LUDWIG LINK

DECEMBER 2020

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

LUDWIG LINK

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LETTER

Welcome to the December issue of Ludwig Link.

Despite the lockdowns, social distancing and sundry inconveniences that have accompanied the COVID-19 pandemic, our researchers found creative ways to continue their work and publish results. There's ample proof of that in this issue's research briefs, which include reports of a potentially new approach to preventing the recurrence of an aggressive brain cancer following radiotherapy, a possible drug target to gum up the machinery of cell motility and stall cancer metastasis and the identification of a "synthetic lethal" interaction that might be exploited to treat triple negative breast cancer.

Along with the usual coverage of some of the awards and honors earned by Ludwig-affiliated researchers, we introduce the community to Juanita Merchant, who has recently joined the Scientific Advisory Committee, and Yang Shi, the newest Member of Ludwig Oxford. You can learn more about Yang in our Q&A, which begins on page 17.

In our Ask a scientist section, we asked a few of your colleagues about the feasibility of a program to accelerate the development of therapeutic vaccines and other immunotherapies for major types of cancer, much as the U.S. government did with Operation Warp Speed for the COVID-19 pandemic. Find out what they said on pages 22 and 23.

Happy reading!

Rachel Reinhardt
Senior Vice President for Communications

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FOR OUTSTANDING ACHIEVEMENTS

Three Ludwig researchers were recognized for their scientific contributions by the American Association for Cancer Research (AACR). In June, Ludwig Harvard's Cigall Kadoch and Ludwig MSK's Jedd Wolchok received the 2020 AACR Award for Outstanding Achievement in Basic Cancer Research and the 2020 AACR-Joseph Burchenal Award for Outstanding Achievement in Clinical Cancer Research, respectively; Ludwig MIT Co-director Tyler Jacks received the 2020 AACR Princess Takamatsu Memorial Lectureship in May. Cigall was recognized for her pioneering biochemical and functional characterization of normal and abnormal SWI/SNF chromatin remodeling complexes, which regulate the packaging and availability of DNA to the cell's gene-reading machinery, and thereby dynamically modulate gene expression. These complexes are frequently disrupted in human cancer and developmental disorders. Jedd received recognition for his leadership in the clinical development of anti-CTLA-4 immunotherapy for melanoma, and for a raft of subsequent work that helped usher in the current era of checkpoint blockade cancer immunotherapy. Tyler, meanwhile, was recognized for his laboratory's prolific development of sophisticated mouse models for the study of tumorigenesis, and for his discoveries related to oncogenes, tumor suppressor genes, cell death, and the immune regulation of tumor progression. The prestigious lectureship is awarded to a scientist whose contributions have "had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of cancer." Tyler gave a virtual lecture at the 2020 AACR Annual Meeting, and Cigall will give hers virtually in 2021.

Ping-Chih Ho
Ludwig Lausanne

FOR TRANSFORMATIVE IMMUNOLOGY

Ludwig Lausanne's Ping-Chih Ho received a Cancer Research Institute CRI Lloyd J. Old STAR award in August in recognition of his contributions to the field of immunometabolism, which explores how the metabolic adaptations of tumors influence the anti-cancer immune response and how that molecular chatter can be disrupted for cancer therapy. In 2019, for example, Ping-Chih and his colleagues discovered that melanoma tumors expressing a metabolic enzyme known as UCP2 draw key anti-tumor immune cells into their microenvironment, making them more susceptible to checkpoint blockade immunotherapy. They also identified a diabetes drug rosiglitazone, that spurs UCP2 expression, making resistant tumors susceptible to checkpoint blockade. More recently Ping-Chih and his team showed that blocking the cell-surface protein CD36 selectively depletes suppressive immune cells known as regulatory T cells within the tumor microenvironment without affecting their counterparts in other tissues. In October, they showed that metabolic stress in the tumor microenvironment hampers antitumor responses in tumor-infiltrating CD8 T cells by disrupting their mitochondrial fitness. These findings could be exploited to boost the effects of checkpoint blockade in a mouse model of melanoma. The STAR award grants $1.25 million over five years to mid-career scientists engaged in highly original research of potentially transformative value to cancer immunology and immunotherapy.

IN MEMORIAM: MARTIN TATTERSALL

Martin Tattersall, who was director of the Sydney Branch of the Ludwig Institute for Cancer Research, died on August 30 in Sydney, Australia. Recruited to the University of Sydney in 1977, Martin joined the Ludwig Branch that same year, was named its director in 1979 and led the Branch until it closed in 1987. He contributed enormously to his chosen field, both in the laboratory—where he explored the cytogenetics and molecular pathology of a wide variety of cancers—and in the clinic, publishing 480 scholarly articles over the course of his career. Hospitalized following a near-fatal skiing accident in the 1990s, Martin was dismayed by the poor communication from his physicians. The experience intensified his interest in the patient experience, and his research increasingly focused on the language, dynamics, optimization and outcomes of communications between cancer patients and doctors, clinical researchers and medical institutions. A lifelong world traveler and adventurer, Martin was a member of the World Health Organization's cancer committee for more than 20 years and worked on their behalf in Iraq in the early 2000s. He mentored a generation of Australian medical students, oncologists and researchers and traveled widely to teach medical oncology to physicians in developing countries.

Juanita Merchant
Ludwig Institute
Scientific Advisory Committee

JOINING THE SCIENTIFIC ADVISORY COMMITTEE

In July, Juanita Merchant was appointed to the Scientific Advisory Committee of the Ludwig Institute for Cancer Research. A gastroenterologist and cancer researcher, Juanita has made notable contributions to our understanding of the molecular mechanisms by which chronic inflammation and *Helicobacter pylori* infection contribute to the development of gastric and intestinal cancers. Juanita is also a practicing clinician and professor and chief of gastroenterology and hepatology at the University of Arizona, Tucson. As a co-investigator in the Partnership for Native American Cancer Prevention, she is studying the potential use of biomarkers to improve gastric cancer diagnosis in Native Americans with *Helicobacter pylori*. She is also working on how to ensure respectful, culturally sensitive and effective interactions between physicians and underserved Native American communities. Juanita earned her MD and PhD from Yale University in 1984 and completed her residency at the Massachusetts General Hospital in Boston, where she also was a research fellow. She is member of the American Academy of Arts and Sciences and of the National Academy of Medicine, for which she currently serves on the Council. Juanita also hosts cooking classes sponsored by the University of Arizona designed to encourage a healthy diet.

