

50 *years*

Ludwig researchers look back
at the past half century,
and look ahead to what's next.

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LUDWIG LINK

AUGUST 2021

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conference on early
detection and epigenetics

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Ludwig investigators
shared their
latest findings

LUDWIG
CANCER
RESEARCH

LIFE-CHANGING SCIENCE

LETTER



Welcome to the 2021 summer issue of Ludwig Link.

In the spirit of our ongoing celebration of the 50th anniversary of the Ludwig Institute for Cancer Research, we asked scientists at our Branches and Centers to share

their views on how far the field has come, and their hopes and expectations for the future of cancer research and care.

Many scientists mentioned the recognition of cancer as a fundamentally genetic disease and the translation of that knowledge into targeted therapies as landmark accomplishments of the past 50 years. Several people also mentioned dramatic advances in tumor immunology and immunotherapy as transformative developments. As to future opportunities and challenges, responses touched on expanding the efficacy of immunotherapy, improving the personalization of cancer treatment and the need to address disparities in access to cancer care. You can read all the responses in our “Ask a scientist” section.

We’ve also included in this issue a report on Ludwig’s presence at the AACR virtual Annual Meeting and another on a two-day virtual Symposium on Cancer Early Detection and Epigenetics that Ludwig co-hosted with Oxford University.

Among the many fascinating Ludwig studies described in our research briefs, you’ll read about how light triggers and sustains optic nerve tumors and a new kind of immunotherapy that targets common genetic drivers of cancer.

We hope you enjoy this issue of Ludwig Link. Happy reading!

Sincerely,

Rachel Reinhardt
Senior Vice President for Communications

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A SYMPOSIUM FOR LUDWIG'S GOLDEN JUBILEE

As part of the ongoing Ludwig Cancer Research 50th anniversary celebrations, Ludwig co-hosted a two-day virtual Symposium on Cancer Early Detection and Epigenetics in partnership with the Cancer Research UK Oxford Centre—which is celebrating its 10th birthday—and the Oxford Centre for Early Cancer Detection. More than 400 people around the world logged in on April 28th and 29th to attend the virtual meeting, which opened with brief addresses from Ludwig Institute Scientific Director Chi Van Dang, Ludwig Oxford Director Xin Lu and Tim Elliott, co-director of the CRUK Oxford Centre.

The scientific proceedings kicked off with a session on new technologies, beginning with a talk by Ludwig Oxford's Chunxiao Song on the use of TAPS, his lab's method for mapping DNA methylation across the genome, to detect liver and pancreatic cancers by analysis of circulating tumor (ct) DNA. Nickolas Papadopoulos followed with a presentation on the Ludwig Johns Hopkins team's experience developing and clinically evaluating its own multi-cancer liquid biopsy CancerSEEK, after which Sangeeta Bhatia of Ludwig MIT described her team's development of a novel nanotechnology that harnesses protein-snipping enzymes expressed by tumors to detect cancer. Ludwig Oxford's Jens Rittscher closed the session with a presentation on his group's computer-aided endoscopy analysis system for identification of the precancerous condition Barrett's esophagus.

The second session that day included talks by three Oxford researchers—Ellie Barnes, Naomi Allen and Gillian Reeves—related to risk stratification for early cancer detection, including ongoing studies on improving early detection of breast and liver cancers, and a talk on how the rich repository of genetic and medical data on a half million participants in the UK Biobank can aid risk-related research.

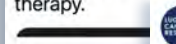
Following a welcome from Ludwig Oxford's Yang Shi, a co-organizer of the symposium, Day 2 started with a talk by Tony Kouzarides of the University of Cambridge, who shared



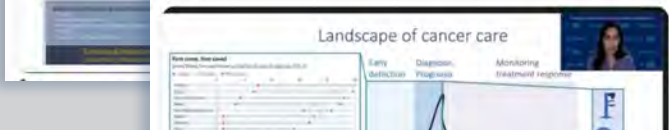
In her opening remarks, Ludwig Oxford director Xin Lu said she hopes that the [#LudwigOxfordSymposium](#) on Cancer Early Detection and Epigenetics will inspire new collaborations to advance our understanding of cancer and improve its diagnosis and care.



Ludwig professor [@HopkinsKimmel](#) Stephen Baylin discusses at [#LudwigOxfordSymposium](#) how chronic inflammation induces epigenetic changes in the genome that drive the genesis of cancer and the potential relevance of these findings to cancer prevention & therapy.



Ludwig [@MIT](#) investigator [@snbhatia](#) contextualized at the [#LudwigOxfordSymposium](#) the place and importance of early cancer detection in the continuum of cancer care.

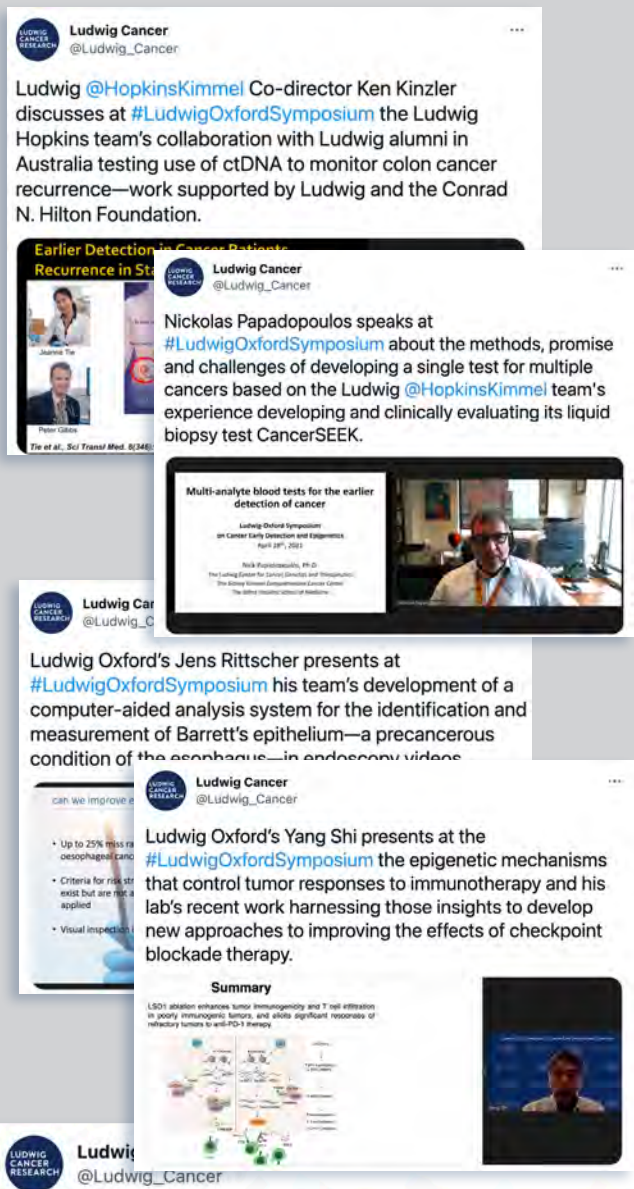


Ludwig Oxford's Chunxiao Song noted at the [#LudwigOxfordSymposium](#) that collecting epigenetic information from cell free DNA has advantage of providing whole-body and tissue-specific information, though it can be hard to capture.



Ludwig Chicago investigator Chuan He presents at [#LudwigOxfordSymposium](#) his lab's genomic mapping of 5-hydroxymethylcytosine across 19 human tissues & its work on epigenetic mapping of DNA shed by tumors into blood for early cancer diagnosis, prognosis & treatment stratification.





his lab's recent work on RNA modifying enzymes in blood, lung and pancreatic cancers. Next, Ludwig's Stephen Baylin surveyed how abnormal DNA methylation and chromatin assembly cooperate to drive the genesis of cancer and the potential relevance of these findings to cancer prevention and therapy.

The second session returned to the business of early cancer detection, beginning with a talk by Ludwig Chicago investigator Chuan He on his lab's mapping of the epigenetic mark 5-hydroxymethylcytosine across 19 human tissues and its studies on epigenetic ctDNA analysis for early cancer diagnosis and therapy. This was followed by a talk by Ludwig Johns Hopkins Co-director Ken Kinzler, in which he presented a new approach to improve the sensitivity and specificity of ctDNA detection in minimal residual disease

The closing session of the symposium began with a presentation by Yang on the epigenetic mechanisms that control tumor responses to immunotherapy and his lab's recent work harnessing those insights to improve the effects of checkpoint blockade. Next, McGill University's Nada Jabado presented her lab's research on the interplay of histone mutations with PDGFRA mutations in glioma. In the last talk of the symposium, Shelly Berger of the University of Pennsylvania spoke about nuclear structures known as "speckles," and their interaction with the tumor suppressor p53 to boost gene expression.

