of DNA elements known as enhancers and promoters that are thought to regulate gene expression. But relatively few of these elements have been functionally defined, especially in cancer cells, where their dysregulation is known to play a central role in the genesis of tumors. In a November paper in *Cell Reports*, researchers led by Ludwig San Diego's Bing Ren described their use of a CRISPR-based perturbation assay coupled with DNA sequencing to conduct a large-scale functional analysis of more than 11,000 putative enhancer elements required for cell proliferation and fitness—which they call essential enhancers—across ten human cancer cell lines. Aside from functionally validating hundreds of essential enhancers, their findings suggest that enhancers necessary for cell fitness typically adopt a modular structure. This structure is composed of activating elements enriched for DNA sequences recognized by transcription factors—proteins that regulate gene expression—that are known to be oncogenic surrounded by repressive elements that are enriched for sequences recognized by transcription factors that suppress tumor growth. Bing and his colleagues also showed, using data from clinical tumor samples, that the accessibility of chromatin harboring some essential enhancers is associated with patient survival.

Bing Ren

Systematic discovery and functional dissection of enhancers needed for cancer cell fitness and proliferation
Cell Reports, 2022 November 8

iASPP, typically a cancer promoter, helps suppress tumors in inflamed, RAS-driven skin cancers

Cancer often stems from a cell's acquisition of both activating mutations that promote its proliferation and the loss of inhibitory factors that suppress unregulated growth. In some cancers, activating mutations in the RAS signaling pathway can provide the former impetus, while mutations of the p53 tumor suppressor gene frequently provide the latter. Cancers driven by RAS signaling that are also associated with inflammation can, however, bypass the need for p53 pathway dysfunction. How they do this was not entirely clear. To find out, researchers co-led by Ludwig Oxford Director Xin Lu explored carcinogenesis in a well-established mouse model of mutant RAS- and inflammation-driven skin cancer. Their findings, described in *Cell Reports* in October, reveal that iASPP, which typically promotes tumor growth by inhibiting p53, unexpectedly suppresses cancer initiation in this context. This is because iASPP has a p53-independent role in skin homeostasis, where it regulates the expression of a subset of genes targeted by the p63 and AP1 transcription factors, including several involved in inflammation and cellular differentiation. iASPP coordinates the crosstalk between the JNK signaling pathway and p53/p63 to maintain homeostasis. This may help explain how it can both drive and suppress cancer, depending on its context.

Xin Lu

Mutant Ras and inflammation-driven skin tumorigenesis is suppressed via a JNK-iASPP-AP1 axis
Cell Reports, 2022 October 18

A nanoparticle boost for radiotherapy and immunotherapy

A team led by Ludwig Chicago's Ralph Weichselbaum, Wenbin Lin and Kaiting Yang published a paper in *Nature Nanotechnology* in late October describing a novel nanoparticle that triggers potent therapeutic immune responses in mouse models of multiple cancers. Named ZnCDA, the nanoparticle is loaded with a drug that activates STING, a protein central to the efficient induction of anti-cancer immunity. STING detects DNA fragments in the cytoplasm that can be generated by infection, radiotherapy and certain chemotherapies. The researchers show that ZnCDA enhances its own accumulation in tumors because STING activation in the cells that line tumor blood vessels disrupts the tumor vasculature. In the tumor, they report, the nanoparticles activate a specific subset of macrophages, pushing them toward a cancer cell-targeting (M1) phenotypic state and enhancing their ability to activate tumor-targeting T cells. A single dose of the nanoparticles suppressed tumor growth in mouse models of colon cancer and of colon cancer metastasis to the liver. ZnCDA also extended survival in a model of B cell lymphoma, suppressed tumors in melanoma and prostate cancer models and induced anti-tumor effects in a model of a type of lung cancer that resists STING activators. Its use in combination with radiotherapy and anti-PD-L1 therapy significantly extended survival in mouse models of pancreatic cancer and glioblastoma, both of which are "cold" tumors and thus typically impervious to immunotherapy.

Zinc cyclic di-AMP nanoparticles target and suppress tumours via endothelial STING activation and tumour-associated macrophage reinvigoration
Nature Nanotechnology, 2022 October 27

Ralph Weichselbaum

Wenbin Lin

Kaiting Yang

Johanna Joyce

Noninvasive imaging of tumor-associated macrophages in mice

Researchers co-led by Ludwig Lausanne's Johanna Joyce and alumnus Davide Croci reported in an October issue of *Science Translational Medicine* a strategy to noninvasively track immune cells known as macrophages within brain and breast tumors in living mice. Cancers often recruit and reprogram these tumor-associated macrophages, or TAMs, to support their own growth and establish resistance to therapies. Johanna, Davide and their colleagues exploited a basic function of macrophages, which is to roam around the body, gobbling up particulate matter. They injected mouse models of gliomas, breast cancer and breast-to-brain metastases with two different types of nanoparticles, both labeled with a fluorine isotope, that each emits a discernible signal detectable by magnetic resonance imaging. Those signals are also distinct from the one transmitted by a hydrogen isotope, which is used to image tissue, including cancerous growths. The researchers demonstrate that the nanoparticles accumulate in TAMs, permitting a non-invasive means to ascertain with "multispectral" MR imaging not just the abundance, but also the location of the immune cells across the geography of tumors. The imaging approaches developed in this study could, with further development, help clinicians noninvasively identify brain tumor types, better monitor prognosis and drug resistance and thus improve the therapeutic management of brain tumors.