Yang Shi
Ludwig Oxford

LUDWIG OXFORD'S NEWEST MEMBER

Yang Shi was appointed Member of Ludwig Oxford in July. Yang is a leader in the field of epigenetics, which explores how chemical modifications made to chromatin—DNA and its histone protein packaging—control the expression of the genome. Aberrations in those processes contribute to a wide variety of cancers. In 2004, Yang and his colleagues identified and characterized an enzyme, LSD1, that erases methyl marks from histones. Their discovery upended a 40-year-old dogma that considered such modifications irreversible, altering longstanding models of genomic regulation. Yang's laboratory has since identified many other histone demethylating enzymes and LSD1 inhibitors are now in clinical trials for cancer therapy. More recently, his group has discovered enzymes that methylate RNA and possibly influence the translation of gene transcripts into proteins. Prior to joining Ludwig, Yang was professor of cell biology and C. H. Waddington professor of pediatrics at Harvard Medical School. He obtained his PhD from New York University and completed his postdoctoral training at Princeton University. He is a fellow of the American Association for the Advancement of Science and a member of the American Academy of Arts and Sciences. To learn more about Yang, check out our interview with him on Page 17 of this issue.

ADDRESSING LOSS

Atypical teratoid rhabdoid tumors (ATRT) are rare and fast-growing cancers of the brain and spinal cord. About half of ATRTs begin in the cerebellum or brain stem and usually strike children three years or younger. The cancer is primarily linked to inactivation of a gene called SMARCB1, a subunit of the BAF complex, which helps regulate gene expression in developmental processes by remodeling chromatin (the collective term for DNA and its protein packaging). In a September paper in *Genes & Development*, a team led by Ludwig San Diego's Frank Furnari described how the loss of the tumor suppressor gene SMARCB1 affects neural development. The researchers engineered human induced pluripotent stem cells to lose SMARCB1 on demand and studied the effects of that loss on the differentiation of the cells into either neurons or cerebral organoids—cultured mimics of brain tissue. Frank and his team identified an interaction between SMARCB1 loss and neural differentiation pressure that causes a resistance to terminal differentiation and a defect in maintaining a normal cell state, which resembled that observed in ATRT. The researchers plan to use their model to identify drug targets that restore normal neural development to treat the cancer.

Frank Furnari
Ludwig San Diego

Skirmantas Kriaucionis
Ludwig Oxford

SUBTLETIES OF REPRESSION

One important way in which cells regulate gene expression is by managing access to DNA, which is wound around protein spools and packed into a structure called chromatin. Accessibility enables interaction with regulatory molecules and the enzymes that transcribe genes. Numerous chemical, or epigenetic, modifications to chromatin are known to alter its structure to govern access, but how they collaborate functionally has been a puzzle. In a September paper in *Genome Research*, a team led by Ludwig Oxford's Skirmantas Kriaucionis reported the analysis of two epigenetic mechanisms—DNA methylation and histone deacetylation—of gene repression. The former acts both directly, by altering the binding of transcription factors, which initiate the reading of genes, and indirectly, by recruiting repressor protein complexes containing histone deacetylases (HDACs). Both processes are targets for cancer therapies. Yet it has been unclear how much of the repressive effect of DNA methylation is due to the downstream activity of HDACs rather than effects independent of deacetylation. To find out, the researchers studied how the two epigenetic events affect chromatin accessibility, the occupancy of transcription factors and gene expression. They report that DNA methylation and HDACs function largely independently, although they can act redundantly on some regions of the genome. This suggests combining HDAC inhibitors with DNA methylation inhibitors might be an effective strategy for cancer therapy.

Karen Oegema
Ludwig San Diego

Andy Shiau
Ludwig San Diego

Arshad Desai
Ludwig San Diego

Franz Meitinger
Ludwig San Diego

CONDITIONAL VULNERABILITY

Centrosomes are cellular organelles that help parcel out equal numbers of chromosomes to daughter cells in the late stages of cell division. But many types of cancer cells can complete that process—chromosomal segregation—even when they lack centrosomes, as Ludwig researchers led by Karen Oegema and Andy Shiau reported in *Science* in 2015. That study found that centrinone, a highly specific inhibitor of PLK4, an enzyme essential for centrosome formation, could reversibly deplete centrosomes from a broad panel of cancer cells but did not block their division. In a study reported in *Nature* in September, a Ludwig San Diego team led by Karen, Arshad Desai and Franz Meitinger demonstrated that specific cancers might indeed be sensitive to PLK4 inhibition. That sensitivity, they showed, depends on the presence of a second enzyme, the ubiquitin ligase TRIM37. When this enzyme is at low levels, cancer cells continue dividing despite PLK4 inhibition. Cancer cells with high levels of TRIM37, however, stop proliferating under such conditions. Notably, subsets of breast cancers and neuroblastomas with known chromosomal abnormalities overexpress TRIM37. The researchers detailed the mechanism of this vulnerability and showed that TRIM37 over-expression could serve as a marker of cancers likely to respond to treatment with an improved PLK4 inhibitor, like those under development by Andy Shiau and Ludwig's Small Molecule Discovery program.

FROZEN MOTION

Metastasis causes approximately 90% of all cancer-related deaths. In August, a team of researchers led by Ludwig Chicago Co-director Ralph Weichselbaum and Ronald Rock of the University of Chicago described in the *Proceedings of the National Academy of Sciences* a potentially new way to hamper the process. They reported that a compound, 4-hydroxyacetophenone (4-HAP), compromises the ability of cancer cells to change shape and migrate by activating a protein in the cancer cell called nonmuscle myosin-2C (NM2C). This protein helps control the stiffness of cells and organizes components of the cytoskeleton known as actin filaments that play a central role in cell motility. On the basis of evidence from some elegant microscopy, Ronald, Ralph and colleagues hypothesized that NM2C's abnormal activation freezes it on certain types of actin filaments, gumming up the machinery of cellular migration. When colon cancer cells were injected into the spleen in a mouse model for liver metastasis, dosing the animals with 4-HAP significantly reduced the burden of tumors compared to untreated counterparts. Although 4-HAP is not likely to work as a drug, the researchers now have a druggable target—NM2C—against metastasis and hope to evaluate the combination of NM2C activation in animals with radiotherapy or chemotherapy.

