LUDWIG LINK

FEBRUARY 2022

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

On the cover: From left, Eileen White, Josh Rabinowitz and Yibin Kang, the founding Members of Ludwig Princeton

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ludwigcancerresearch.org FEBRUARY 2022

LETTER

Our first newsletter of 2022 is packed with exciting news. You'll read in our Ludwig research roundup about how "cold" tumors can be made responsive to immunotherapy with low-dose radiation and rationally selected therapies, a potentially new approach to treating the brain metastases of breast cancer, a surprising yet apparently common mechanism by which tumor suppressor dysfunction contributes to tumorigenesis—and much, much more.

Our scientists continue to earn awards and accolades and, as always, we mention some of them here. We also recap a recent virtual panel discussion—part of the Ludwig Scientific Insights Webinar series—with the founding Members of Ludwig Princeton. Another feature highlights the recently launched Ludwig Tumor Atlas Project, which brings together Ludwig investigators in the U.S. and Europe for the high-dimensional mapping of tumors, with a special focus on their immune landscapes and mechanisms of therapeutic resistance and response to immunotherapy.

And in light of the new year, we asked Ludwig scientists to weigh in on their top scientific goals for 2022 and the biggest challenges they anticipate in pursuit of those goals. You'll read their answers in our Ask a scientist section.

Happy reading!

Sincerely,

Rachel Reinhardt
Senior Vice President for Communications

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FOR GENERAL EXCELLENCE

Ludwig Stanford's Maximilian Diehn and Michelle Monje were elected to the National Academy of Medicine in October. Max was recognized for "developing and clinically translating novel diagnostic technologies for facilitating precision medicine techniques, and for integrating advanced precision medicine into the area of liquid biopsies." He has made major contributions to the development of several sophisticated technologies for tissue analysis, the early detection of malignancies and the prediction of patient prognoses and treatment outcomes. Several of his lab's discoveries and technologies are currently being evaluated in clinical trials. Michelle was recognized for "making groundbreaking discoveries at the intersection of neurodevelopment, neuroplasticity and brain tumor biology." An authority on diffuse intrinsic pontine glioma, Michelle has pioneered the development of new therapies now in clinical trials for the devastating pediatric brain tumor. She has, in addition, made groundbreaking discoveries on the neuroscience of pediatric and adult brain tumors and the cognitive effects of chemotherapy that hold great promise for translational development. Earlier last year, Michelle also received the MacArthur Award, given "to talented individuals in a variety of fields who have shown exceptional originality in and dedication to their creative pursuits." Click here for a short video of Michelle describing her work and here and here for our profiles of Michelle and Max.

Maximilian Diehn
Ludwig Stanford

Michelle Monje
Ludwig Stanford

George Coukos
Ludwig Lausanne

FOR TRANSLATIONAL DEXTERITY

Ludwig Lausanne Director George Coukos received the 2021 ESMO Translational Research Award for his contributions to research on the immunology and treatment of ovarian cancer. George's early research revealed the existence of infiltrating T cells in ovarian tumors and linked their presence to a lower severity of disease. That discovery, which he built upon in a recent publication (see page 6), indicated that some ovarian tumors might be responsive to immunotherapies under the right conditions. Since then, he has led efforts to devise personalized immunotherapies for ovarian cancer and other malignancies that have traditionally resisted such interventions. His laboratory has also made key contributions to our understanding of how tumors exploit regulatory T cells and myeloid cells of the immune system to suppress anti-cancer immune responses and advanced strategies to undo such resistance. His keynote lecture *Mobilizing Immunity against cancer from bench to bedside* was given on September 17th at ESMO 2021. Read an interview published in the *ESMO Daily Reporter* where George discusses his enduring passion for tumor immunology.

NEW LEADERSHIP FELLOW

Parinaz Mehdipour joined Ludwig Oxford in October as a leadership fellow from the University Health Network, Princess Margaret Cancer Center in Toronto, Canada, where she was a post-doctoral researcher in Daniel De Carvalho's laboratory. She earned her PhD in 2016 from the University of Milan in collaboration with SEMM, European School of Molecular Medicine. Parinaz will lead her first independent research program, focused on cancer epigenetics—the study of how chemical modifications, such as methylation, made to DNA and the histone proteins in which it is packaged affect gene expression—and epitranscriptomics, which examines the influence of similar modifications made to RNA. Her lab investigates immunogenic double-stranded RNAs (dsRNAs) that are induced by inhibitors of DNA methylation. These dsRNAs mimic viral infection and trigger innate immune responses. In her postdoctoral work, Parinaz discovered the genomic source of immunogenic dsRNAs induced by treatment of colorectal cancer cells with DNA methylation inhibitors.