Attendees seemed quite engaged throughout the symposium, judging from the lively virtual discussions that followed each talk. As Chi noted in his closing remarks, cancer epigenetics has come a long way over the past few decades, though the successful translation of its insights to diagnostics and therapies will require sustained, multidisciplinary research. "The task in front of us," he said, "requires a Herculean team effort, so I hope that the symposium was not only stimulating but stimulates collaboration and new friendships as we join together to eliminate the suffering of cancer."



Crystal Mackall
Ludwig Stanford

FOR TACKLING CHILDHOOD CANCER

Ludwig Stanford's Crystal Mackall received two awards from the American Association for Cancer Research (AACR) and one from the American Society of Clinical Oncology (ASCO) for her work on childhood cancers, tumor immunology and immunotherapy. As co-leader of the St. Baldrick's Foundation-Stand Up 2 Cancer Pediatric Cancer Dream Team, Crystal received on behalf of her team the 2021 Team Science Award from the AACR for outstanding achievement in pediatric cancer research. Ludwig Stanford's Michelle Monje is also a member of the team. Over

the past eight years, the Pediatric Cancer Dream Team has worked on developing new immunotherapies and improving their efficacy against a broader range of cancers—especially solid tumors—while minimizing their side effects. Crystal also received the AACR-St. Baldrick's Foundation Award for Outstanding Achievement in Pediatric Cancer Research and ASCO's 2021 Pediatric Oncology Award and Lecture.



Don Cleveland
Ludwig San Diego

NEW FELLOWS OF THE AACR

Ludwig San Diego's Don Cleveland and Ludwig Harvard Co-director George Demetri were named Fellows of the Academy of the American Association for Cancer Research (AACR) in April. Election to the Academy, the AACR notes, recognizes and honors "distinguished scientists whose scientific contributions have propelled significant innovation and progress against cancer." Nominees are elected through an annual peer review process conducted by existing members of the AACR Academy and ratified by the AACR Academy Steering Committee and AACR Executive Committee. The Academy recognized Don for his discovery and development of antisense oligonucleotide therapy, and his extensive contributions to our understanding of the molecular biology of cell division, chromosome movement and the mechanisms of genome evolution in cancer. George was honored for his landmark contributions to the development of targeted drugs and personalized cancer care regimens for sarcomas.



George Demetri
Ludwig Harvard

NEW MEMBERS OF THE NAS

Ludwig Princeton's Associate Director Eileen White and Ludwig Harvard investigator Alan D'Andrea were elected to the National Academy of Sciences in April in recognition of their distinguished and continuing contributions to cancer research. Eileen has made many notable discoveries that have advanced our understanding of programmed cell death, autophagy and metabolism in cancer. Her early work revealed roles of the p53 tumor suppressor in activating programmed cell death and suppressing cancer, and of the counteracting Bcl-2-related proteins in promoting cancer. More recently, her research has established that tumor cells activate autophagy—in which cells cannibalize their own proteins and organelles—to tolerate metabolic stress. Alan is known for his landmark elucidation of how DNA damage and repair defects drive Fanconi anemia, and his studies of the various protein complexes involved in the cell cycle, chromatin remodeling, DNA repair and the maintenance of genome stability.



John O'Boyle

▶ Eileen White
Ludwig Princeton



▶ Alan D'Andrea
Ludwig Harvard



▶ Beata Mierzwa
Ludwig San Diego

FOR ART AND SCIENCE

Ludwig San Diego postdoc Beata Mierzwa was honored as a female STEM leader by Lyda Hill Philanthropies' IF/THEN Initiative in an exhibit that opened in Dallas, Texas in May. Beata is one of the 125 women in STEM who in 2019 were named IF/THEN Ambassadors by the American Association for the Advancement of Science and the Lyda Hill Philanthropies. The [exhibition](#) of 125 3D-printed statues of IF/THEN Ambassadors seeks to inspire young girls to pursue careers in the fields of science, technology, engineering, or mathematics (STEM). A molecular biologist, Beata combines science, art and fashion to "share the beauty of biology with the world." Her work was also featured in April in the award-winning series *Mission Unstoppable* on the U.S. television channel CBS. The show celebrates diverse female STEM professionals as role models to educate and inspire the next generation of STEM pioneers. The *Mission Unstoppable* clip featuring Beata is available [here](#), and you can read a profile of her published in ASBMB Today [here](#).



Stefan Constantinescu
Ludwig Institute

NEW PRESIDENT OF FEAM

Ludwig Member Stefan Constantinescu was elected [President](#) of the Federation of European Academies of Medicine (FEAM) in May for a three-year term. FEAM is a European network of 23 National Academies focused on human and veterinary medicine and pharmacy representing over 4,000 European biomedical scientists. Stefan is best known for his extensive studies on the molecular biology and genetics of myeloproliferative neoplasms, work that has led to the development of new

therapies for this family of slow-growing blood cancers. He is a fellow of the Romanian and Royal Belgian Academies of Medicine and President of the Cell Signaling Pol at the de Duve Institute of the Université catholique de Louvain. Most recently, he has also accepted an appointment at Ludwig Oxford. Stefan's Ludwig Oxford lab will focus on signaling and epigenetic regulation during oncogenesis in chronic myeloid cancers and their progression to secondary acute myeloid leukemia.



Lieping Chen
Ludwig Oxford

VISITING PROFESSOR AT LUDWIG OXFORD

In May, Lieping Chen, professor of immunobiology and medicine, and co-director of the cancer immunology program at the Yale Cancer Center at Yale University, joined Ludwig Oxford as a visiting professor of cancer immunotherapy. A renowned immunologist, Lieping is best known for his seminal work on the discovery of the PD-1/PD-L1 immune suppressive pathway and the development of anti-PD-1/PD-L1 cancer immunotherapy. He discovered PD-L1 (originally termed B7-H1)

as a member of the B7 family ligands that have immune suppressive functions, characterized its role in suppressing anti-tumor immunity and led the first-in-human clinical trial of a therapy targeting the PD-1/PD-L1 pathway. He also developed an immunohistochemistry assay for PD-L1 detection in human cancer tissues to predict better response to anti-PD-1/PD-L1 therapy. Lieping is a member of the U.S. National Academy of Sciences and a Fellow of the American Association for Cancer Research.

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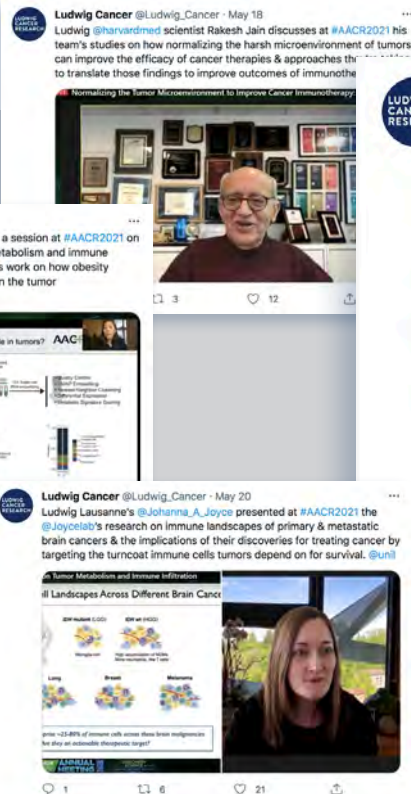
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Conferences



He also explained why the Ludwig Johns Hopkins team chose to analyze multiple protein and DNA markers in their liquid biopsy technology.

In the meeting's second week, Ludwig Lausanne's Johanna Joyce joined an AACR session on "navigating the path to a successful career in cancer research" as a mentor, and also presented her lab's work on the immune landscapes of brain cancers on a panel chaired by Ludwig Harvard's Marcia Haigis. She also discussed the implications of her research for the treatment of primary and metastatic brain tumors. In that same session, Marcia discussed her own lab's studies on how obesity affects immune interactions with cancer cells in the tumor microenvironment.

Other Ludwig researchers also touched on the extensive influence of the tumor microenvironment on tumor immunology and therapy. Ludwig Harvard investigator Rakesh Jain presented his extensive studies on normalizing the vasculature and harsh microenvironment of tumors and described the approaches he and his colleagues are taking to apply their findings to boost the

efficacy of immunotherapy. Matthew Vander Heiden of Ludwig MIT, meanwhile, returned in the second week to present his team's investigation of the effects of tumor metabolism on therapy and how tissue-specific nutritional dependencies can expose vulnerabilities that might be targeted for cancer therapy.