Ralph Weichselbaum
Ludwig Chicago

Paul Mischel
Ludwig San Diego

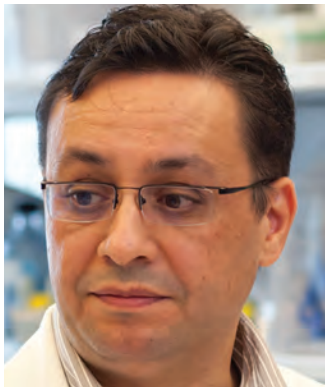
DANGEROUS CIRCLES

In a study reported in *Nature Genetics* in August, Ludwig San Diego's Paul Mischel and colleagues showed that the amplification of cancer genes located on free-floating circles of DNA in the nucleus, or extrachromosomal DNA (ecDNA), is associated with poor patient outcomes across multiple types of cancer. Paul and his colleagues have previously shown that ecDNA is hardly ever seen in healthy cells and is associated with accelerated tumor evolution and high cellular heterogeneity in tumors, which often drive drug resistance. But it wasn't entirely clear how common ecDNA is across cancer types and what its clinical impact might be. Paul and his team found that ecDNA occurs at minimum in 14% of human tumors, and much more frequently in the most malignant forms of cancer, such as the brain cancer glioblastoma, sarcoma, and esophageal, ovarian, lung, bladder, head and neck and gastric cancers. The ecDNAs were found to be significantly enriched for oncogenes. Patients with ecDNA amplification have significantly worse five-year survival outcomes than those without, so strategies that target ecDNA for cancer therapy could yield significant dividends. Paul is co-founder of a startup, Boundless Bio, that plans to develop such therapies.

AN EVIL AXIS

Ludwig MSK's Jedd Wolchok, Taha Merghoub and their colleagues described the mechanism by which the aryl hydrocarbon receptor (AHR) suppresses anti-tumor immune responses in tumors that express high levels of IDO and TDO, enzymes associated with immune suppression in a wide variety of cancers. The study, reported in an August paper in *Nature Communications*, found that AHR signaling is selectively activated in such tumors and examined the effects of its inhibition. A product of IDO/TDO activity, L-kynurenine, interacts with AHR in the tumor microenvironment to drive the generation of suppressive immune cells—regulatory T cells (Tregs) and myeloid derived suppressor cells—and prompts killer T cells to express PD-1, which dampens their anti-tumor activity. Jedd, Taha and their colleagues showed that the AHR signaling pathway drives resistance to immune checkpoint blockade. This mechanism of immune suppression, they found, stems from an interplay between Tregs and tumor-associated macrophages. Targeting this axis with an AHR inhibitor reverses IDO/TDO-mediated immune suppression and slows tumor growth in mice. This effect is amplified when the treatment is combined with PD-1 blockade immunotherapy, suggesting the combination should be tested in a clinical trial and could be a basis of personalized medicine for patients with tumors expressing IDO, TDO or showing IDO/TDO-Kyn-AhR pathway activation.

Jedd Wolchok
Ludwig MSK



Taha Merghoub
Ludwig MSK

Richard Kolodner
Ludwig San Diego

DEADLY SYNERGY

Ludwig San Diego's Richard Kolodner and colleagues reported in the *Proceedings of the National Academy of Sciences* in July a "synthetic lethal" interaction that might be exploited for therapy in cancers with mutations in their BRCA1 and 2 genes, which are implicated in breast, ovarian and other cancers. Synthetic lethality occurs when the mutation of two genes—neither of which is on its own vital to cell survival—causes cell death. Building from their studies on yeast cells, Richard's team discovered that disabling or removing FEN1, a mammalian gene that is important for DNA replication and repair, is deadly to cancer cells with BRCA mutations. Similarly, a drug-like FEN1-blocking molecule they synthesized, C8, replicated the effects of FEN1 loss and proved to be an effective killer of such cells. The researchers then grafted C8-sensitive and C8-resistant tumors into mice and showed that C8 significantly inhibited the growth of the C8-sensitive tumors but not the C8-resistant tumors. Notably, not all the cancer cell lines and tumors that responded to C8 treatment were BRCA deficient, indicating that FEN1 has synthetic lethal interactions with other genes as well. These findings identify FEN1 as a novel target for drugs to treat a variety of malignancies.

MOUSE ENHANCEMENT

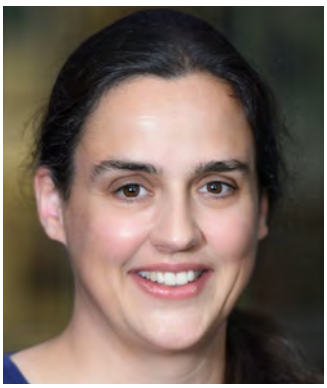
Cells typically burn sugars to generate energy. When short on nutrients, however, they switch over to burning fats. In a paper published in *Cell Metabolism* in July, Ludwig Harvard investigator Marcia Haigis and her colleagues detailed the central role played by the enzyme PHD3 in making that switch. Most intriguingly, they found that a deficiency of PHD3 dramatically boosts exercise endurance in mice. Marcia and her team had previously shown that the loss of PHD3 makes some types of cancer cells dependent on burning fat. In this study, they show that in healthy cells PHD3 works as a sensor of nutrient availability.

When nutrients are abundant, PHD3 chemically modifies and inhibits another enzyme, ACC2, to curtail the passage of fats into the mitochondrion, where they are burned for energy. But when the nutrient supply drops, an enzyme named AMPK activates ACC2—and tags it with a different chemical modification that shields it from PHD3's activity—to drive fat metabolism. Mice engineered to lack PHD3 showed enhanced exercise endurance. They could run 50% farther and 40% longer than their unaltered counterparts and boasted a much higher VO2 max, a measure of maximum oxygen uptake during exercise.