Parinaz Mehdipour
Ludwig Oxford

NEW ADJUNCT SCHOLAR

Ellie Barnes joined Ludwig Oxford in September as a Ludwig adjunct scholar. She is an authority on Hepatitis C virus (HCV) infection, which causes progressive liver damage and can result in cirrhosis of the liver and hepatocellular carcinoma, the most common type of liver cancer. Ellie previously led the UK Medical Research Council's STOP-HCV stratified medicine consortium, which identified immune parameters and blood biomarkers of HCV infection. Each of these parameters can be used to identify markers linked to treatment failure and the development of liver cancer. Ellie's research program is focused on the T cell immunology of gut and liver diseases, including cancer, and the development of T cell vaccines for HCV prevention and a hepatitis B virus cure. She also leads the Cancer Research UK-funded DeLIVER program to profile pre-cancerous changes in the liver and develop new technologies for the earlier detection of liver cancer. In this effort, she is collaborating with Ludwig Oxford's Chunxiao Song and Benjamin Schuster-Böckler to apply TAPS—a new technology for mapping DNA methylation—for the identification of early indicators of liver cancer.

Ellie Barnes
Ludwig Oxford

Mikaël Pittet
Ludwig Lausanne

LUDWIG LAUSANNE'S LATEST MEMBER

Mikaël Pittet joined Ludwig Lausanne as a full Member in August. Mikaël's research focuses on myeloid cells, frontline soldiers of the innate immune system that infiltrate tumors and, depending on their functional states, support tumor growth, suppress anti-tumor immunity or target cancer cells. His laboratory employs advanced imaging and the comprehensive profiling of gene expression patterns in individual cells to unravel the subtle but functionally important differences between myeloid cells, such as neutrophils, dendritic cells and macrophages. These studies have exposed previously unknown vulnerabilities in tumors and furnished potential leads for the development of novel immunotherapies. Before moving to Switzerland in 2020, Pittet was a full professor at Harvard Medical School. He currently holds the ISREC Foundation Chair in immuno-oncology and is a professor at the University of Geneva Faculty of Medicine. Pittet completed his graduate research and first postdoctoral fellowship at the original Lausanne Branch of the Ludwig Institute before leaving for the U.S. in 2003. His exploration of myeloid cells and their functional states, captured in more than 150 research publications, has earned him recognition as a leader in the field. Learn more about Mikaël and his work in this profile in our annual report.

George Coukos
Ludwig Lausanne

LICENSE TO KILL

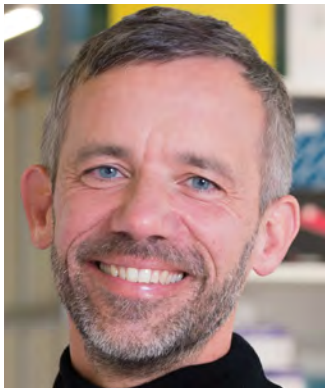
A study led by Ludwig Lausanne Director George Coukos uncovered a cellular interaction essential to the ability of the immune system's cytotoxic T lymphocytes to destroy ovarian tumors in response to immunotherapy. George and his colleagues reported in a November issue of *Cancer Cell* that infiltrating T lymphocytes (TILs) best able to kill cancer cells reside in islets within ovarian tumors. These islets additionally house antigen presenting cells (APCs), like dendritic cells and macrophages, which support TIL activity. The APCs stimulate a protein, CD28, on TILs to boost and sustain their functionality. George and his team showed that TILs activated by PD-1 blockade have to be simultaneously stimulated by APCs through CD28 to be effectively licensed to kill cancer cells. The researchers showed that adding a stimulator of APCs, known as CD40L, in combination with anti-PD-1 and anti-CTLA-4 checkpoint blockade therapies restored the anti-tumor activity of unresponsive TILs in cell cultures. Testing this approach in studies on mice implanted with ovarian tumors, George and his colleagues demonstrated that a combination of the three therapies resulted in much better tumor control in the mouse model than did either single or dual therapy. Their data also show that the identified mechanism is likely to be of relevance in many other cancers as well.