Multispectral fluorine-19 MRI enables longitudinal and noninvasive monitoring of tumor-associated macrophages | *Science Translational Medicine*, 2022 October 19

New link established between the biological clock and the genesis of clear cell kidney cancer

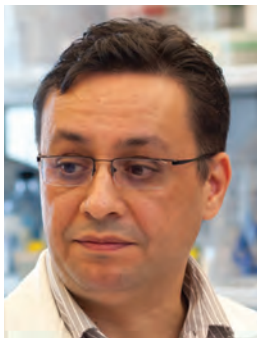
An October study published in *Cell Reports* led by Ludwig Institute Scientific Director Chi Van Dang and former graduate student Rebekah Brooks uncovered a new link between the biological clock and cancer. Rebekah, Chi and colleagues found that ADIRF-AS1, a long noncoding RNA that oscillates every 24 hours, drives a type of kidney cancer by inhibiting a tumor suppressor named PBAF. The tumor suppressor is one of three multi-subunit components of a giant protein complex (named SWI/SNF) that modifies chromatin to regulate gene expression. The SWI/SNF complex is mutated in various ways in about 20% of all cancers. ADIRF-AS1, meanwhile, is known to interact with PBAF in a type of bone cancer cell and, as it happens, one of the components of PBAF is mutated in 40% of clear cell renal carcinomas. Rebekah, Chi and team therefore explored the effects of the ADIRF-AS1 interaction with PBAF in clear cell kidney cancer. They showed that CRISPR-mediated genome editing to delete ADIRF-AS1 caused dampening of many genes associated with the biological clock that oscillate daily and completely suppressed the growth of clear cell kidney cancer in mice. The studies also suggest that ADIRF-AS1 has a function independent of PBAF that involves the extracellular matrix, or the molecular stuffing that surrounds cells.

Chi Van Dang

Circadian lncRNA ADIRF-AS1 binds PBAF and regulates renal clear cell tumorigenesis
Cell Reports, 2022 October 18

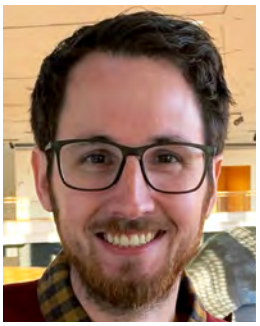
Why a signaling molecule suppresses cancer cell growth only if it's produced in the nucleus

A study co-led by Ludwig Weill Cornell's (formerly MSK) Taha Merghoub uncovered how a signaling molecule known as cyclic AMP (cAMP) either stimulates or suppresses tumor growth depending on where it is produced within the cell. To do that, the researchers developed a new, tunable method to target cAMP signaling to distinct compartments in cancer cells in culture and in mice. Taha and his colleagues reported in a September issue of *Cell Reports* that cAMP signaling generated distinct gene expression profiles depending on its intracellular location. They found that cAMP production in the nucleus suppresses tumor growth in a wide variety of cancers. It does so, they showed, through a previously unknown effect it has on the Hippo signaling pathway, which drives cancer cell proliferation and invasion: cAMP inhibits a key effector protein of that pathway known as YAP. The findings suggest that pharmacologically boosting cAMP levels in the nucleus could represent a new cancer therapy. One approach to doing so might be to target an enzyme known as phosphodiesterase, which breaks down cAMP, perhaps using one of several candidate drugs that are already in clinical use. The trick, of course, would be finding—or making—one that works mainly in the cell's nucleus.



Taha Merghoub

A nuclear cAMP microdomain suppresses tumor growth by Hippo pathway inactivation
Cell Reports, 2022 September 27



Connor Jankowski

Joshua Rabinowitz

How high-dose vitamin C kills cancer cells suggests dietary strategy for enhancing therapy

In an October paper published in *Cancer Research*, Ludwig Princeton's Connor Jankowski and Director Joshua Rabinowitz reported their examination of a pair of hypothesized mechanisms for vitamin C's (a.k.a. ascorbate) ability to kill cancer cells when supplied at high doses. These are the generation of toxic levels of hydrogen peroxide by ascorbate, and the depletion of an essential factor known as glutathione by an oxidized derivative of the vitamin. Josh and Connor showed that the former mechanism is responsible for the cytotoxicity observed in cell cultures. That lethality, they showed, can be suppressed by a species of antioxidant enzymes that have a selenium atom at their core, including one named GPX1. This selenoprotein-mediated protection is fueled by a hydrogen-donating molecule named NADPH that is generated by a core sequence of metabolic reactions known as the pentose phosphate pathway. Depriving mice implanted with glioblastoma tumors of dietary sources of selenium made their tumors exceptionally susceptible to high dose vitamin C therapy and extended the survival of the mice. These findings establish selenoproteins as key mediators of redox balance in cancer cells, suggest a dietary approach to enhancing the efficacy of therapies—including high-dose vitamin C—that generate oxidative free radicals to kill cancer cells and support the targeting of selenoproteins as a strategy to enhance such therapies.

Selenium Modulates Cancer Cell Response to Pharmacologic Ascorbate | *Cancer Research*, 2022 October 1