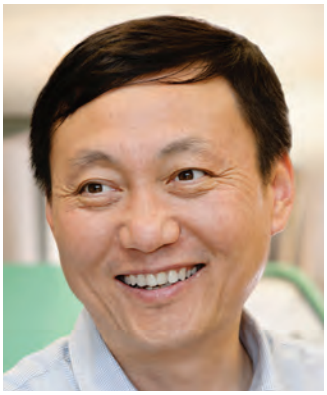
Marcia Haigis
Ludwig Harvard

CELLULAR TWOFER

In the immune system's scheme of things, killer T cells are the assassins of infected and cancerous cells, while helper T cells are like generals, orchestrating and managing multiple aspects of the immune response. Killer T cells are the primary focus of cancer immunotherapies now in use and under development. But helper T cells can be engineered—with the addition of a killer T cell antigen receptor and the distinguishing markers of these cells, CD8α and β—to generate hybrid helper-killer T cells that are potent destroyers of cancer cells. In a July *Science Advances* publication, Ludwig Lausanne's Caroline Arber and her colleagues detailed the gene expression programs that give these hybrids their potency. By profiling the global gene expression patterns of individual hybrid helper-killer T cells and comparing them to those of regular killer T cells, the researchers identified multiple genetic programs activated in the hybrid cells that appear to account for their heightened efficacy—showing, for example, that they appear to be more resistant to exhaustion and primed for proliferation. The findings not only contribute to the design of such hybrid T cells for cancer therapy, but provide insights that can be applied to improve the potency of T cells used in other types of cellular immunotherapies.



Caroline Arber
Ludwig Lausanne



Bing Ren
Ludwig San Diego

ELEMENTAL MURINE MAP

The Encyclopedia of DNA Elements (ENCODE) project just published in July its third installment of papers detailing the regulatory DNA sequences across the human and mouse genomes. Ludwig San Diego's Bing Ren led one of the studies reported in *Nature*. Bing's study charted the gene expression patterns, histone modifications (chemical marks that regulate gene expression) and accessibility of DNA to the cell's gene reading and regulatory machinery in 12 distinct tissue types over the course of eight developmental stages in mice. Integrating these data revealed the activity of thousands of genes across tissues and developmental stages and more than 500,000 candidate DNA sequences that regulate their expression across various stages of mouse fetal development. They discovered that genetic risk variants for a variety of human diseases are located in regions of the human genome that share evolutionary origins with regulatory sequences mapped on the mouse genome. The findings shed light on the genetic origins of a number of developmental diseases and have reassuring implications for the use of mouse models for the study of a variety of diseases.

Johanna Joyce
Ludwig Lausanne

THERAPEUTIC RECONVERSION

Ludwig Lausanne's Johanna Joyce and colleagues reported in *Science Translational Medicine* in July how radiotherapy affects immune cells known as macrophages in glioblastoma (GBM) tumors and showed how these cells might be reprogrammed to control GBM recurrence. Gliomas harbor both the brain's resident macrophages, microglia (MG), and recruited monocyte-derived macrophages (MDM), which ordinarily patrol the body. Gliomas can push both into an alternative activation state—the M2-like phenotype—in which they support tumor growth. The researchers found both MG and MDMs flood into GBM tumors in mice following an initial course of radiotherapy, and their M2-like phenotype is further exacerbated. When the gliomas recur, it is MDMs that predominate within them. Johanna's lab has previously reported that CSF-1R inhibitors can reverse the M2-like phenotype. In the current study, they used one of these drugs to show that a daily regimen of CSF-1R inhibition following radiotherapy effectively reprogrammed TAMs and extended survival through the full six months of the study for 95% of the mice, compared to a survival increase of nearly three weeks observed with radiotherapy alone. By contrast, short-term CSF-1R inhibition (for 12 days) plus radiation resulted in only a transient improvement, which may have implications for the evaluation and dosing regimens of such drugs in clinical trials.

TARGET: TRIPLE-NEGATIVE BREAST CANCER

A set of intracellular signaling cascades referred to as the SMAD pathway are involved in controlling the proliferation and optimal maintenance of epithelial cells, which line body cavities. Ludwig Stanford researcher Michael Clarke and colleagues reported in *Cell Stem Cell* in July that a factor secreted by mammary stem cells, LEFTY1, inhibits SMAD2 and plays a central role in breast development and maintenance as well as in the genesis of certain breast cancers. LEFTY1, they found, is produced by mammary progenitor cells and drives proliferation of both normal and malignant mammary epithelial stem cells. The protein opposes an anti-proliferative signal transmitted to mammary stem cells by a protein named BMP7. Studies in xenografts of triple-negative breast cancer revealed that in breast cancer stem cells, LEFTY1 interacts with a protein named BMPR2—a transducer of the BMP7 signal—to drive cell proliferation. Such cells, it turns out, are highly dependent on LEFTY1 for proliferation. This suggests LEFTY1 might be a target for the development of drugs that disable cancer stem cells in triple-negative breast tumors, which remain notoriously difficult to treat.

Michael Clarke
Ludwig Stanford

Alex Toker
Ludwig Harvard

DANGEROUS MALINGERING

In a June *Cancer Discovery* paper, researchers led by Ludwig Harvard investigator Alex Toker and alumnus Hui Liu described a novel molecular mechanism that drives a large proportion of triple-negative breast cancers. About 80% of all TNBC tumors are characterized by the loss of the tumor suppressor INPP4B. The team developed a genetically engineered mouse model that lacked one or both of its INPP4B genes and showed that the lower the levels of INPP4B, the more tumors developed in the mice. As expected, cells from those tumors displayed an abnormal activation of the PI3K/AKT signaling pathway. But, surprisingly, an additional pathway that drives cell proliferation—driven by the EGF receptor, which signals through a protein named MEK—was also potently active in the tumors. After it is activated, the EGF receptor is internalized and continues signaling until it is either returned to the surface or degraded and digested. The loss of INPP4B, it turns out, suspends the movement of the EGF receptor, prolonging its signaling and fueling an additional pathway conducive to cell proliferation. The researchers reported that a number of drugs that target MEK and PI3K signaling inhibited tumors in the mouse model, with an approved PI3K inhibitor extending the survival of mice most significantly.