Ludwig Harvard researcher Sandro Santagata presented the work he has done with Ludwig support on high-dimensional imaging using dozens of molecular markers for the generation of tumor atlases and clinical pathology. Finally, in a fascinating talk apparently delivered from the command bridge of the Starship Enterprise (courtesy, *Star Trek*), Ludwig Stanford's Howard Chang discussed how circles of DNA unassociated with chromosomes—found in half of all tumor types and called ecDNAs—are organized in hubs in the cell nucleus in a manner that fuels the evolution and aggressive growth of tumors.

Ludwig Link can confirm that the quality of the video-link from 24th century interstellar space—and that of the Ludwig presentations in general—was outstanding.

VITAMIN FEEDBACK LOOP

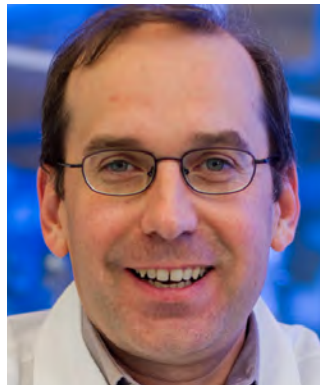
Radiotherapy works in large part by stimulating an immune response against cancer cells damaged by ionizing radiation. But that event itself can stimulate the production of factors by tumor cells that suppress those immune responses. A study led by Ludwig Chicago Co-director Ralph Weichselbaum and investigator Hua Laura Liang found that the vitamin A derivative all-trans retinoic acid (RA) helps reprogram the immune microenvironment of tumors and can enhance the effects of radiotherapy in mice. The combination treatment increased the induction within both treated and untreated tumors of inflammatory macrophages. The inflammatory macrophages in turn boosted IFN- γ -producing CD4+ and CD8+ T cells, both of which play critical roles in tumor rejection. The researchers found that these T cells and the IFN- γ they produce feed back into the anti-cancer cascade by further boosting the numbers of inflammatory macrophages in tumors. The researchers [reported](#) in *Science Immunology* in June that the improved therapeutic effects of combining oral ATRA with targeted radiation could be extended to unirradiated tumors in mice with the addition of anti-PD-L1 checkpoint blockade immunotherapy, suggesting a novel and relatively nontoxic intervention to improve treatment outcomes.



◀ Ralph Weichselbaum
Ludwig Chicago



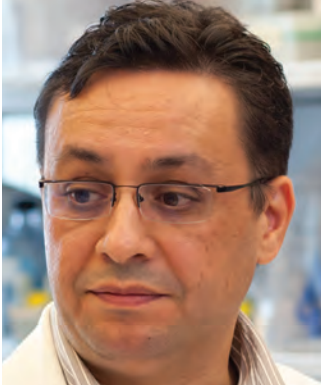
◀ Hua Laura Liang
Ludwig Chicago



Anthony Letai ▶
Ludwig Harvard

DEATH ON THE BALANCE

A study led by Ludwig Harvard investigator Anthony Letai and former postdoctoral researcher Veerle Daniels and [published](#) in *Science Signaling* in June demonstrated how a drug screening method developed in the Letai lab, dynamic BH3 profiling (DBP), can swiftly identify potentially effective combinations of existing drugs for highly personalized cancer therapy. Drugs often induce in cancer cells a type of programmed death known as apoptosis, which is orchestrated by an elaborate protein machinery. Cells, however, also produce anti-death proteins that inhibit key elements of that machinery. DBP exposes cells to drugs and then measures how the balance of pro- and anti-death proteins is altered to predict the likely efficacy of the drug against a patient's cancer. The researchers used DBP to find a specific metabolic dependency—on an enzyme named NAMPT—in triple negative breast cancer cells from a patient and targeted it in mouse models with low, and likely less toxic doses of a metabolic drug to tip the balance toward death. They then used DBP to identify the specific protein with which the cancer cells resisted death, and targeted it with a drug known as a BH3 mimetic to induce programmed cell death and so treat the tumors. The strategy, they note, could be extended to develop personalized therapies against multiple cancers.



Taha Merghoub
Ludwig MSK



Jedd Wolchok
Ludwig MSK



Andrew Chow
Ludwig MSK

DEADLY DISTRACTION

A study led by Taha Merghoub, Jedd Wolchok and Andrew Chow, Ludwig investigators at Memorial Sloan Kettering (MSK), and Charles Rudin of MSK showed that immune cells known as macrophages residing in body cavities can aid tumor growth by distracting the immune system's cancer-killing CD8+ T cells. The researchers [reported](#) in the June issue of *Cancer Cell* that cavity-resident macrophages express high levels of Tim-4, a receptor for phosphatidylserine (PS), a molecule they found to be highly expressed on activated and proliferative CD8+ T cells. Clinical samples revealed that while Tim-4 on such macrophages varied among lung cancer patients, those

with higher levels of the receptor tended to have fewer CD8+ T cells responding to the tumor. The researchers explored whether blocking Tim-4 would enhance PD-1 blockade in mouse models of colon and lung cancer. While blocking Tim-4 alone didn't reduce tumor growth or improve survival, it did enhance efficacy of PD-1 blockade and boost the numbers of CD8+ T cells in the peritoneal cavity. The researchers also showed in a preclinical model that Tim-4 blockade reduces immunosuppression in adoptive T-cell therapy, in which tumor targeting T cells are grown and re-infused into patients. The authors are exploring means to develop this approach for therapy.

LIGHT SOURCE

A [study](#) published in *Nature* in May and led by Ludwig Stanford's Michelle Monje and David Gutmann of Washington University in St. Louis showed in a mouse model that neural activity triggered by light can both initiate and drive the growth of optic nerve tumors, which develop in about 15% of children diagnosed with the cancer predisposition syndrome neurofibromatosis type 1 (NF1), and can cause vision loss. Michelle's team [discovered](#) in 2015 that neural activity fuels high grade gliomas, and that the malignant growth is driven by the shedding of a synaptic protein named neuroligin 3. She and her colleagues show in this study that the initiation of optic nerve tumors in NF-1 depends on light exposure (visual experience) of mice during a critical

period 6 to 16 weeks after birth, and light deprivation in that period prevents tumor initiation. In retinal neurons, mutations that cause NF1 in the mice result in abnormal shedding of neuroligin-3, whose soluble form was found at high levels in tumors from the mouse model and patients. An experimental drug that blocks neuroligin-3 shedding also prevented development of optic nerve tumors when it was given to mice in the period when they form, and decreased tumor growth when given after tumor formation—suggesting a strategy for the prevention and treatment of this cancer.



Michelle Monje
Ludwig Stanford

INTELLIGENCE ARTIFICIAL, BENEFITS GENUINE

Pathologists use several tissue architecture and cellular cues to diagnose prostate cancer. But in 25–50% of cases, the initial staining of biopsies does not provide sufficient evidence for diagnosis, requiring immunohistochemistry (IHC)—the detection of molecular markers—to further study cellular features. Determining the necessity of this additional step is one bottleneck in the current pathology workflow. To address this challenge, a team led by Ludwig Oxford's Jens

Rittscher and Oxford University's Clare Verrill conducted a systematic study in what specific cases require IHC and developed an artificial intelligence (AI) tool to automate this analysis. They [reported](#) in a May paper in *Modern Pathology* that the tool agreed with the pathologist's review in 81% of cases on average. By enabling automated request of IHC based on the AI tool results, a pathologist would only need to review the case once all necessary staining had been carried out.



Jens Rittscher
Ludwig Oxford



Ping-Chih Ho
Ludwig Lausanne

TIL REVIVAL

Among the T lymphocytes that infiltrate tumors (TILs), a species known as “terminally exhausted” TILs is best equipped to detect and destroy cancer cells. Its members are, however, functionally disabled, prone to self-destruction and unresponsive to current immunotherapies. A [study](#) led by Ludwig Lausanne’s Ping-Chih Ho and Li Tang of the École Polytechnique Fédérale de Lausanne examined whether an engineered, long-lived version of the immune factor IL-10 (IL-10/Fc) could revive these chronic underperformers. They reported in May in *Nature Immunology* that adding IL-10/Fc to adoptive cell therapy (ACT)—the infusion of T cells to treat cancer—boosted the number and

functionality of terminally exhausted TILs in a mouse model of melanoma and led to tumor regression and cures in 90% of treated mice, compared to limited regressions with IL-10/Fc alone and none with ACT alone. Notably, 80% of surviving mice developed an immune memory for the cancer. Ping-Chih and colleagues also tested IL-10/Fc on CAR-T cells, which are engineered to target cancer cells bearing specific markers, and achieved cures in roughly 90% of mice implanted with colon tumors. IL-10/Fc, they showed, acts specifically on terminally exhausted TILs, reprogramming their metabolism in a manner that induces sweeping changes in their gene expression programs, driving their activation and proliferation.