Peter Ratcliffe

A new approach to measuring protein translation yields translational insights

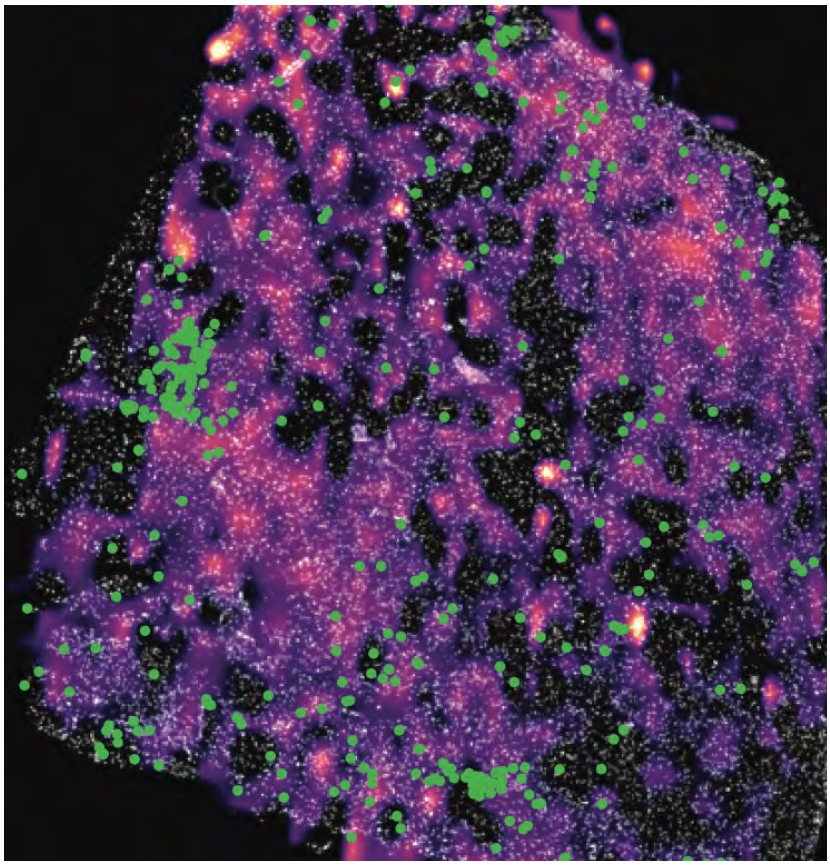
The HIF and mTOR pathways orchestrate responses to oxygen and nutrient availability. They are frequently dysregulated in cancer and are both prime targets for therapy. Yet their interplay in cancer cells is poorly understood due to technical difficulties of simultaneously measuring both global translation of gene transcripts, or mRNAs, into proteins and the translation of specific mRNAs. Ludwig Oxford's Peter Ratcliffe and his colleagues reported in a September study in *Nature Structural & Molecular Biology* a new approach to measuring both at the same time and the application of their method to analyzing the interplay of transcriptional and translational regulation by the two signaling pathways in the most common type of kidney cancer, clear cell renal carcinoma. The findings show that mTOR dysregulation broadly alters protein translation, exerting an effect on many metabolic pathways. HIF pathway dysregulation, on the other hand, has an effect on a more limited set of genes. Their analysis shows that specific classes of HIF1A and HIF2A transcriptional target genes manifest different sensitivity to mTOR and do so in a manner that supports combined use of HIF2A and mTOR inhibitors in the treatment of this type of kidney cancer.

Isoform-resolved mRNA profiling of ribosome load defines interplay of HIF and mTOR dysregulation in kidney cancer | *Nature Structural & Molecular Biology*, 2022 September 12

A cancer cell metabolite that drives malignant growth also inhibits anti-cancer immunity

Researchers led by Ludwig Harvard's Marcia Haigis identified a previously unknown metabolic mechanism by which tumor cells can suppress T cell attack. She and her colleagues reported in *Science* in late September that $_{D}$-2-hydroxyglutarate ($_{D}$2HG), a metabolite that accumulates in cancer cells that have mutations in an enzyme named isocitrate dehydrogenase (IDH), can impair glucose metabolism in mouse T cells and suppress anti-tumor immunity. IDH mutations are found in about 3.5% of cancers, including brain and blood cancers. The researchers found that when taken up by T cells, $_{D}$2HG inhibits the activity of an enzyme involved in glucose metabolism known as lactate dehydrogenase. This drives a metabolic program that inhibits the proliferation of T cells, their production of immunostimulatory factors called cytokines and their ability to kill cancer cells—effects that are reversible with the withdrawal of $_{D}$2HG. The molecular signature associated with these effects was recapitulated in samples taken from patients with IDH1-mutant brain tumors. In these tumors, areas with high concentrations of $_{D}$2HG also had a sparse presence of cytotoxic T cells, and vice versa, supporting the findings made in mice. The findings suggest that the oncometabolite, which is already known to promote cancer growth, may also help tumors resist immune clearance.

Oncometabolite $_{D}$-2HG alters T cell metabolism to impair CD8+ T cell function | *Science*, 2022 September 29



This image shows killer T cells (green) in human IDH-mutant gliomas are found mainly in regions of low $_{D}$2HG concentration (dark/purple areas).

Marcia Haigis

George Coukos

Melita Irving

Two studies take on challenges posed by solid tumors to adoptive T cell therapies

A number of factors play into the limited success of adoptive cell therapies (ACT)—including chimeric antigen receptor (CAR) T cell therapies—against solid tumors. For one thing, finding CAR-targetable antigens that are stably expressed by cancer cells but not by healthy ones has proved challenging. Another problem is that cancer cells compete for nutrients, including glucose, that are essential to the function and persistence of T cells used for ACT. A pair of studies led by Ludwig Lausanne researchers and published in *Frontiers of Immunology* addressed each of these challenges. In a September paper, a study led by Ludwig Lausanne Director George Coukos and Hi-TIDe group leader Melita Irving explored whether the enforced expression of the high-affinity glucose transporter GLUT3 by cytotoxic T lymphocytes could improve their efficacy in ACT. The first author of the study, former graduate student Elisabetta Cribioli, showed that T cells so engineered displayed enhanced glucose uptake, improved mitochondrial fitness and better resistance to stress, among other indicators of fitness. Use of the engineered cells in ACT significantly improved the control of tumors and survival in a mouse model of melanoma. Some mice were even cured of the cancer and able to reject subsequent efforts to implant the same melanoma tumors.

The other study, published in August and led by Melita, developed and evaluated three CARs targeting an antigen that is associated with cancer—but not healthy tissues—in humans and expressed in a variety of malignancies, including melanoma, lymphoma and ovarian and breast cancers. The antigen, N-glycoslylated ganglioside monosialic 3 (NGcGM3), is metabolically incorporated onto the cell surface from nutrients derived from nonvegetarian dietary sources. The two lead scientists, Elisabetta and research associate Greta Giordano Attianesse, constructed three CARs using a well-characterized monoclonal antibody against this antigen, 14F7. They showed that T cells bearing those CARs attacked a variety of tumor fragments isolated from patients and could control NGcGM3-expressing ovarian tumors in mice without causing any toxicity, even though the antigen is found in healthy tissues in mice. The researchers suspect this is because antigen levels must reach a certain threshold to elicit CAR-T attack, and those levels were not reached in the mice because they were fed vegetarian diets—a possibility that could have implications for the clinical evaluation of these CAR T cells. Taken together, the studies hold promise for extending the viability of ACT against a broader range of cancers.