POINT OF NO RETURN

Stem cells balance their self-renewal with their differentiation into mature cells. An intriguing question is when during the process of maturation a progenitor cell reaches a point of no return, losing its capacity to self-renew and becoming committed to generating a specific cell type. Ludwig Oxford's Yang Shi and colleagues reported in a paper published in November in *Cell Reports* that a combination of remodeling of chromatin structure, activation of gene control elements (enhancers) and changes in transcription factor usage contribute to an irreversible commitment to differentiation. The researchers examined how progenitor cells become committed to the production of terminally differentiated neutrophils, a type of white blood cell, from blood stem cells known as hematopoietic myeloid progenitors. They found that the changes they identified result in reduced accessibility to regulatory DNA sites and disruption of a positive feedback transcription factor activation loop that prevents differentiation. The new findings have relevance for acute myeloid leukemia (AML), in which differentiation is arrested. By helping to define the molecular processes involved in differentiation, the researchers hope to identify targets against which to develop new AML therapies.

Yang Shi
Ludwig Oxford

Rakesh Jain
Ludwig Harvard



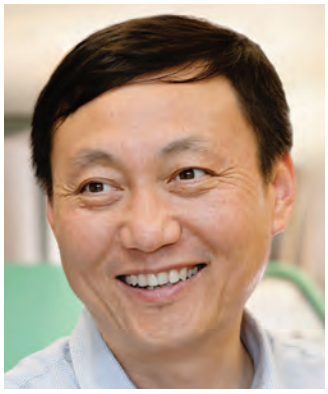
Mikaël Pittet
Ludwig Lausanne

IMPORTANCE OF PLACE

Liver metastasis is a major cause of death for patients with colorectal cancer (CRC), 95% of which are proficient in a type of DNA repair known as mismatch repair and resist immune checkpoint blockade (ICB) therapy. Researchers led by Ludwig Harvard's Rakesh Jain, Ludwig Lausanne's Mikaël Pittet and Harvard's Dai Fukumura explored the causes of this resistance in mouse models of CRC liver metastases. They reported in a November paper in the *Proceedings of the National Academy of Sciences* that while such cancers implanted subcutaneously in mice respond readily to ICB, those implanted in the colon or liver are as resistant to the immunotherapy as tumors seen in patients—demonstrating the importance of using models, in which tumors are implanted in the tissues where they are normally found. The researchers showed that resistance to ICB is associated with a paucity of dendritic cells—which direct and stimulate T cell responses—in CRC liver metastases. Giving the mice a dendritic cell growth factor, Flt3L, boosted the number of dendritic cells and infiltrating T cells in tumors and sensitized the liver metastases to ICB therapy. The findings suggest new strategies for inducing vulnerability to ICB in CRCs.

SILENT SEQUENCES

About 98% of the human genome encodes no proteins. But many sequences in these noncoding expanses do regulate where, when and how avidly the genes in the remaining 2% are expressed, and variations and mutations in these regions contribute enormously to disease. Active regulatory sequences are found in stretches of chromatin—the term for DNA and its protein scaffolding—that are open and accessible to the cell's gene reading machinery, while latent sequences are bundled up and packed away. To capture how active regulatory sequences vary between cell types, a team led by Ludwig San Diego's Bing Ren assayed chromatin accessibility in 600,000 individual cells from 30 adult human tissues to produce a single-cell chromatin atlas of the genome. The researchers then integrated that information with similar data from 15 fetal tissue types to generate a map identifying about 1.2 million regulatory DNA sequences in 222 distinct cell types. Their study, reported in *Cell* in November, identified the regulatory elements active in each cell type and described thousands of them associated with one or more of 240 complex human traits and diseases.