Crystal Mackall
Ludwig Stanford

CAR-T REVIVAL

T cells get tired out by continuous activation, suffering an epigenetic reprogramming of their gene expression that leaves them in a state of sluggish apathy. This condition, known as “exhaustion,” is the bane of T cell-based therapies for cancer, even those that employ chimeric antigen-receptor (CAR) T cells to target cancer cells bearing specific molecular markers. Exhaustion was until recently considered generally irreversible. No longer. Adding to a growing body of evidence that exhausted T cells can in fact be revived (see previous feature), a team of researchers led by Ludwig Stanford investigator Crystal Mackall [reported](#) in

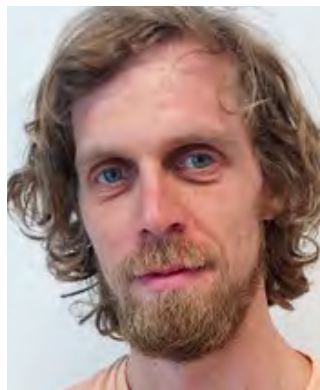
Science in April that all exhausted CAR-T cells may really need is a little rest. The researchers gave CAR-T cells their time out in two ways: by using synthetic biology to regulate degradation of the chimeric antigen receptor protein, or with the use of an existing small molecule that temporarily suppresses CAR-T activity. In both cases, the CAR-T cells took their time off to rewrite the epigenetic programming of their genomes, reviving vital gene expression programs and regaining their cancer-killing capabilities. Given just four days of rest, the rejuvenated cells leapt back into action, significantly extending survival in mouse models of cancer.

BENEFITS OF SELECTIVITY

Postmenopausal women with estrogen receptor (ER)-positive breast cancers are initially treated with drugs that block the production of estrogen, whose binding to the ER drives such cancers. When the tumors become resistant to these therapies, they're treated with more potent drugs—such as fulvestrant—that bind to and inhibit ER activity. ER inhibitors, however, have side effects that mimic the unpleasant consequences of menopause. A study led by Ludwig Chicago Co-director Geof Greene examined whether the selective ER inhibitor lasofoxifene might also be used to treat estrogen resistant breast cancers in mouse models of human tumors driven by two common ER mutations, Y537S and D538G ER α . Lasofoxifene, which has anti-estrogenic effects in some tissues and pro-estrogenic effects in others, improves bone density in postmenopausal women and significantly reduces the incidence of ER-positive breast cancer. But its therapeutic utility hasn't yet been determined. Geof and his colleagues [reported](#) in *Breast Cancer Research* in May that lasofoxifene was more effective than fulvestrant—when either drug was used alone or in combination with a common chemotherapy—in inhibiting both primary tumor growth and metastasis in the cancer models. Because lasofoxifene is relatively less toxic, it could potentially improve the treatment of progressive breast cancer. Clinical trials are underway to evaluate lasofoxifene in women with endocrine therapy resistant, ER+ metastatic breast cancer.



▶ Geof Greene
Ludwig Chicago



▶ Massimo Andreatta
Ludwig Lausanne



▶ Santiago Carmona
Ludwig Lausanne

A FRAME OF REFERENCE

Single-cell RNA sequencing (scRNA-seq) captures the global expression of genes in individual cells, enabling a granular understanding of the diverse cellular states that underlie tissue biology. Tumor infiltrating T lymphocytes (TILs) are prime candidates for such analysis, as they exist in multiple states in response to varying conditions of the microenvironment. But the use of RNAseq to understand these states is not only inherently complex, given the diversity of gene expression programs associated with TIL states, but also challenged by a lack of a clear reference against which to measure variations. This is further complicated by the sheer variety of tissues, animal models and methods used in such studies. Researchers led by Ludwig Lausanne's Massimo Andreatta and Santiago Carmona [reported](#) in a May publication in *Nature Communications* their solution to these challenges. Their paper describes a computational framework, ProjectTILs, for projecting scRNA-seq data onto a T cell reference atlas to capture the state of TILs in a sample and even identify novel states. ProjectTILs works smoothly with gene expression datasets produced from heterogeneous samples and generated with varying methods and technologies. Massimo, Santiago and colleagues validated their method by interpreting the effects of T cell perturbations in multiple model systems of cancer and infection.

CONVERTING THE ENEMY

A [study](#) in mouse models of the brain cancer glioblastoma multiforme (GBM), led by Ludwig Harvard's Rakesh Jain and Hye-Jung Kim of the Dana-Farber Cancer Institute, found that regulatory T cells (Tregs), which suppress anti-tumor immune responses, are primarily responsible for the cancer's uniform resistance to immunotherapy. Rakesh and his colleagues reported in a May issue of *Nature Communications* that selectively targeting the GITR receptor on Tregs with an antibody (α GITR) that activates its signaling transforms Tregs within GBM tumors into highly unusual CD4+ effector cells that not only lift the Treg-mediated suppression of immune responses but also kill cancer cells themselves. Combining

α GITR with anti-PD1 checkpoint blockade immunotherapy increased survival in three different mouse models of GBM, resulting in complete cures of some mice. That combination, the researchers show, also induced an immunological memory of the cancer and synergized with standard of care therapy for GBM. Treg cells are abundant in the tumor microenvironment of GBMs but are usually absent in healthy brain tissue, suggesting that this therapy could be well tolerated and has the potential to produce large numbers of anti-tumor effector cells for GBM therapy.



Rakesh Jain
Ludwig Harvard

A PUSH FOR DIFFERENTIATION

Acute myeloid leukemia (AML) is a blood cancer in which the process of forming mature, differentiated and non-dividing myeloid white blood cells is blocked. This causes immature white blood cells to build up in the bone marrow and disrupt normal blood cell production. One approach to treating the cancer involves targeting of the epigenetic regulator LSD1 to overcome the differentiation blockade. But because LSD1 is also involved in other steps of myeloid cell differentiation, its inhibition was not well tolerated by patients in a clinical trial. A study led by Ludwig Oxford's Yang Shi and published in a May issue of *iScience* [reported](#) the identification

of metabolic processes that could be targeted in tandem to improve this strategy and lower the required dosage of LSD1 inhibitor. Screening a library of drugs, Yang and his colleagues found that targeting fatty acid and purine metabolic pathways in combination with LSD1 inhibition improved significantly on LSD1 inhibition alone in cell culture models of AML differentiation. The team also performed mathematical modeling of the potential effects of varying the concentrations and dosing intervals of such drug combinations on cell maturation and tumor burden. The study establishes a basis for preclinical development of a new AML treatment approach.



Yang Shi
Ludwig Oxford



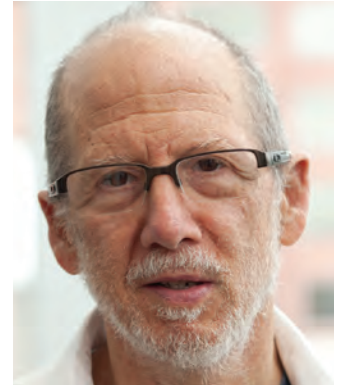
Joshua Cohen
Ludwig Johns Hopkins



Kenneth Kinzler
Ludwig Johns Hopkins



Nickolas Papadopoulos
Ludwig Johns Hopkins



Bert Vogelstein
Ludwig Johns Hopkins

BETTER DETECTOR

In a May [paper](#) in *Nature Biotechnology*, Ludwig Johns Hopkins researchers Joshua Cohen, Bert Vogelstein, Kenneth Kinzler and Nickolas Papadopoulos reported an improved next-generation DNA sequencing technology named SaferSeqS (for “Safer Sequencing System”). Such technologies are critical to liquid biopsies, which detect cancer by analyzing DNA fragments shed by tumors into body fluids. SaferSeqS, they show, is a major improvement over widely used methods adapted from one developed at Ludwig Johns Hopkins a decade ago named Safe Sequencing System. It improves the sensitivity and reduces the baseline error rate of mutation detection more than 100-fold in comparison to other methods. SaferSeqS involves tagging both

strands of each isolated DNA fragment with a unique DNA sequence equivalent to a barcode and employing duplex sequencing, which relies on the structural redundancy of DNA to distinguish real mutations from errors: If both strands of a DNA molecule have corresponding mutations at the same spot, it is more likely to be authentic than an experimental artifact. The researchers compared their analysis of samples to previous [results](#) from the CancerSEEK test, a liquid biopsy for eight common cancers that was developed at Ludwig Johns Hopkins. SaferSeqS significantly improved sensitivity, detecting mutations not previously captured in 68% of the samples tested.