Enforcing GLUT3 expression in CD8+ T cells improves fitness and tumor control by promoting glucose uptake and energy storage | *Frontiers in Immunology*, 2022 September 20

CAR T cells targeting the ganglioside NGcGM3 control ovarian tumors in the absence of toxicity against healthy tissues | *Frontiers in Immunology*, 2022 August 05

Preclinical study suggests three-drug combination may elicit therapeutic immune responses against GBM

Researchers led by Ludwig Lausanne's Douglas Hanahan reported in September in *Cancer Cell* a combination of three existing drugs that significantly prolongs survival in mouse models of the lethal brain cancer glioblastoma multiforme (GBM). The drugs—the antidepressant imipramine, an anti-PD-L1 antibody and an analog of the anti-angiogenic therapy bevacizumab—synergize to unleash potent anti-tumor immune responses. Bevacizumab is known to quasi-normalize leaky tumor blood vessels, whose abnormalities compromise chemotherapy and immunotherapy. The bevacizumab analog also remodels the tumor vasculature to facilitate T cell infiltration, while imipramine hyperactivates cancer cell autophagy to stimulate anti-tumor immunity. The antidepressant, the researchers found, additionally reprograms macrophages from an M2 state, in which they promote tumor growth and survival, into an M1 state, in which they support T cell infiltration and killing of cancer cells. Remarkably, the findings implicate histamine receptor signaling in the programming of immunosuppressive macrophages—signaling activity that imipramine inhibits. GBM patients taking antihistamines had modestly better survival in a small cohort, consistent with the observed benefits of inhibiting histamine signaling in the mouse model. Together, the drugs induced potent anti-tumor immune responses and delayed tumor progression, extending survival of the mice. Added to this, the anti-PD-L1 checkpoint blockade antibody enhanced the therapeutic effects and further prolonged survival. Planning is underway for a phase I pilot trial to evaluate the drug combination in GBM patients.

Douglas Hanahan

Cancer cell autophagy, reprogrammed macrophages, and remodeled vasculature in glioblastoma triggers tumor immunity | *Cancer Cell*, 2022 September 15

How PI3K signaling, activated by many oncogenes, controls production of a key metabolic cofactor

Many of the most common mutations that drive cancers activate a signaling network mediated by PI3 kinase (PI3K). Researchers co-led by Ludwig Harvard's Alex Toker used mass-spectrometry-based metabolomics and isotope tracing to examine the key metabolic effects of PI3K activation. They reported in *Nature* in late July that PI3K activation stimulates the cellular generation of a pivotal metabolic cofactor, coenzyme A (CoA). CoA is a carrier of a small molecular unit that cells use to build a variety of large biomolecules, like the lipids that compose their membranes. Alex and colleagues identify PANK4 as a key substrate of AKT, an enzyme activated by PI3K signaling. They show that PANK4 suppresses CoA synthesis, and that it is in turn regulated by AKT. The researchers argue that the PI3K–PANK4 axis regulates processes such as lipid metabolism and cell proliferation and helps coordinate cellular CoA supplies with the demands of normal hormone- and growth factor-driven as well as oncogene-driven metabolism and growth.

Alex Toker

PI3K drives the de novo synthesis of coenzyme A from vitamin B5 | *Nature*, 2022 July 27

Alexander Rudensky

Novel antigen presenting cell imparts Treg-dependent tolerance to gut microbiota | *Nature*, 2022 September 7

Novel cell aids development of T regs that suppress immune reactions to gut bacteria

To prevent autoimmune and other harmful reactions, the immune system must be taught to ignore the body's own antigens and those associated with harmless and even beneficial things like food and commensal bacteria. A study co-led by Ludwig MSK Director Alexander Rudensky and published in a September issue of *Nature* identified and characterized four types of antigen-presenting cells, named Thetis cells (TCs), that become prominent within intestinal lymph nodes and appear to play a critical role in the induction of tolerance in infants to commensal bacteria and food. One well known step of establishing tolerance occurs in the thymus, where medullary thymic epithelial cells eliminate auto-reactive T cells—preventing their dangerous persistence in the immune system—and promote the development of regulatory T cells (Treg), which suppress such responses. After exposure to antigens associated with food and commensal bacteria, a separate wave of Treg cell differentiation outside the thymus—in the "periphery"—occurs a few weeks after birth to ensure the suppression of T cells dangerously prone to reacting to these ordinary stimuli. The cells orchestrating this second wave of Treg development were, however, unknown. Alexander and his colleagues showed that a subset of Thetis cells are central to this second wave of Treg cell differentiation. Their studies suggest type IV TCs, which express high levels of molecules known to be essential for Treg differentiation, are the antigen presenting cells that participate in the induction of Treg-mediated tolerance to gut microbiota.

Joshua Rabinowitz

Gut bacterial nutrient preferences quantified *in vivo* | *Cell*, 2022 September 7

Mapping the dietary sources and preferences of gut bacteria

Ludwig Princeton Director Joshua Rabinowitz and his colleagues reported in a September issue of *Cell* their use of isotope tracing to map the nutrients consumed by bacteria in the mouse gut and their findings on the nutritional preferences of different types of bacteria in the microbiome. Tracing the incorporation of isotopes into bacteria-specific antigens, they found that fiber and protein are the main inputs that originate from the host diet. Major inputs generated by the host were found to be lactate, 3-hydroxybutyrate and urea, but not glucose or amino acids. Josh and his colleagues also mapped the nutrient preferences of different types of bacteria by tracing isotope incorporation into genus-specific proteins. For example, most genera in the phylum *Firmicutes* prefer dietary protein, while those belonging to *Bacteroides* have a predilection for dietary fiber. Changes in the relative diversity of microbiota that are induced by diet can be explained by the nutrient preferences of different microbes. Isotope tracing revealed that adding fiber to the host's diet boosts the proportion of microbes that thrive on fiber, while a diet rich in protein similarly affects the proportion of those with a taste for protein. The study lays the foundations for understanding how diet controls the composition of the host microbiome, which is emerging as a significant determinant of responses to cancer immunotherapy.