Irv Weissman
Ludwig Stanford

DIETARY INTERVENTION

In a June paper in *mBio*, a team of researchers from Ludwig Stanford led by Irv Weissman and colleagues at the National Institutes of Health reported that cells infected with many viruses (including SARS-CoV-2, which causes COVID-19) and bacteria like the one that causes tuberculosis step up expression of a protein named CD47. This protein, which Irv and his team have shown is expressed by a broad variety of cancer cells, transmits a "don't eat me" signal to immune cells known as macrophages, which would otherwise gobble up sick cells. Irv and his colleagues found that mouse and human cells boost CD47 expression within 24 hours of infection, likely as a measure of control over the mounting immune response, which can cause deadly, systemic inflammation when uncontrolled. They also showed that an antibody to CD47 analogous to one developed by Irv and colleagues that is now in clinical trials against multiple cancers could suppress viral load in all stages of infection by a virus that causes meningitis. Further, mice lacking CD47 were far more resistant to infection by the tuberculosis bacterium. The finding opens a new approach to treating infectious diseases like COVID-19 and multiple drug-resistant tuberculosis.

HEARTBREAKING SIGNALS

A team led by Ludwig Stanford's Irv Weissman and his Stanford colleague Nicholas Leeper reported in the *Proceedings of the National Academy of Sciences* in June an intriguing similarity between cancer and atherosclerosis. Their study revealed that an abnormal proliferation of smooth muscle cells that line blood vessels plays a central role in the formation of atherosclerotic plaques. The researchers discovered that in the early stages of plaque formation in a mouse model, a single smooth muscle cell begins to multiply abnormally—an event detectable in human plaques as well. As the descendants of that cell proliferate, they also express high levels of C3, an inflammatory factor associated with atherosclerotic plaques. These proliferating, inflammatory cells would normally be cleared by the immune system's macrophages but that they also step up their expression of CD47, which transmits a "don't eat me" signal to macrophages—a tactic employed by cancer cells as well. Knocking down CD47 expression or deleting its gene reduced C3 levels in mice and restored the ability of their macrophages to clear the proliferating cells. This suggests CD47 blockade, which Irv and his team have already developed as a cancer treatment, could also be applied to treat cardiovascular diseases.

SPEEDY SCREEN

In a June paper in *Science Signaling,* Ludwig Harvard's Anthony Letai, Patrick Bhola and colleagues describe a technology that can swiftly screen hundreds to thousands of drugs against tumor samples freshly taken from cancer patients, often within a day. Named high-throughput dynamic BH3 profiling (HT-DBP), the microscopy-based technology determines how close individual tumor cells are to programmed cell death, or apoptosis. It relies on measuring the changing balance between molecules within mitochondria—the power-generators of cells—that drive cells to apoptosis. HT-DBP exposes tumor mitochondria to fragments of apoptosis-driving proteins—specifically, their BH3 domains— following exposure to a drug. Drugs that render mitochondria more sensitive to BH3 peptides are identified as active in inducing apoptotic signaling. Anthony and his colleagues used HT-DBP to screen 1,650 drugs in fresh breast tumors from mice and identified drugs that shrank the tumors but might have been missed on samples grown for several days, since the cells of such cultures adapt and evolve over time. Similar screens on mouse avatars of colorectal cancer identified a drug combination that delayed tumor growth in a mouse model. This new technology could help improve the personalization of cancer therapy.