Douglas Hanahan
Ludwig Lausanne

DEADLY REVERSION

A study led by Ludwig Lausanne's Douglas Hanahan and [published](#) in an April issue of *Cancer Discovery* described a previously unrecognized mechanism by which cancer cells of a relatively benign subtype of pancreatic tumors methodically revert—or “de-differentiate”—to a progenitor, or immature, state of cellular development to spawn aggressive, metastatic tumors. Engagement of the mechanism is associated with poorer outcomes in patients diagnosed with pancreatic neuroendocrine tumors (PanNETs). These tumors originate from the islet beta-cells of the pancreas and can be divided into a relatively benign, well-differentiated subtype that maintains many features of insulin-producing beta cells, and an

aggressive, poorly differentiated subtype that lacks those features. Using a PanNET mouse model, Doug and his colleagues showed that the progression from benign to aggressive PanNET tumors requires cancer cells to retrace the pathway of beta cell differentiation and maturation to assume the progenitor state. Tumor cells poised to de-differentiate step up production of microRNA18, which ultimately causes the activation of Hmgb3, a protein that controls the expression of a suite of genes that induce the progenitor state. The study furnishes preliminary evidence supporting the inclusion of dedifferentiation as a distinct and separable step, or perhaps sub-step, in the journey to malignancy.



Ash Alizadeh
Ludwig Stanford

A MEASURE OF BIAS

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. Unfortunately, patients with DLBCL in need of immediate therapy are largely under-represented in clinical trials. Shorter diagnosis-to-treatment interval (DTI) is associated with poorer outcomes, and it has been proposed as a measure by which researchers might quantify selection bias in clinical studies of DLBCL and its treatment. A team led by Ludwig Stanford investigator Ash Alizadeh examined whether circulating tumor DNA (ctDNA), shed by dead cancer

cells into the blood, might also be usefully measured to that end. The researchers [reported](#) in the *Journal of Clinical Oncology* in April that short DTI is associated with a greater baseline tumor burden and can be more objectively tracked by measures of ctDNA to quantify and account for patient selection bias in clinical studies. ctDNA levels were also reliably associated with event-free and overall survival in multivariable analyses. The study involved 217 patients with DLBCL treated at six centers in the U.S. and Europe, and ctDNA was detectable in 98% of the patients.

A METABOLIC MARK

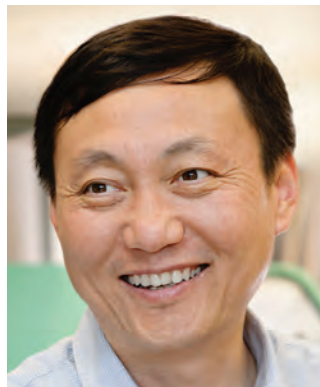
A quarter to half of all women diagnosed with HER2-positive breast cancer develop brain metastases, and these frequently lethal tumors are largely resistant to the drugs used to treat systemic disease. A study led by Ludwig Harvard investigator Rakesh Jain and Ludwig MIT investigator Matthew Vander Heiden examined whether metabolic adaptations essential to the growth and survival of these metastases might expose vulnerabilities that can be targeted for therapy. The researchers [reported](#) in an April publication in *Nature Cancer* that—based on the profiling of metabolites, gene expression analyses and other studies in mouse models—brain metastases manufacture their own fats at a much higher rate than do their counterparts growing in the breast or as metastasis to other tissues. This adaptation is necessary, they showed, because accessible fats are in short supply for breast cancer cells in brain tissue. The researchers also demonstrate that an enzyme essential to the production of fat molecules—fatty acid synthase—is expressed at high levels in mouse models and in biopsies obtained from HER2-positive breast cancer patients. Genetic or pharmacological inhibition of the enzyme suppressed breast tumor growth in the mouse brain, suggesting that targeting fat synthesis could improve the treatment of these breast cancer brain metastases.



◀ Rakesh Jain
Ludwig Harvard



◀ Matthew Vander Heiden
Ludwig Harvard



Bing Ren ▶
Ludwig San Diego

A TWOFER TECHNOLOGY

In a February [paper](#) in *Nature Methods*, a team led by Ludwig San Diego's Bing Ren reported its development of a technology named Paired-Tag (for parallel analysis of individual cells for RNA expression and DNA from targeted tagmentation by sequencing) that enables the simultaneous analysis of gene expression and epigenetic modifications made to histones in the chromatin of individual cells on a massive scale. Several new technologies now permit the separate profiling of epigenetic marks, chromatin structure and all expressed genes in individual cells, but rigorously and comprehensively profiling the causal relationships between those phenomena has proved to be technically challenging. Bing and his colleagues applied their method to two regions of the adult mouse brain (the frontal cortex and the hippocampus), generating the first cell-type-resolved maps of chromatin state and global gene expression for 22 cell types. Paired-Tag will be useful to researchers exploring the broad gene regulatory programs that distinguish distinct types of cells in both healthy and diseased tissues and the molecular biology underlying the subtlest of functional differences between cells within tissues.

NASCAR: iCAR vs. CAR

Researchers led by Ludwig Johns Hopkins Co-director Kenneth Kinzler and investigator Shibin Zhou [reported](#) in a March issue of the *Proceedings of the National Academy of Sciences* the prototype of a new cancer immunotherapy. The approach, relying on a biochemical approximation of Boolean logic, uses chimeric antigen receptor (CAR) T cells to target a common and largely exclusive genetic aberration of cancers: the loss of expression of one of the usual two copies (or alleles) of a gene due to chromosome losses commonly known as “loss of heterozygosity” (LOH). The NASCAR T cell expresses the CAR that targets an allele expressed on the cancer cell as well as an inhibitory CAR (iCAR) against the allele product that is missing due to LOH. If both proteins—equivalent to the expression, A and B—are expressed on a cell encountered by the NASCAR T cell, the iCAR is simultaneously activated, and the presumably normal cell is left untouched. If, however, one allele product is present and the other missing—A and NOT B—the NASCAR T cell is activated to kill the deficient, cancerous cell. The researchers designed NASCAR T cells that target LOH cell surface molecules known as HLA and tested it successfully on three independent cell lines and in mouse models.



◀ Kenneth Kinzler
Ludwig Johns Hopkins



◀ Shibin Zhou
Ludwig Johns Hopkins



Yang Shi ▶
Ludwig Oxford

THREEFER FOR SUCCESS

Researchers are exploring multiple strategies to overcome resistance to anti-PD-1 checkpoint blockade immunotherapy, which is only effective against a limited subset of patients and cancer types. These include the manipulation of epigenetic regulators, which control the expression of genes. But perturbation of these enzymes can have opposing effects on various aspects of the anti-tumor response, resulting in dampened or no overall benefit. Ludwig Oxford’s Yang Shi and colleagues [reported](#) in *Cancer Discovery* in March their examination of the opposing effects of inhibiting one such epigenetic regulator, LSD1. They showed in mouse and cell models that suppressing LSD1 boosts killer T cell infiltration into tumors. But this effect is counteracted by the increased production of a signaling protein called TGF- β that suppresses the activity of these cells. Depleting both LSD1 and TGF- β during anti-PD-1 therapy increased T cell infiltration and improved their function, eradicating tumors that were previously resistant to checkpoint blockade and establishing an immune memory of the tumor in the mice. Yang and his coauthors suggest combining LSD1 inhibition with TGF- β and PD-1 blockade could expand the utility and efficacy of the immunotherapy.



Lana Kandalaft
Ludwig Lausanne



Cheryl Chiang
Ludwig Lausanne

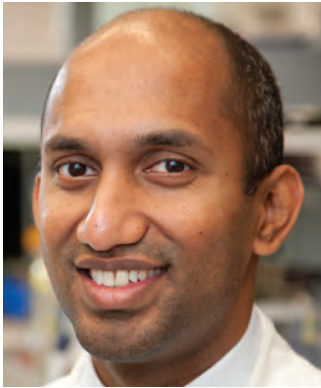


Alexandre Harari
Ludwig Lausanne

SPIKED VACCINE

Researchers led by Ludwig Lausanne's Lana Kandalaft, Cheryl Chiang and Alexandre Harari published the results of the latest study advancing a personalized dendritic cell vaccine for ovarian cancer (OCDC) in a March [paper](#) in *Nature Partner Journals: Vaccines*. The OCDC vaccine involves pulsing dendritic cells—which direct T cells to tumors and stimulate their activity—from a patient with an extract of her ovarian tumor to create a personalized dendritic cell vaccine. When combined with standard ovarian cancer therapies cyclophosphamide and the angiogenesis inhibitor bevacizumab in an open label clinical trial, the vaccine was [previously](#) shown to extend the lives of patients with late stage ovarian cancer.