Spatial organization of purinergic signaling in glioma suggests immunotherapy target

A team co-led by Ludwig Harvard investigator Sandro Santagata reported in *Nature Communications* in August the findings from a study integrating a system for multiplexed tissue imaging developed at the Harvard Center and single-cell RNA-sequencing to explore the spatial organization and significance of purinergic signaling in high-grade gliomas (HGGs). Extracellular purinergic signaling involves the breakdown of ATP into adenosine, which is an important regulator of the tumor microenvironment and anti-tumor immune responses. CD39, an enzyme expressed by immune cells, and CD73, an enzyme expressed on cancer cells, cooperate to generate adenosine. Sandro and his colleagues found that CD73 levels in HGGs correlate with the differentiation state of tumor cells and the cancer-fueling amplification of EGFR. The spatial proximity of cancer cells expressing CD73 and immune cells expressing CD39 correlates with poor patient outcome in adult glioblastoma. Though pediatric high-grade gliomas, including diffuse intrinsic pontine glioma (DIPG), harbor genetic drivers distinct from those in adults, they too feature elevated interaction between cancer cell CD73 and microglial CD39. These results suggest that inhibiting this signaling pathway could be an attractive immunotherapeutic strategy in both adult and pediatric HGGs, as well as other brain tumors.

Single cell spatial analysis reveals the topology of immunomodulatory purinergic signaling in glioblastoma | *Nature Communications*, 2022 August 16

Sandro Santagata

Chi Van Dang

Immune cells can be engineered to counter the inhibitory effects of tumor acidity

High acidity in solid tumors can inhibit the function of the immune system's T cells and natural killer cells and compromise adoptive cell therapy and other immunotherapies. In this proof-of-concept study, researchers led by Ludwig's Scientific Director Chi Van Dang and former graduate student Yao-Yu Gong tested the metabolic engineering of immune effector cells to mitigate the inhibitory effect of tumor acidity. A common feature of advanced tumors, acidity suppresses the activity of a key regulator of metabolism known as mTOR complex 1 (mTORC1) in immune cells. Many studies have found that systemically countering acidity can reverse this effect and support checkpoint blockade immunotherapy. But Chi, Yao-Yu and colleagues reported in *Cancer Research Communications* in August that in MYC-driven liver cancer, such systemic buffering against acidity enhanced tumor cell mTORC1 activity and thereby dampened the effects of anti-PD-1 checkpoint blockade. To get around this problem, they engineered a natural killer cell line to express a permanently activated ion-exchanging protein, NHE1; SLC9A1, that counters acidity in the immune cells. This resulted in enhanced target engagement and antitumor activity of the cells in mice, demonstrating that the metabolism of immune cells employed for adoptive cell therapies can be engineered to overcome challenges posed by the tumor microenvironment.

Na+/H+-exchanger 1 Enhances Antitumor Activity of Engineered NK-92 Natural Killer Cells | *Cancer Research Communications*, 2022 August 22

Howard Chang

Multiomic analysis reveals conservation of cancer-associated fibroblast phenotypes across species and tissue of origin | *Cancer Cell*, 2022, November 14

Analysis of tumor fibroblast sub-populations reveals new strategies for cancer therapy

Cancer-associated fibroblasts (CAFs) are integral to the tumor microenvironment, but were long considered to be pretty uniform in nature and involved solely in the production of proteins for the extracellular matrix—or the stuffing between cells. But it is now clear that CAFs are far more active and complex constituents of tumors and display a variety of phenotypes, or functional states. Researchers co-led by Ludwig Stanford's Howard Chang probed CAF heterogeneity using a "multi-omics" approach examining chromatin accessibility and gene expression in single cells in relation to their spatial distributions in tumors and integrating these data to identify distinct phenotypic subtypes of CAFs in mice and in human tumors.

Howard and his colleagues identified three phenotypic superclusters of CAFs that they call steady state-like, mechanoresponsive, and immunomodulatory CAFs. These clusters, they reported in a November issue of *Cancer Cell*, are recapitulated across multiple tissue types and species. Immune checkpoint blockade therapy or disruption of underlying mechanical force induces shifts in CAF subpopulation distributions that influence tumor growth. The researchers suggest that tweaking the balance of CAF superclusters could be a novel strategy for cancer therapy and identify regulatory pathways responsible for distinct CAF phenotypes that point to potential therapeutic targets.

Michael Clarke

An oncogene expressed by a minority of breast cancer cells drives metastasis

Studies led by Ludwig Stanford's Michael Clarke have shown that a small population of cancer cells that exist in an immature state in breast tumors are primarily responsible for metastatic outgrowths. In a November paper in *Science Advances*, Michael and his colleagues reported that among these cells, those that express the oncogene LMO2 and display angiogenic features appear to be especially prone to initiating metastasis. Cells derived from this lineage, they show, integrate into the tumor vasculature in mouse models and have a higher propensity to metastasize. Suppressing LMO2 expression in human breast tumor cells reduced lung metastases in mice by compromising their ability to squeeze into blood vessels. This led to a reduction in the number of circulating cancer cells in the mice. The researchers also showed that higher expression of the oncogene in breast basal cells predicts poor distant metastasis-free survival in patients. They found that Lmo2 exerts its effects through regulation of the STAT3 signaling pathway, and that it is required for STAT3 activation by tumor necrosis factor-α and interleukin-6. They suggest that the STAT3-LMO2 signaling axis could be a key target for breast cancer therapy.