Bing Ren
Ludwig San Diego

Alexandre Harari
Ludwig Lausanne

George Coukos
Ludwig Lausanne

SPECIAL FORCES

A team led by Ludwig Lausanne's Alexandre Harari and Director George Coukos devised a highly efficient method to generate large numbers of immune cells specifically engineered to recognize neoantigens—small fragments of randomly mutated proteins unique to a patient's cancer—and destroy the tumors that express them. The method, named NeoScreen and described in *Nature Biotechnology* in November, could significantly improve the generation of engineered T cells for personalized cancer immunotherapies. Alexandre, George and their colleagues computationally analyzed the genomes of tumor cells and identified potential neoantigens. They then engineered B cells to be antigen presenting cells, pulsed them with the potential neoantigens so that they'd present the peptides and grew them in co-cultures with tumor infiltrating T lymphocytes (TILs). This approach resulted in the selective and dramatic expansion of the most useful T cells—the ones specifically equipped to target tumor cells—against melanoma and lung, ovarian and colon cancers. The T cell receptors on these cells could be cloned and inserted into other T cells to generate large numbers of tumor-targeting cells. T cells produced using NeoScreen recognized genuine neoantigens in tumors and could be used for adoptive cell therapy to induce tumor regressions in mouse models.

A MATTER OF FAT

A study led by Ludwig MIT's Matthew Vander Heiden compared the effects of calorie restricted diets and ketogenic—high fat, moderate protein and very low carbohydrate—diets in mouse models of pancreatic cancer. Matthew and his colleagues reported in an October issue of *Nature* that both diets similarly reduced the amount of sugar, an important nutrient, available to tumors, yet only caloric restriction slowed tumor growth. They further found that with caloric restriction, lipid levels also dropped dramatically, while they actually climbed in mice fed a ketogenic diet. Fatty acids are required to make membranes and are therefore essential to rapidly dividing cells. When levels drop, cells can make their own fatty molecules, but this process requires an enzyme known as stearoyl-CoA desaturase (SCD), which converts saturated fatty acids into unsaturated fatty acids. The researchers found that both diets reduced SCD activity, but mice on the ketogenic diet had lipids available to them from their diet, so they weren't as reliant on the enzyme. Mice on the calorie-restricted diet, however, didn't have that resource, which is why their tumor growth slowed significantly. The dependence on unsaturated fats exposed by this study suggests how different components of the diet can interact to determine whether they affect the growth of pancreatic cancer.

Matthew Vander Heiden
Ludwig MIT

Johanna Joyce
Ludwig Lausanne

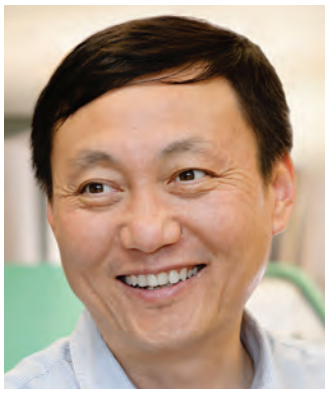
Florian Klemm
Ludwig Lausanne

RESISTANCE UNDONE

A study co-led by Ludwig Lausanne's Johanna Joyce and Florian Klemm, along with Lisa Sevenich of the Georg-Speyer-Haus Institute for Tumor Biology and Experimental Therapy, in Frankfurt, identified and preclinically validated combination treatments for the typically deadly brain metastases of breast cancer. The combination therapy, reported in October in *Nature Cancer,* targets tumor-associated macrophages and microglia (TAMs), immune cells found within brain metastases that cancer cells can manipulate to support their growth and survival. In earlier studies, Johanna's lab had found that inhibiting the CSF1 receptor (CSF1R), an essential signaling protein on TAMs, reprograms these cells into an anti-tumor state and significantly prolongs survival in preclinical mouse models of gliomas. The current study, in brain metastasis, shows that targeting CSF1R is initially effective but ultimately fosters an adaptive resistance mechanism in TAMs in breast-to-brain metastases. That mechanism centers on another signaling protein on TAMs, the CSF2 receptor, and a protein that helps transmit its signals, STAT5. The mechanism revives tumor growth by promoting the expression of genes involved in inflammation and wound repair. Blockade of this adaptive signaling pathway, in concert with CSF1R inhibition, reeducates TAMs into an anti-cancer state and significantly extends survival in mouse models of breast-to-brain metastases.