In the current study, the researchers showed that adding aspirin and the immune factor IL-2 to the mix elicited vaccine-specific T-cell responses that positively correlated with patients' prolonged time-to-progression and overall survival in a small clinical trial. Aspirin counteracts a mechanism by which tumors inhibit T cell infiltration, while IL-2 is a potent stimulator of T cell proliferation. Those results were reflected in the ID8 ovarian cancer mouse model. An immunological analysis of the mice confirmed that the two new drugs added to the mix had the intended effect of suppressing mechanisms of T cell exclusion from tumors and boosting T cell numbers.



Chetan Bettegowda
Ludwig Johns Hopkins



Jacqueline Douglass
Ludwig Johns Hopkins



Emily Han-Chung Hsiue
Ludwig Johns Hopkins



Kenneth Kinzler
Ludwig Johns Hopkins

IMMUNOTHERAPEUTIC TOUR DE FORCE

Researchers at Ludwig Johns Hopkins, including graduate students Emily Han-Chung Hsiue and Jacqueline Douglass, Co-directors Bert Vogelstein and Kenneth Kinzler, and investigators Shibin Zhou, Nick Papadopoulos and Chetan Bettegowda, as well as their Johns Hopkins colleagues Katharine Wright and Sandra Gabelli developed and demonstrated a new strategy for immunotherapy that targets specific genetic alterations commonly associated with cancer, including those of the TP53 tumor suppressor gene and cancer-driving RAS genes to generate a therapeutic immune response. The strategy and its preclinical evaluation in mouse models were described in two March papers in [Science Immunology](#) and [Science](#).

The Ludwig Johns Hopkins team first developed antibody fragments to recognize the targeted mutant antigens,

called neoantigens, and used them to design bispecific antibodies that recognize two distinct molecules: the antigens bound to the protein machinery that presents them to the immune system's T cells, known as HLA, and a receptor on T cells that is critical to their function. By linking the two, the bispecific antibodies prompted the T cells to kill the cancer cells presenting the targeted antigens. The researchers demonstrated that the immune attack elicited by the bispecific antibodies is restricted to cancer cells bearing the neoantigens, does not affect healthy cells and prompts the destruction of human cancer cells harboring TP53 and RAS mutations in xenograft mouse models.

The strategy's success depends on a cancer expressing at least one targeted neoantigen and the patient having

continued on next page



Nickolas Papadopoulos
Ludwig Johns Hopkins



Bert Vogelstein
Ludwig Johns Hopkins



Shibin Zhou
Ludwig Johns Hopkins

the particular HLA type that presents that antigen to the immune system. It has several advantages. Importantly, neoantigens derived from genetic alterations represent the most specific targets possible. Therefore, targeting these antigens minimizes the chances of causing so called “on-target, off-tissue” toxicities observed when targeting tumor-associated antigens that can also be expressed in certain normal tissues.

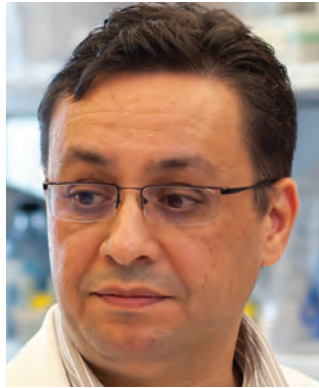
Another potential benefit would be that such products could work on a wide variety of patients, so long as they have the HLA subtype and any type of cancer that expresses the mutant TP53 or RAS gene—both of which are very common drivers of cancer. The antibody-based approach should also be comparatively simple to apply because it does not entail any isolation and engineering of patient immune cells. The researchers are now further studying the strategy to assess its potential toxicities and adapting

their approach to target other common cancer-related mutations.

In a third March paper published in [Science Translational Medicine](#), the team led by Bert Vogelstein and a Johns Hopkins colleague Suman Paul devised similar bispecific antibodies to target T-cell lymphomas. In this approach, the target antigen is a T-cell receptor (TCR) instead of a neoantigen. Each normal T cell expresses a unique TCR type generated from one of approximately 30 different TCR β chain variable gene families. But all cancer cells in a patient express one particular TCR type because all cancer cells are derived from a single original T cell. By targeting the particular cancer cell-expressed TCR, the new approach would kill all cancer cells and only a very small fraction of normal T cells. The efficacy and specificity of this approach were shown both in culture dishes and in mouse models of the disease.

HIGH SUGAR SOLUTION

In a February [paper](#) in *Nature*, researchers led by Ludwig MSK's Taha Merghoub, Jedd Wolchok and former postdoc Roberta Zappasodi, now at Cornell, described a mechanism by which the immunotherapy CTLA-4 blockade can disable suppressive immune cells to aid the destruction of certain tumors. The researchers used a model system in which tumors are relatively less reliant on burning sugar through glycolysis. In a mouse model of glycolysis-deficient breast tumors, CTLA-4 blockade not only stimulated cancer-targeting T cells but also reprogramed regulatory T cells (Tregs), which suppress anti-cancer immune responses. CTLA-4 blockade extended the survival of mice in which tumors were surgically removed compared to identically treated mice implanted with glycolysis-competent tumors. The effect correlated with increased infiltration of T cells into tumors and the establishment of a strong immune memory of the cancer in the mice, and Tregs in responsive tumors had lost their suppressive ability and were producing interferon- γ and TNF- α , which are normally produced by killer T cells. The researchers showed that depletion of glucose in the microenvironment by tumor glycolysis reinforces the functional stability of Tregs and described the signaling that destabilizes Tregs in an environment rich in glucose following CTLA-4 blockade. They are now looking for drugs that can suppress glycolysis in tumors to test as therapies in combination with CTLA-4 blockade.



◀ Taha Merghoub
Ludwig MSK



◀ Jedd Wolchok
Ludwig MSK



Ralph Weichselbaum ▶
Ludwig Chicago

TER-RIFIC TARGETS

"Ter" cells (officially CD45-Ter119+CD71+ erythroid progenitor cells), precursors to certain types of blood cells, are induced in the spleen by tumors and are thought to promote tumor progression by secreting a factor known as artemin. Now a study led by Ludwig Chicago's Ralph Weichselbaum and Yang-Xin Fu of the University of Texas Southwestern Medical Center has found that both targeted radiotherapy and anti-PD-L1 immunotherapy deplete Ter cells in the spleens of mouse models and reduce artemin levels outside the field of radiation. The researchers [reported](#) in a February paper in *Science Translational Medicine* that Ter cell depletion or the blockade of artemin or its signaling partners boosted the therapeutic effects of both IR and anti-PD-L1 immunotherapy against various tumor types. That effect was mediated by killer T cells, which target cancer cells, and the production of interferon- γ , an immune-stimulating factor. Conversely, giving mice erythropoietin—which promotes Ter cell proliferation—induced resistance to those therapies. An examination of samples from patients with melanoma who had received immunotherapy or patients with lung cancer who received radiotherapy demonstrated that favorable responses were associated with a reduction of Ter cells, artemin or its signaling partners. The researchers note that their study identified several potential drug targets to improve outcomes of radiotherapy and immunotherapy.



Galit Lahav
Ludwig Harvard



Ralph Weissleder
Ludwig Harvard

A MATTER OF TIME

The varying sensitivity of different tissues to radiation has long been a bit of a puzzle. It is known that the tumor suppressor p53 mediates responses to radiation, which induces programmed death in seriously damaged cells. Recent studies on cell cultures have, meanwhile, suggested that variations in radiosensitivity correlate with the temporal dynamics of p53 levels within cells. To further explore this possibility, researchers led by Ludwig Harvard investigators Galit Lahav and Ralph Weissleder examined how p53 levels change over time in distinct tissues of living mice in response to irradiation. The researchers focused on tissues in the intestine, thymus and spleen, which express p53 at similar levels yet have

varying sensitivities to ionizing radiation. They [reported](#) in a February paper in *Nature Communications* that p53 levels in highly sensitive tissues tended to spike and then remain on a high plateau following irradiation. In tissues better able to resist radiation, on the other hand, p53 levels tend to oscillate over time. They also evaluated the effects of an inhibitor of MDM2, a regulatory protein in cells that promotes the degradation of p53, on cancer cell responses to radiotherapy. Exposure to the drug reduced the viability of cancer cell lines and, even when given only in a single dose immediately following radiotherapy, suppressed tumor growth in a mouse model of colon cancer.