Identification of a minority population of LMO2+ breast cancer cells that integrate into the vasculature and initiate metastasis | *Science Advances*, 2002 November 9

A new way to study the altered activity of molecular scissors in living models of cancer

Researchers led by Ludwig MIT's Sangeeta Bhatia reported in an October issue of *Nature Communications* their development of an integrated set of methods to measure, at various scales, the activity of specific proteases—enzymes that snip protein molecules and are dysregulated in cancer. Studying enzyme activity in living cancerous tissue provides insight on their pathological roles and reveals clues to appropriately targeting specific enzymes for therapy. Sangeeta and her colleagues used a mouse model of *Alk*-positive lung cancer to study how targeted therapy affected the behavior of proteases in tumors. Applying multiplexed nanosensors and machine learning to analyze protease activity *in vivo* in lung tumors, the researchers observed extensive dysregulation of proteases, and zeroed in on the enhanced cleavage of one peptide nanosensor for further study. Analysis of enzymatic activity in tumors mapped this enhanced protease activity to their vasculature. The researchers also showed that the rate of nanosensor cleavage diminishes quickly in response to targeted therapy. Using a novel, high-throughput method to isolate and characterize proteolytically active cells, Sangeeta and colleagues uncovered a pro-angiogenic phenotype in those that cleave the nanosensor's peptide sequence. This work offers a widely applicable framework for studying protease dysregulation in cancer and highlights the therapeutic potential of targeting the tumor microenvironment along with cancer cells.

Sangeeta Bhatia

Multiscale profiling of protease activity in cancer | *Nature Communications*, 2022 October 03

Insights from integrating single cell gene expression and spatial profiling of pancreatic tumors

Researchers led by Ludwig MIT Co-director Tyler Jacks and alum Aviv Regev constructed a high-resolution molecular landscape of the cellular subtypes and spatial communities that compose pancreatic ductal adenocarcinoma tumors using single-nucleus RNA sequencing and whole-transcriptome digital spatial profiling on specimens that either received neoadjuvant therapy or were treatment naive. They reported in *Nature Genetics* in July their discovery of recurrent gene expression programs across malignant cells and fibroblasts, including what they describe as a neural-like progenitor malignant cell program associated with poor prognosis that rose in prominence following chemotherapy and radiotherapy. Their integration of spatial and cellular profiles uncovered three multicellular communities that had distinct contributions from subtypes of fibroblasts, cancer cells and immune cells. They suggest their refined molecular and cellular taxonomy offers a framework for patient stratification in clinical trials and could inform the targeting of specific cellular states and multicellular interactions.

Tyler Jacks

Single-nucleus and spatial transcriptome profiling of pancreatic cancer identifies multicellular dynamics associated with neoadjuvant treatment | *Nature Genetics*, 2022 July 28

ED McDERMOTT

A conversation with the president

Ed McDermott on his teachers, mentors and experiences over 34 years at the Ludwig Institute

Few people know as much about the anatomy, physiology, evolution and basic chemistry of Ludwig Cancer Research as Ed McDermott, president and CEO of the Ludwig Institute for Cancer Research. Ed has had a hand in the financing and functioning of the Institute for more than three decades, having worked at a law firm that represented various legal interests of our founder, Daniel K. Ludwig, before joining the Ludwig organization in 1988. Though trained as a lawyer, he started out overseeing the sprawling businesses—from tanker ships to international oil and gas interests to commercial real estate—that initially financed Ludwig's research. He very quickly became involved in the Institute itself after he was named secretary to Ludwig's Board of Directors in 1989 and then president of the organization in 1995.

We spoke with Ed about his youth, his mentors, teachers and formative experiences and his early years at Ludwig. We also asked him about his experience managing the

operations of the Institute, the thinking that shaped its strategy—and his thoughts about its future. We enjoyed the conversation immensely and are sure you will as well.

Where were you born and raised?

I was born in a town of about 60,000 in the Midwest—Dubuque, Iowa—on the Mississippi River, and I lived there till I was 12 years old, when our family moved to Washington, D.C. At that time, my father joined the John F. Kennedy White House, where he was on the National Security Council, head of what would be called the Federal Emergency Management Agency and part of the representation to NATO. He served in the White House until 1964, and we remained in the Washington, D.C., metropolitan area. So, I went to high school in D.C., went away for college and law school and then returned to start my law career.

Where were you educated?

In Iowa, I went to a Catholic grade school through sixth grade. And when we moved to Washington, I attended a Jesuit high school. Upon graduation I attended Colgate University in upstate New York and then Duke Law School.

Which of your teachers influenced you the most?

Among them was Sister Valerian, a young Dominican nun, who was my sixth grade teacher. She taught me to always do more, go beyond the limits of an assignment. When we moved, my sister, brothers and I had these little books, keepsakes, in which our friends wrote us notes. I still remember Sister Valerian's message in my book, which was two words: "Will it." That really stuck with me.

What inspired you to study law?

I had an obvious interest because that was my father's profession. I was interested in politics, and I spent two summers being a summer page in the U. S. Senate—one of the people who run around delivering messages to and from senators. Those were formative years, as it was during the start of the Vietnam War and the protests. I was there for the vote on the '64 Civil Rights Act and '65 Voting Rights Act. In those days, when Senators filibustered they had to stand and talk the whole time. That tended to discourage frequent use of the procedure. I think we need to go back to that. There were these filibusters by Senator Ernest Gruening from Alaska, and a Senator Wayne Morse from Oregon who early on opposed the war in Vietnam. And we'd sit there all night and serve them coffee. Seeing the process led to my majoring in political science in college, which contributed to my fascination with the law.

> "At their peak Mr. Ludwig's businesses were of unbelievable scale, employing some 35,000 people."

What did you do after law school?

I came back from North Carolina and joined a law firm in Washington D.C., where I became a partner. I practiced there for 14 years, and that's where I became acquainted with the Ludwig organization. I focused on commercial transactions, mergers and acquisitions, as well as administrative law—representing clients before administrative agencies.

How did you get involved with the Ludwig Institute?