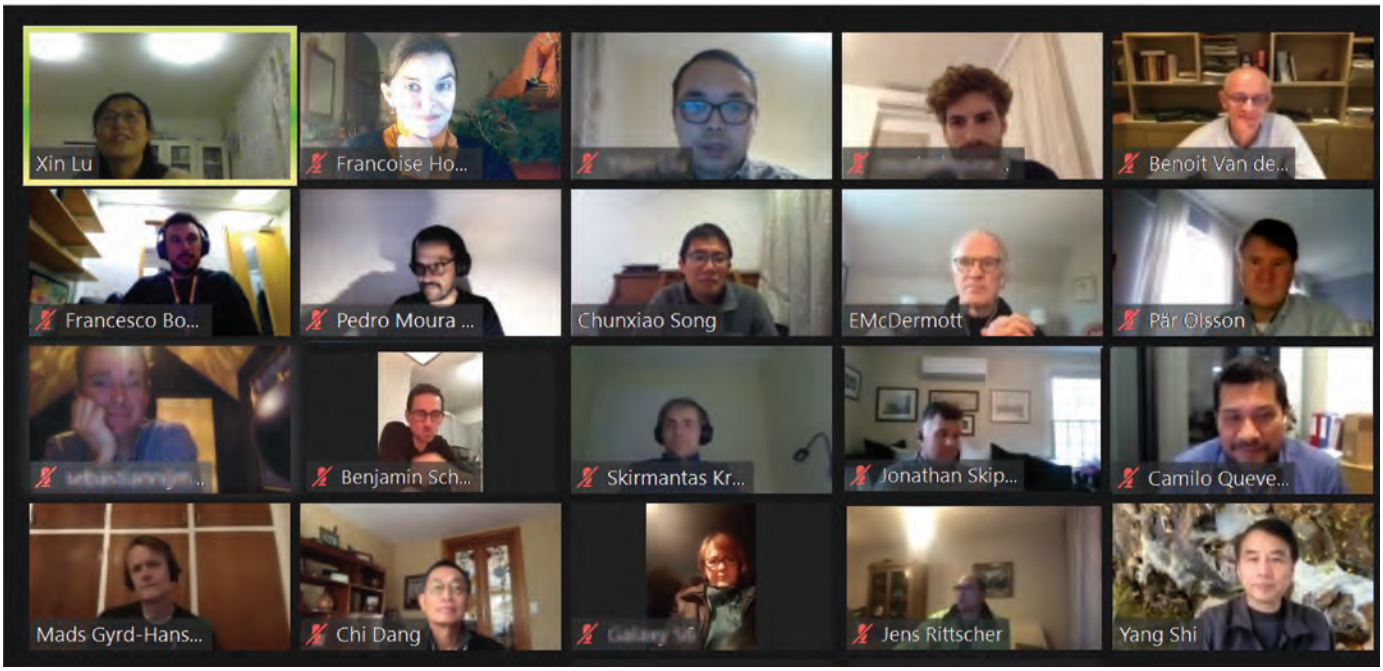
Anthony Letai
Ludwig Harvard

Patrick Bhola
Ludwig Harvard

Colin Goding
Ludwig Oxford

ASSUMPTION UNDONE

Transcription is step one in gene expression. To start the process, proteins known as transcription factors bind the regulatory regions of a gene. It is typically assumed that the more tightly they bind these regulatory DNA sequences, the better they perform their function. Now a team led by Ludwig Oxford's Colin Goding has demonstrated, using the melanoma-associated transcription factor MITF as a model, that this isn't always true. They showed that a chemical modification to MITF known as acetylation, which weakens its binding to DNA, actually increases MITF's occupancy of regulatory sequences. The researchers argue that transcription factors need to find regulatory sites against a high background of similar, but low affinity, sites in the genome. Weakening MITF's DNA-binding releases it from this reservoir of background sites and so increases the likelihood of its binding to its actual regulatory sites. This explains their finding that a low-DNA-binding-affinity MITF mutation that mimics acetylation supports melanoma development and drives tumorigenesis, whereas a high-affinity mutant resistant to such acetylation does not. This redistribution mechanism, controlled by oncogenes such as BRAF, allows fine-tuning of transcription factor availability and the control of genes that can influence tumorigenesis and development. The study was published in June in *Molecular Cell*.



Members of Ludwig Oxford and the New York office celebrated the sale of Base Genomics via Zoom on November 3.

TAPS TAPPED FOR DIAGNOSTICS

Ludwig spin-off Base Genomics, launched in June 2020 with a license granted by Ludwig Cancer Research to commercialize a technology, TET-assisted pyridine borane sequencing (TAPS), was acquired by Exact Sciences for $410 million. The technology, developed in Chunxiao Song's laboratory at Ludwig Oxford, is designed to detect early-stage cancer in blood tests through the highly sensitive detection of epigenetic modifications made to trace amounts of circulating tumor DNA. Liquid biopsies of the sort Base Genomics hopes to develop would permit continuous monitoring of treatment responses in patients undergoing cancer therapy and, eventually, perhaps even routine screening of people for the early detection of cancer.

YANG SHI

LUDWIG OXFORD'S NEWEST MEMBER

Prior to joining Ludwig Cancer Research, what were your most exciting discoveries and research accomplishments?

The one that stands out is the discovery of LSD1—the first histone methyl eraser, which showed that histone methylation is dynamically regulated. This overturned a 40-year dogma that these modifications were static and irreversible. In addition to LSD1, we and others have also identified many other histone demethylases, which have critical roles in development, differentiation and diseases like cancer. We've recently become interested in epigenetic regulation in antitumor immunity and tumor responses to immunotherapy. We were excited to find that inhibiting LSD1 may make tumors more susceptible to checkpoint blockade immunotherapy. In addition to scientific discoveries, what makes me very proud is the fact that my lab has contributed to the training of new generations of scientists who have gone on to start their own labs in academia or who have successfully transitioned to the pharmaceutical and biotech industry.

What motivated you to join the Oxford Branch?

Ludwig Oxford is a fantastic place to do science, and Oxford is a lovely town. But to be honest, it wasn't an easy decision to make because Boston is my home. I was initially attracted to Oxford because of the opportunity to forge close interactions

with clinicians. My understanding is that due to the UK National Health Service (NHS), there are unified treatment protocols for all cancer patients across the country. This allows clinical-related studies to be conducted at multiple centers countrywide to speed up patient recruitment and to expand clinical sample collection. I'm a basic scientist, but I have a lot of interest in seeing how some of these basic findings can be translated to the bedside. In practical terms, my decision was also based on the fact that core funding is provided by Ludwig. This will give me more free time to think about problems and how I can move the science forward in an efficient and expeditious way. There are so many questions waiting to be addressed and no time to lose.

Has your vision of what you would like to accomplish in the next 10 years changed now that you have joined a cancer research organization?

Yes and no. No, because I am still fundamentally interested in the basic underpinnings of how things work

biologically. And yes, because now I will be even more focused on cancer.

Could you elaborate on being more focused on cancer?
In my Boston lab, in addition to cancer, we are also working with mouse models and patient cells to understand the epigenetic mechanisms underlying intellectual disability. But after moving to Oxford, we may have to re-prioritize to allow my lab to focus more on cancer.

Will acute myeloid leukemia and glioma still be a priority in Oxford?
Yes. Our lab is studying the role of epigenetic modifiers in Diffuse Intrinsic Pontine Glioma (DIPG) and acute myeloid leukemia (AML). Epigenetics has been shown to play a crucial role in both DIPG and AML. We are interested in identifying epigenetic regulators whose inhibition induces differentiation of cancer cells that can potentially be therapeutically beneficial.

We're also exploring epigenetic regulators in order to find ways to turn 'cold' tumors 'hot' and ways to generate sustained responses to immune checkpoint blockade therapy. We are interested in understanding what role epigenetic factors play in the tumors and the host immune system, which both impact patients' response to checkpoint blockade therapy.

How will your research impact cancer patient care?
We are a basic science lab, and our goal is to understand these pathological processes by addressing the role and mechanisms of action of epigenetic regulators in cancer. In so doing, not only will we learn more about the fundamental mechanisms, but also uncover new targets for cancer therapy. And I firmly believe that forging closer interactions between basic science researchers the clinicians in Oxford will translate to greater impact on patient care.

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What breakthroughs are needed in epigenetics in order to advance cancer research and patient care?
We need to have a solid understanding of the basic mechanisms that control the different processes that lead to cancer. But at the same time, we need to enhance the interactions between scientists and clinicians to really understand cancer. We know that cancer is many diseases, so we need to understand them at the level that will allow us to design better treatment strategies.