As part of our ongoing commemoration of Ludwig's 50th anniversary, we asked scientists at our Branches and Centers to share their views on how far the field has come, and their hopes and expectations for the future of cancer research and care. Their answers touched on multiple scientific disciplines, challenges and issues, with some common themes offering a rough measure of where frontline physicians and cancer researchers feel their field is right now and where they think—or hope—it's heading. In the interests of keeping our own biases out of this compilation and letting the overlapping ideas and issues raised by Ludwig researchers speak for themselves, we've organized the responses we received in plain old alphabetical order. Read on!

What do you think have been the **most surprising accomplishments** in cancer research since the Ludwig Institute for Cancer Research was born 50 years ago?



The discovery that cancer is, in essence, a genetic disease, and the identification of the major genes responsible for it.

CHETAN BETTEGOWDA
Ludwig Johns Hopkins

I think the success of immunotherapy has been one of the more surprising accomplishments over the past 50 years. Even in the age of the genomic revolution and numerous therapies targeted at the cancer genome, this mutation-agnostic approach has still resulted in some of the best improvements in patient outcomes in certain settings.

THOMAS CARROLL
Ludwig Oxford



Paradigm shifting discoveries since 1971 that have changed the lives of patients include mapping of the human genome, and the discovery of oncogenes and immune checkpoints. Translation of these discoveries dramatically improved cancer diagnostics and treatment through new targeted drugs and immunotherapy.

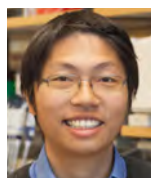
CHI VAN DANG
Ludwig Institute for Cancer Research

At the time, it was a surprise when human oncogenes were found to be related to viral oncogenes, and tumor suppressors were identified. A more recent surprise was that metastatic dissemination is driven

Ask a scientist

less by pro-metastasis mutations, but rather by the combination of cell plasticity and microenvironment-driven phenotype switches.

COLIN GODING
Ludwig Oxford



The decisive advances in cancer immunotherapy have been widely feted, and for good reason. Separately, I am also inspired by how multiple blood cancers can be treated by depleting a patient's cancerous blood system and replacing it with a healthy one ("bone marrow transplantation"), which recently saved a friend's life.

KYLE LOH
Ludwig Stanford

What I've really come to find mind-blowing is how our understanding of the tumor microenvironment has evolved, not just when it comes to its complexity but also the different technologies that we now have the privilege to use, allowing us to decode information right down to the level of single cells.

SAMANTHA MAHFOUD
Ludwig Lausanne



There have been so many discoveries in the past 50 years, it is difficult to choose! But amongst them, the discovery that gut microbiota regulate responses to cancer therapies is the one I personally find fascinating. The idea of interorgan communication and viewing cancer as a whole-body

disease really speaks to me, especially because we work on blood and lymphatic vessels, which are types of highways connecting all parts of our body.

TANYA PETROVNA
Ludwig Lausanne

The advent of computerized radiation therapy to treat patients with diverse solid tumors without the need for radical surgery.

SEAN PITRODA
Ludwig Chicago



There have been so many amazing breakthroughs in the last 50 years, it is difficult to choose the most surprising ones. The fact that mutations in the replicative polymerase epsilon are a common driver mutation was certainly unexpected and shows how cancers can actively tune the speed of evolution to their advantage.

BENJAMIN SCHUSTER-BÖCKLER
Ludwig Oxford

We now understand in amazing detail the genetic underpinnings of cancer and how genetic aberrations drive cancer progression. But, more importantly, we see how even single agent antagonists of key drivers have remarkable clinical benefit (e.g. Gleevec). That reprogrammed T-cells (CAR-T therapies) can provide nearly single dose cures for patients with acute lymphoblastic leukemia and myeloma. That harnessing the body's immune system in general can provide remarkable

Ask a scientist

and sustained benefit across a diversity of human cancers.

BILL SELLERS
Ludwig Harvard



The past half-century has brought great advancements in our knowledge on cancer, leading to multiple new therapies. During this time, it also became clear that cancer is a collection of different diseases. Most surprising, it was discovered that each cancer can be extremely heterogenous, explaining why they are so hard to treat. This realization now serves as a platform for designing next-generation therapies that target the evolvability of cancer cells, thereby limiting the development of therapy resistance, and improving patient prognosis.

OFER SHOSHANI
Ludwig San Diego

In the last few decades, cancer research has achieved astonishing results, bringing insights into the basic mechanisms of tumorigenesis and cancer progression. Discovery of key players driving tumor growth and invasion led to identification of the first therapeutic targets. These milestones made possible the development of a wide range of cancer treatments.

ARTEM SMIRNOV
Ludwig Oxford



The level of molecular understanding we have now is totally incomparable to 50 years ago. From a rudimentary understanding of morphology, we now measure and interpret thousands of molecules in every single cell routinely.

PETER VAN GALEN
Ludwig Harvard

For me, one of the most remarkable achievements in cancer research has been the development of cancer immunotherapy. Over the past 50 years, we have discovered multiple regimens that notably harness the immune system to eliminate cancer cells, like immune checkpoint inhibitors and chimeric antigen receptor immune cells.

NEHA WALI
Ludwig Oxford



Identification of the genetic alterations that cause cancer and the underlying mechanisms by which they function, and the development of therapeutic approaches that target those mechanisms for cancer therapy.

EILEEN WHITE
Ludwig Princeton

Although I should not be surprised to have seen this, I must comment on the now-widespread use of immunotherapy for numerous different cancers. The impact of this form of treatment has been significant in some diseases, like melanoma, and I credit the stalwart support of LCR in making this a reality. I also am continually impressed by how quickly we, as

Ask a scientist

clinicians, can obtain detailed genomic information about literally hundreds of genes in a patient's tumor. This is actionable information in many instances and happens within a timeframe that is clinically realistic. The fact that we can now even get some of the same information from cell free DNA in blood and other body fluids is similarly impressive (thank you Ludwig Center @ Johns Hopkins!).

JEDD WOLCHOK
Ludwig MSK

What are the most pressing cancer research needs moving forward?



Treatment innovations have greatly improved the expected lifespan for many cancer patients over the past 50 years. However, many metastatic cancers still remain difficult to treat. In my opinion, increased research focus on cancer prevention and early detection methods would be an important step towards reducing the number of patients with metastatic disease.

THOMAS CARROLL
Ludwig Oxford

Drug resistance and our incomplete understanding of patient-to-patient variability remain significant barriers to curing cancers. Further research is critically

needed to reveal exploitable vulnerabilities of the tumor immune microenvironment and to understand how individual genetic, dietary and behavioral differences contribute to therapeutic response.

CHI VAN DANG
Ludwig Institute for Cancer Research



One of the most pressing research needs moving forward is a more complete understanding of the state of the immune response in cancer patients and its relationship to the genetic alterations in the neoplastic cells.

JACKIE DOUGLASS
Ludwig Johns Hopkins

An ability to target the multiple different phenotypic states in cancers that can act as a reservoir for drug or immunotherapy tolerant cells, in particular cancer stem-like cells and dormant cancer cells. There is also a related need to understand and overcome mechanisms of resistance to immunotherapies.

COLIN GODING
Ludwig Oxford

Cancer immunotherapy (specifically, immune checkpoint blockade) is remarkably effective against certain cancers (e.g., melanoma and certain lung cancers). These cancers are riddled with DNA mutations and consequently present many mutant proteins ("cancer neoantigens") for the immune system to target. Cancers with lower mutational burdens may necessitate alternate therapeutic interventions.

KYLE LOH
Ludwig Stanford

Ask a scientist



We currently hold a huge amount of data from both mouse tumor models and patient samples, especially after the single cell RNA sequencing era I am lucky to be part of. Now, what I think we are in need of, with the help of bioinformatics, is to delve deeper into finding new therapeutic options and make the current ones more specific to prevent off-target adverse effects.

SAMANTHA MAHFOUD
Ludwig Lausanne

Again—so many of those! My personal pick is bringing in mathematicians, physicists, programmers and collecting whole-body information for next-level analysis of data, and developing quantitative, systemic models for cancer and its responses to therapies. A totally different challenge is the recruitment of young talent in an increasingly consumerist world 😊. But I am resolutely optimistic, and thrilled to interact daily with so many great young scientists.