I joined the organization in July 1988. Mr. Ludwig had been a client of the firm for some

years, particularly for his shipping activities. He also owned financial institutions operating in five Western states. In the early 1980s, I started to represent him in those interests and, ultimately, joined the boards of those financial institutions. Mr. Ludwig, who was born in 1897, was well on by then and had delegated overall management responsibility to a good friend of his by the name of Jim Kerr, who lived in La Jolla, California. In 1988, I had closed a deal for the Ludwig organization in Hawaii and Jim asked me to stop in California on my way back to DC. When we met, he said to me, 'I want you to come and work with me.' And I said, 'Well, I'm very, very flattered, but I'm not really interested in being in-house counsel.' And he said, 'No, I want you to come on the business side.' And I thought to myself, 'he must not know me very well.' Initially my engagement was with Mr. Ludwig's commercial entities, not the Ludwig Institute, but Jim quickly introduced me to the Institute and gave me responsibilities with that as well.

Tell us about the "business side." What was its relationship to the Ludwig Institute?

At this time, the Ludwig Institute sat at the pinnacle of a pyramid, which was a vast commercial enterprise. It wholly owned a range of companies that were run below the Institute level by Jim Kerr. I joined initially as a senior officer of the tank ship company. We had a fleet of super tankers, and we had oil and gas exploration interests in Indonesia and the North Sea. We had 50% ownership of 3 million square feet of commercial office space in Manhattan. At their peak Mr. Ludwig's businesses were of unbelievable scale, employing some 35,000 people.

How did your role then evolve over time?

I joined in July of 1988, and I think I attended my first Ludwig Institute Board meeting in September of the same year. I became president of Universe Tankships Inc. in 1991 and had responsibilities with National Bulk Carriers as well. I learned more from Jim in about six or seven years than I did from anybody else in my lifetime. He could see around corners; he saw a problem coming that you didn't even have a hint was there. And he was very demanding. I think I must have given him six letters of resignation because I felt I had so disappointed him in things.

Did you work closely with Lloyd Old?

Lloyd had initially been an advisor to Mr. Ludwig on the formation of the Institute. Jim brought him on as scientific director right around the same time I came aboard. Lloyd and I worked closely together for his entire time here.

Can you tell us a little about your move into the Ludwig Institute and your role?

It was really Lloyd Old who got me more and more involved in the intricacies of the

> "One of the things I would like our staff members to always remember is that the asset base that supports Ludwig was built with the sweat and blood of thousands of people. It didn't just didn't arrive here from nowhere."

Institute. I became secretary to the Board in 1989. I was general counsel for a time, and then became president in 1995. At that time, we had 10 Branches, and all the staff at those Branches were Ludwig employees. So, we had to be aware of the labor and social rules in each country in which the Branches operated. There was a lot more nuance to the management of the Branches those days. Lloyd had a vision, and I was there to help implement it.

What was the Institute like at the time?

Ludwig's operations were expanding through the nineties. One of the great attributes of the Ludwig Institute is how it takes on responsibility for the full continuum of discovery. And at the time, that led us to start our own clinical trials program, to build our own GMP manufacturing facilities because the pharmaceutical companies wouldn't produce the small, pilot grade quantities of agents that we needed. No other academic institution had these capabilities. We also brought the management of clinical trials in house because although there were commercial contract research organizations, they didn't have the expertise in immunology that we required. We disbanded the production facilities when circumstances changed, and you could go out and commission small lots commercially. Similarly, with the clinical trials group, it's now possible to harness the immunology expertise we need commercially rather than having to support it internally.

Which of the decisions you've made have been most rewarding to you?

When I first joined, the Ludwig Institute sat at the top of a formidable commercial pyramid. After the Exxon Valdez disaster in Alaska in the late 1980s, the U.S. Congress passed a law that essentially exposed everyone in the chain of transportation of oil to unlimited liability. Our ships were chartered out to major oil companies, but when I saw news clips of people with towels dabbing rocks on the coast that were slick with oil from the spill, I realized that as fiduciaries, we could not continue to operate in this manner. It took a great deal of confidence on Jim Kerr's part to dismantle Mr. Ludwig's commercial empire, but that's what we did. Converting and diversifying the asset base to a much more conventional endowment structure and composition was a very important moment for the Institute's future, though that was not immediately apparent. On August 1st, 1990, we deposited $500 million in sales proceeds with two groups of asset managers, and in the first month we lost $50 million because, on August 3rd, Iraq invaded Kuwait. Reporting at the first Board meeting on how we'd diversified to lower the Institute's risk profile was less than convincing.

Then again, on the financial side, at the beginning we had outsourced the management of the LICR Fund assets to consultants, but I was never particularly satisfied with what we were getting as a result. When I became president of the

Institute and the Fund, we started to develop in-house capabilities for managing our financial assets. Our performance went from matching peers to progressively doing much better than them, and that continues.

And on the Institute side?

A real point of pride for the Institute was, again, embracing and demonstrating the capability to handle the full discovery spectrum from lab to early clinical trials. Another was our restructuring in the 2011-2012 period, when we consolidated from 10 Branches to three. The effects of the recession of 2008 on our asset base were very distressing. But they forced us to really consider how sustainable the 10 Branch structure was and the way we were organized. It was very administratively top heavy. Due to audit requirements, you needed checks and balances, so you needed an administrative team of a certain number at each Branch, whether you had five staff members or 50. In addition, team science was becoming more and more what we thought needed to be done, so we wanted more critical mass. For example, a million dollars for a piece of equipment wasn't outrageous, but you wanted it someplace where it was going to be used 24/7, not three days a week. I think focusing on three core sites, though initially painful—we had great scientists at these other sites—was imperative for the long term.

Has the pandemic affected how we think about collaboration?

Clearly the pandemic demonstrated that we could effectively maintain activities virtually. The experience caused many people to look at how much time was spent traveling or commuting and realize how unproductive that use of time can be. By the same token, now that we can meet together, I sense a level of resistance sometimes to having an in-person meeting as opposed to a virtual meeting. That's particularly the case when travel is involved. And I think the one thing that I've really missed through the pandemic and working virtually is the personal interactions.