If you could talk to the 10-year-old version of yourself, what would you tell yourself about your career?
Things happen in life that are often not by design. I did not initially plan to pursue a career in research. But the more I do it, the more I like it. Although I have had my lab for many years, I feel as if I have only started. I would tell my younger self that research is a career that has satisfied my curiosity but it's also one where I think I've been able to make a small difference. I've uncovered some basic biological processes that have implications for understanding cancer and other human diseases and hopefully opened some doors for developing specific, targeted therapies against cancers. I hope what I do will ultimately help humankind by contributing to the development of new therapeutic strategies.

Was there something in particular that inspired you to follow this career? How did you end up with a career in research?
Many people who go into research may tell you that they loved science from a very young age or spent their early years doing science experiments in the basement. None of that happened to me. But I'm really very lucky to have landed in research. I wouldn't trade it for anything else.

What has been the most satisfying part of your research?
First, it has really satisfied my curiosity. Research is a very free career and has allowed me to pursue important questions and find ways to address those questions. You never feel restricted. You can read papers, listen to talks and say, those are really important and interesting questions, and I should go ahead and look into some of them. Second, you always work with young people who are creative and passionate about what they do. They allow me to be a part of their career development, part of their years either as a PhD student or a postdoctoral fellow just coming out of their PhD training. I get to play an important role in their world.

What is your guiding philosophy for running your lab?
I want my lab members to be free to develop their research interest and passion. I work with them to find out what they are truly interested in and passionate about. But it's a balancing act. While giving them the freedom to develop their research interests and directing their projects, we have ongoing discussions to help them form their interests, so they have a solid blueprint for initiating and completing a research project.

Do you have any hobbies outside science?
When you're in science, science is your hobby. That's first and foremost. I want to be able to do and enjoy other things as much as science once I stop doing science, which seems almost unthinkable at this moment. I like to read, and I enjoy music. But I am completely illiterate when it comes to music, and I may want to spend time on learning music, and possibly picking up an instrument to amuse myself.

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What has changed for you during the COVID quarantine?
I've actually had an opportunity to learn more. I attend more meetings, virtually. For example, I attended several Cold Spring Harbor meetings that are outside of my field because I didn't have to travel. It's really amazing. From the comfort of your home, you can also just click and listen to really cool talks in another state or in another part of the world. And, since I'm not at the bench, I can work anywhere. I don't have to be in the office all the time, although I still try to go in regularly. And even though I can't meet with people in person, my lab knows I'm there if they need me. We Zoom from separate rooms in the lab all the time. I could do those meetings from home but just walking up and down the hallways at work and knowing I'm close by makes us all feel connected.

Operation Warp Speed, which is fueling the race to develop COVID-19 vaccines, seems to have dramatically shortened the time-horizon of preventive vaccine development. Would it be possible to devise a program to similarly accelerate the development of therapeutic vaccines (and other immunotherapies) for major types of cancer?

COVID-19 vaccine development is based on generations of scientific know-how about making preventative vaccines for viruses, where neutralizing antibodies are sufficient to confer protection. From a scientific standpoint, there is very little new that needs to be learned to implement the first wave of COVID-19 vaccines. The influx of funding (from government, philanthropic, and industry sources) is going to accelerate the manufacturing, development and production pipeline. Cancer vaccines are in a very different position, since neutralizing antibodies are inadequate to fight the disease. Funding at this point goes to basic science discoveries, which are fueled by human creativity and ingenuity. To truly advance the field of cancer immunotherapies, the best government approach would be a continued investment in the National Cancer Institute, an open and welcoming visa policy to recruit international talent and a commitment to science education in the United States at every level from elementary school through graduate training.

STEPHANIE DOUGAN
Ludwig Harvard

Building on our experience with COVID-19, a two-pronged strategy could be devised. First, massive population screens for different cancer types would enable early detection and significantly improve prognosis. Second, making cancer treatment truly personalized to increase therapy efficacy and overcome drug resistance in patients.

OFER SHOSHANI
Ludwig San Diego

Making an anti-viral vaccine is, for most viruses (including COVID-19), relatively trivial, given existing technology. However, making an anti-cancer vaccine is, by comparison, extraordinarily challenging for a number of reasons. These include identifying antigens whose display is critical for the continued viability and proliferation of cancer cells; the fact that cancer cells may shift their display of displayed antigens in response to immune therapy; the fact that many cancer-associated antigens are also displayed by normal cells throughout the body—and, as such, cannot be targeted, since the immune therapy (whatever its nature) may damage normal tissues, creating a clinically unacceptable side-effect toxicity.

ROBERT A. WEINBERG
Ludwig MIT

Unlike COVID-19, cancer is not a single disease. Thus, most cancer vaccines may benefit only select patient groups with particular underlying tumor mutations. Operation Warp Speed's success has depended on rapidly recruiting large, relatively non-specific patient cohorts, which is not easily translated to cancer trials. However, this program has demonstrated that with strong financial backing and public support, federal approval of new therapies can be accelerated.

EMILY STEFFKE
Ludwig Oxford

Facing a pandemic with an unfathomable toll on life and economy, public-private partnerships are on track to deliver SARS-CoV-2 vaccines in record time. While science and "warp speed" are not a natural marriage, programs that limit regulatory friction and financial risk for companies willing to translate high-risk, high-reward cancer immunotherapies directly from research labs to the clinic may be transformative.

MAX KONIG
Ludwig Johns Hopkins

Required reading

Ludwig Chicago

Proceedings of the National Academy of Sciences USA 2020 August 26 Online ahead of print.

4-Hydroxyacetophenone modulates the actomyosin cytoskeleton to reduce metastasis.

Bryan DS, Stack M, Krysztofiak K, Cichoń U, Thomas DG, Surcel A, Schiffhauer ES, Beckett MA, Khodarev NN, Xue L, Poli EC, Pearson AT, Posner MC, Robinson DN, Rock RS, Weichselbaum RR.

Ludwig Harvard

Cell Metabolism 2020 July 13 (Epub)

PHD3 loss promotes exercise capacity and fat oxidation in skeletal muscle.