TANYA PETROVNA
Ludwig Lausanne

Immediate cancer research needs include cancer prevention, early detection and monitoring, vaccination strategies, personalization of treatment approaches, and reducing side effects of cancer treatment.

SEAN PITRODA
Ludwig Chicago

Targeted therapies against specific cancer driver gene variants and newer systemic therapies such as

checkpoint blockade are becoming available at the moment. What is lacking, in my opinion, is a better prediction of which combination of treatments is best suited for which patient, and a faster way to monitor the success of treatment.

BENJAMIN SCHUSTER-BÖCKLER
Ludwig Oxford



Methods to preclinically model the full spectrum of human cancer so we can elucidate curative treatments without sequential empirical clinical trials. Also, the ability to selectively detect and remove early-stage cancers that are likely to develop into lethal disease.

BILL SELLERS
Ludwig Harvard

Notwithstanding the huge progress, a deeper understanding of oncogenic pathway complexity has raised even more questions to solve, for instance, drug resistance. Therefore, I believe that new therapeutic strategies will need to switch from general to personalized cancer treatment to address this important question before choosing a specific treatment.

ARTEM SMIRNOV
Ludwig Oxford

Cellular heterogeneity at the level of genetic, transcriptional and epigenetic states is still an enormous challenge. Small populations of cancer cells that evade therapy are often the source of relapse, a major clinical challenge. That, and tumor-immune cell interactions.

PETER VAN GALEN
Ludwig Harvard



Despite durable clinical benefits in some patients with cancer who receive immunotherapy, most patients still fail to respond to treatments. As a result, there is still a lot more work to do to elucidate mechanisms of response and resistance to immunotherapy and discover new potential biomarkers and therapeutic targets.

NEHA WALI
Ludwig Oxford

Immunotherapy is changing the course of cancer therapy, providing long lasting tumor regression and cures in patients afflicted with what was previously a lethal disease. Expanding the success of immunotherapy to more patients and tumor types through research is a pressing need.

EILEEN WHITE
Ludwig Princeton

The costs of cancer care and disparities in access are highly urgent needs. New and better therapies for disease with a dire prognosis such as GBM and pancreatic cancer are also areas of immediate importance.

JEDD WOLCHOK
Ludwig MSK

What would you **most like to see happen** in cancer research in the next 50 years? And are we well-positioned to achieve that?

Next-generation sequencing datasets are now key tools for cancer research, and their importance will only continue to grow over the next 50 years. Meaningful analysis can be done on a single dataset, but integration of multiple datasets helps us derive more insight and potential benefit for patients. Therefore, it will be crucial for our field to promote seamless access to raw data and reproducible code in the coming decades.

THOMAS CARROLL
Ludwig Oxford



We hope that our liquid biopsy research will enable a future where a majority of cancers are detected earlier, when they are still treatable and curable, by routine screening. Accomplishing this goal will be a key to reducing cancer deaths, hand-in-hand with the development of new therapeutics.

JOSH COHEN
Ludwig Johns Hopkins

The Ludwig Institute for Cancer Research is uniquely positioned to deploy precious sustainable resources in orthogonal strategies to contribute to cancer research

Ask a scientist

breakthroughs. Similar to the paradigm used by the Defense Advanced Research Program Agency (DARPA) that contributed to the development of the internet, GPS technology, and unmanned aerial vehicles, Ludwig can and will embrace high-risk projects that will uncover unforeseen novel therapeutic and early detection strategies.

CHI VAN DANG

Ludwig Institute for Cancer Research



Following targeted therapy to dramatically reduce tumor burden, for example by inhibiting mutant BRAF in melanoma, targeting minimal residual disease (MRD) will reduce the probability of emergence of genetic drug resistance. This requires detailed understanding of the mechanisms that generate and maintain MRD and a reassessment of clinical ethical considerations.

COLIN GODING

Ludwig Oxford

History suggests that cancer research will be transformed in the next 50 years in ways that we cannot possibly imagine. 50 years ago—in 1971—cancer immunotherapy or CAR-T cells would have been inconceivable. The serendipity of basic research will continue to delight and surprise us in hitherto unimaginable ways.

KYLE LOH

Ludwig Stanford

In coming years, what I long to see the most is for cancer treatments to become more personalized and,

importantly, accessible to patients worldwide. As a Lebanese graduate, I see that we are still on the lower part of the scale when it comes to bridging cancer research and clinical trials. I hope that with help and support from countries with advanced technologies, like Switzerland, more countries will have the opportunity to see what research is truly about and how it is being translated in daily life.

SAMANTHA MAHFOUD

Ludwig Lausanne

If you are asking about my dream, here goes: I would like to see the transition to improved diagnostics, prevention and treatment of pre-cancerous and early cancerous lesions combined with effective, minimal-side-effects treatment of advanced cancers. These goals have a big social component, so I am in two minds as to how we stand currently—technologically I think we are in a good shape, but socially there is much room for progress to guarantee access to information, diagnostics and treatment for everyone.

TANYA PETROVNA

Ludwig Lausanne



By leveraging brilliant minds in translational and basic sciences, I believe we are well-positioned over the next 50 years to cure many or most patients with metastatic disease.

Sean Pitroda

Ludwig Chicago

Our current understanding of molecular pathways is often not quantitative but only descriptive. In the next

Ask a scientist

50 years, we need to move from a reductionist view of gene function to a model-based approach that is able to integrate the complex interactions that control cellular behavior and make testable predictions. I am confident that technological development both on the experimental and computational side will soon make this possible.

BENJAMIN SCHUSTER-BÖCKLER
Ludwig Oxford

That we cure cancer—and while, scientifically, we are making tremendous progress with regards to our ability to harness discoveries to that end, we are not well positioned to achieve this goal.

Bill Sellers
Ludwig Harvard

This new and exciting era of big data and -omics that reveal cancer genomes in base-pair resolution, combined with cutting edge microscopy approaches and powerful genome editing tools, provides great promise for the future of cancer research, with the hope that within the next half century humanity would win the fight against cancer.

OFER SHOSHANI
Ludwig San Diego



Recent development of cost-effective sequencing will allow rapid analysis of tumor DNA and RNA to identify specific therapeutic targets for every single patient. I trust that new technologies like these will help us find the most efficient strategies to fight cancer.

ARTEM SMIRNOV
Ludwig Oxford

I would like to see that all the molecular insights the field has gained and the technologies we have developed are translated into improved targeted, combination or personalized therapies. We are in a great position to do that, but much work needs to be done.

PETER VAN GALEN
Ludwig Harvard

In the next 50 years, I would like to see an even stronger integration of immunotherapies and computational algorithms that predict clinical response. Given the constant and rapid growth of bioinformatics, new sequencing technologies and artificial intelligence, I do believe the field is in a good position to achieve this.

NEHA WALI
Ludwig Oxford

I would like all cancer researchers to seek employment in other areas because cancer is history. This is an achievable goal.

EILEEN WHITE
Ludwig Princeton



I would like to see more global efforts to ensure access to cancer care and more attention to blood-based diagnosis and biomarker assessment for more precise treatment planning.

JEDD WOLCHOK
Ludwig MSK

Required reading

Ludwig Chicago

Science Immunology
2021 June 11

All-trans retinoic acid overcomes solid tumor radioresistance by inducing inflammatory macrophages

Rao E, Hou Y, Huang X, Wang L, Wang J, Zheng W, Yang H, Yu X, Yang K, Bugno J, Ding X, Vokes EE, Fu Y-X, Weichselbaum RR, Liang HL.

Breast Cancer Research
2021 May 12

Lasofloxifene as a potential treatment for therapy-resistant ER-positive metastatic breast cancer.

Lainé M, Fanning SW, Chang YF, Green B, Greene ME, Komm B, Kurlito JD, Phung L, Greene GL.

Science Translational Medicine
2021 February 24

Radiotherapy and immunotherapy converge on elimination of tumor-promoting erythroid progenitor cells through adaptive immunity.

Hou Y, Liang HL, Yu X, Liu Z, Cao X, Rao E, Huang X, Wang L, Li L, Bugno J, Fu Y, Chmura SJ, Wu W, Luo SZ, Zheng W, Arina A, Jutzy J, McCall AR, Vokes EE, Pitroda SP, Fu YX, Weichselbaum RR.

Ludwig Harvard

Science Signaling
2021 June 8

Metabolic perturbations sensitize triple-negative breast cancers to apoptosis induced by BH3 mimetics.

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Ludwig Lausanne

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