I think those are very important. I mean, people talk about water cooler conversations. For example, with our Board, important conversations often happen over breakfast or dinner or during breaks in one-on-one conversations, rather than at the formal meeting. So, the tension of what can be done best virtually and what really is best done in interpersonal meetings is going to be something that has to be worked out. I think the hybrid in-office model that we have in New York is an effective accommodation.

What are your hobbies or other avocational interests?

I run, I cycle, I boat, I ski, I play squash. But I'm not a golfer. I try to be active, as most of my work life is pretty sedentary. I enjoy reading, I enjoy history—especially political history—more than fiction.

Is there anything else you like to say that we haven't touched on here?

One of the things I would like our staff members to always remember is that the asset base that supports Ludwig was built with the sweat and blood of thousands of people. It didn't just didn't arrive here from nowhere. It is Mr. Ludwig's legacy, but it's also the legacy of the many thousands of people who worked at his companies over the decades. We owe it to them as much as we owe it to Mr. Ludwig to produce.

What aspect of tumor metabolism is most promising in terms of a target for novel cancer therapy or immunotherapy?

CAROLINE BARTMAN
Ludwig Princeton

Strategies to starve cancer of energy, like mitochondrial uncoupling drugs or very low-carbohydrate diets. We recently discovered that tumors make cellular energy much slower than most healthy tissues, meaning that tumors live and proliferate using an extremely tight energy budget. When cancer starvation is combined with chemotherapy or radiation, starved cancer cells may not have the energy to repair the damage.

ELISABETTA CRIBIOLI
Ludwig Lausanne alum

Tumor cells fiercely compete with T cells for a limited supply of nutrients that are needed as 'building blocks' or as energy sources. One promising approach to improving adoptive T cell therapy (ACT) is to engineer T cells to boost their metabolic fitness. For example, we enforced expression of the high affinity glucose transporter GLUT3 in cytotoxic T lymphocytes and demonstrated that the cells had higher energy storage and superior ability to control tumors when they were used for ACT.

ALEX MUIR
Ludwig Chicago

It is hard to pick a single target. This field is blossoming with many promising ideas and targets. One area in particular our team is excited about is lipid metabolism. Cancer biologists have learned much about how lipid metabolism is rewired in many tumors, especially those that become metastatic and therapy resistant. I think the field is primed to translate this knowledge into new therapeutics.

SILVIA PANETTI
Ludwig Oxford

The aspect of tumor metabolism that I find most intriguing is the competition between the tumor and the immune system for nutrients at the tumor site. From glucose to amino acids, a decisive element for immunotherapy success is the ability to fuel the anti-cancer response and overcome those metabolic checkpoints encountered. A promising therapeutic strategy would be to modulate the ability of cellular immunotherapies to take up essential molecules, thereby enabling the therapies to reach their full potential in the harsh tumor microenvironment.

Ask a scientist

Augmenting nutrient availability to tumor-fighting T cells. The tumor metabolic microenvironment is depleted in critical nutrients, including oxygen, glucose, glutamine and nucleotide precursors. Bolstering these helps T cells fight tumors. For example, we've recently found synergy in mice between checkpoint blockade and dietary supplementation with one-carbon units, a key feedstock of nucleotide synthesis.

JOSHUA RABINOWITZ
Ludwig Princeton

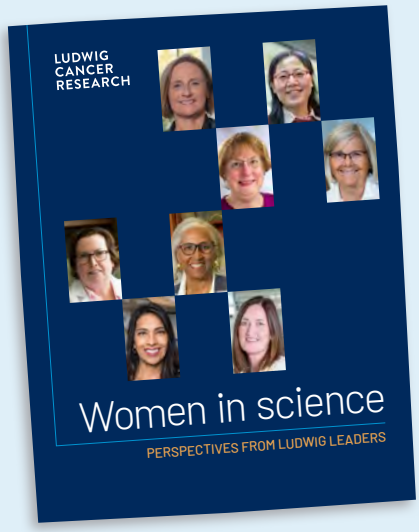
Tumor metabolism provides intrinsic and extrinsic support for tumor outgrowth and immune evasion. Elucidating the metabolic processes and underlying mechanisms by which tumor cells disarm anti-tumor immunity will be a springboard for the development of new cancer immunotherapies.

PING-CHIH HO
Ludwig Lausanne

Immune effector cell therapies have huge therapeutic potential and can prolong lives of cancer patients. Yet we have much to learn about preparing products with long lasting anti-tumor activity and memory functions. Metabolic intervention during cell manufacture may help produce fitter cells with enhanced expansion, function and persistence upon adoptive transfer, even in tumors with complex microenvironments.

CAROLINE ARBER-BARTH
Ludwig Lausanne

SPECIAL REPORT



A celebration of women scientists and leaders from across Ludwig Cancer Research

The Communications team released a report in November, *Women in Science: Perspectives from Ludwig leaders*, profiling a handful of women leaders from across Ludwig Cancer Research—principal investigators, advisors, directors—covering their lives, careers and views on gender-related issues. The report sought to contribute to an ongoing global discourse on the challenges faced by women in science and serve as a celebration of women leaders in the Ludwig community, sharing their insights on matters ranging from science to leadership to family. Many of the scientists we profiled spoke about how essential it was for them, early on, to develop confidence in their scientific acumen, and all recalled with gratitude the mentors who shaped their careers. Several also described how they try to open doors and extend opportunities to other talented women in their field. Much of the advice they offered to young scientists is of relevance to all genders: to be prepared to accept the opportunities for advancement, for example, or to take educated risks and remain unperturbed by the failure of experiments. Almost all emphasized the importance of reserving time and attention for family and explicitly advocated for more institutional support for scientists—men and women—raising young children or caring for elderly parents.

If you haven't yet seen the report, you can access it by clicking here.

LUDWIGCANCERRESEARCH.ORG