Yoon H, Spinelli JB, Zaganjor E, Wong SJ, German NJ, Randall EC, Dean A, Clermont A, Paulo JA, Garcia D, Li H, Rombold O, Agar NYR, Goodyear LJ, Shaw RJ, Gygi SP, Auwerx J, Haigis MC.

Science Signaling 2020 June 16

High-throughput dynamic BH3 profiling may quickly and accurately predict effective therapies in solid tumors.

Bhola PD, Ahmed E, Guerriero JL, Sicinska E, Su E, Lavrova E, Ni J, Chipashvili O, Hagan T, Pioso MS, McQueeney K, Ng K, Aguirre AJ, Cleary JM, Cocozziello D, Sotayo A, Ryan J, Zhao JJ, Letai A.

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The INPP4B tumor suppressor modulates EGFR trafficking and promotes triple-negative breast cancer.

Liu H, Paddock MN, Wang H, Murphy CJ, Geck RC, Navarro AJ, Wulf GM, Elemento O, Haucke V, Cantley LC, Toker A.

Ludwig Lausanne

Science Translational Medicine 2020 July 15

Dynamic changes in glioma macrophage populations after radiotherapy reveal CSF-1R inhibition as a strategy to overcome resistance.

Akkari L, Bowman RL, Tessier J, Klemm F, Handgraaf SM, de Groot M, Quail DF, Tillard L, Gadiot J, Huse JT, Brandsma D, Westerga J, Watts C, Joyce JA.

Science Advances 2020 July 3 (eCollection)

Single-cell transcriptomics identifies multiple pathways underlying antitumor function of TCR- and CD8[redacted]-engineered human CD4+ T cells

Rath JA, Bajwa G, Carreres B, Hoyer E, Gruber I, Martínez-Paniagua MA, Yu YR, Nouraee N, Sadeghi F, Wu M, Wang T, Hebeisen M, Rufer N, Varadarajan N, Ho PC, Brenner MK, Gfeller D, Arber C.

Ludwig MSK

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Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-Kynurenine

Campesato LF, Budhu S, Tchaicha J, Weng CH, Gigoux M, Cohen IJ, Redmond D, Mangarin L, Pourpe S, Liu C, Zappasodi R, Zamarin D, Cavanaugh J, Castro AC, Manfredi MG, McGovern K, Merghoub T, Wolchok JD.

Ludwig Oxford

Genome Research 2020 September 22 (Epub)

Distinct contributions of DNA methylation and histone acetylation to the genomic occupancy of transcription factors.

Cusack M, King HW, Spingardi P, Kessler BM, Klose RJ, Kriaucionis S.

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Tuning transcription factor availability through acetylation-mediated genomic redistribution.

Louphrasitthiphol P, Siddaway R, Loffreda A, Pogenberg V, Friedrichsen H, Schepsky A, Zeng Z, Lu M, Strub T, Freter R, Lisle R, Suer E, Thomas B, Schuster-Böckler B, Filippakopoulos P, Middleton M, Lu X, Patton EE, Davidson I, Lambert JP, Wilmanns M, Steingrímsson E, Mazza D, Goding CR.

Ludwig San Diego

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SMARCB1 loss interacts with neuronal differentiation state to block maturation and impact cell stability.

Parisian AD, Koga T, Miki S, Johann PD, Kool M, Crawford JR, Furnari FB.

Nature 2020 September 9 (Epub)

TRIM37 controls cancer-specific vulnerability to PLK4 inhibition.

Meitinger F, Ohta M, Lee KY, Watanabe S, Davis RL, Anzola JV, Kabeche R, Jenkins DA, Shiau AK, Desai A, Oegema K.

Nature Genetics 2020 August 17 (Online ahead of print)

Extrachromosomal DNA is associated with oncogene amplification and poor outcome across multiple cancers.

Kim H, Nguyen NP, Turner K, Wu S, Gujar AD, Luebeck J, Liu J, Deshpande V, Rajkumar U, Namburi S, Amin SB, Yi E, Menghi F, Schulte JH, Henssen AG, Chang HY, Beck CR, Mischel PS, Bafna V, Verhaak RGW.

Nature 2020 July 29 (Epub)

An atlas of dynamic chromatin landscapes in mouse fetal development.

Gorkin DU, Barozzi I, Zhao Y, Zhang Y, Huang H, Lee AY, Li B, Chiou J, Wildberg A, Ding B, Zhang B, Wang M, Strattan JS, Davidson JM, Qiu Y, Afzal V, Akiyama JA, Plajzer-Frick I, Novak CS, Kato M, Garvin TH, Pham QT, Harrington AN, Mannion BJ, Lee EA, Fukuda-Yuzawa Y, He Y, Preissl S, Chee S, Han JY, Williams BA, Trout D, Amrhein H, Yang H, Cherry JM, Wang W, Gaulton K, Ecker JR, Shen Y, Dickel DE, Visel A, Pennacchio LA, Ren B.

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Upregulation of CD47 Is a host checkpoint response to pathogen recognition.

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Proceedings of the National Academy of Sciences 2020 July 27 (Epub)

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Guo E, Ishii Y, Mueller J, Srivatsan A, Gahman T, Putnam CD, Wang JYJ, Kolodner RD.

Ludwig Stanford

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Zabala M, Lobo NA, Antony J, Heitink LS, Gulati GS, Lam J, Parashurama N, Sanchez K, Adorno M, Sikandar SS, Kuo AH, Qian D, Kalisky T, Sim S, Li L, Dirbas FM, Somlo G, Newman A, Quake SR, Clarke MF.

Proceedings of the National Academy of Sciences 2020 June 15 (Epub)

Clonally expanding smooth muscle cells promote atherosclerosis by escaping efferocytosis and activating the complement cascade.

Wang Y, Nanda V, Direnzo D, Ye J, Xiao S, Kojima Y, Howe KL, Jarr KU, Flores AM, Tsantilas P, Tsao N, Rao A, Newman AAC, Eberhard AV, Priest JR, Ruusalepp A, Pasterkamp G, Maegdefessel L, Miller CL, Lind L, Koplev S, Björkegren JLM, Owens GK, Ingelsson E, Weissman IL, Leeper NJ.

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