COMMAND CENTER CIRCUITRY

A study led by Ludwig San Diego's Bing Ren, published in *Nature* in October—among a series of papers reporting brain census of human and mouse brains from the NIH Brain Initiative Cell Census Network—generated an atlas of gene regulatory elements in the mouse cerebrum, which performs high-level sensory perception, motor control and cognitive functions. Both the mouse and the human cerebrum contain hundreds of neural cell types found at specific locations, but relatively little was known about the gene expression programs that give each cell type its distinct traits. Bing and his team investigated the accessible chromatin in more than 800,000 cells from 45 distinct regions of the adult mouse brain. They used the data to map the state of 491,818 candidate cis-regulatory elements (cCREs), which are noncoding DNA sequences that regulate the transcription of genes, in 160 distinct cell types. They showed how both the location and function of distinct neurons in specific cortical regions correlate to the activity of unique sets of CREs. These data will support comprehensive analysis of gene expression programs in the mammalian brain and provide insight into how variations in non-coding DNA sequences contribute to many neurological diseases and traits.



◀ Bing Ren
Ludwig San Diego

Ping-Chih Ho ▶
Ludwig Lausanne

Giusy Di Conza ▶
Ludwig Lausanne

A MALIGNANT POLARIZATION

A study led by Ludwig Lausanne's Ping-Chih Ho and postdoctoral fellow Giusy Di Conza identified a means by which cancer cells engineer the conversion of immune cells known as macrophages from destroyers of tumors to supporters of their growth and survival. The study, published in October in *Nature Immunology*, showed that this transformation is triggered by β-glucosylceramide, a lipid secreted by cancer cells, and identified some of the key events that drive the pro-tumor "polarization" of tumor-associated macrophages (TAMs). Giusy, Ping-Chih and their colleagues report that β-glucosylceramide binds to a receptor named Mincle on TAMs, triggering a stress response within the endoplasmic reticulum. That stress response is partly mediated by a signaling protein named XBP1, and the researchers found that it is not only vital for TAM polarization, but also supports cancer cell survival. They also report that another signaling cascade coordinates with the one involving XBP1 to induce TAM polarization. This one involves a signaling protein named STAT3 that directly regulates the expression of genes. The findings suggest new drug targets to reprogram TAMs for cancer therapy.

SEED COUNT

Cells shed by tumors into the blood circulation can seed metastases. Their capture and analysis could help clinicians determine how well patients are responding to therapy. But because circulating tumor cells (CTCs) are rare, they can be very hard to study, especially in mice, which have very little blood in their bodies. A team led by Ludwig MIT's Scott Manalis developed an exchange system that allows blood from a healthy mouse to flow into a tumor-bearing mouse and vice versa, while detecting, isolating and counting CTCs. The researchers used their system to analyze CTC dynamics in real-time in mouse models of three types of cancer: small-cell lung cancer (SCLC), a pancreatic cancer and non-small cell lung cancer (NSCLC). The half-lives of the CTCs for the three cancers, they reported in a September paper in *Nature Communications*, range from 40 seconds to about 250 seconds. SCLC tumors, which tend to be highly metastatic, shed more than 100,000 cells per hour into the blood, while pancreatic tumors released as few as 60 in that period. Just 1%-2% of CTCs shed by SCLCs in a day could seed large metastases in healthy recipient mice.

◀ Scott Manalis
Ludwig MIT

Aaron Newman ▶
Ludwig Stanford

Ash Alizadeh ▶
Ludwig Stanford

TUMOR PORTRAITURE

In a pair of September papers published in *Cell* and *Cancer Cell,* researchers led by Ludwig Stanford's Aaron Newman and Ash Alizadeh described their implementation of EcoTyper—a new machine learning framework that combines multiple algorithms previously developed by the researchers for the large scale analysis of cell types, genomic expression patterns in single cells and databases of cellular and molecular information—to categorize clinically relevant cell states and ecosystems of cells from tumor specimens at unprecedented scale. Applied to human carcinoma and diffuse large B cell lymphoma (DLBCL), the most common types of solid cancer and blood cancer, respectively, EcoTyper revealed a surprising diversity of cellular ecosystems in which distinct cell states interact with each other, including multiple ecosystems associated with different molecular subtypes and survival outcomes for patients. For example, EcoTyper defined new cell states and ecosystems in carcinoma, including ones associated with immunotherapy response and early lung cancer development. In DLBCL, it also identified five states of malignant B cells that vary in prognostic association and differentiation status, and significant variations in cell states for a dozen other lineages in the tumor microenvironment. The results paint a granular yet sweeping portrait of the microenvironment of human tumors and offer clues to new approaches to treating cancer.

Tyler Jacks
Ludwig MIT

UNDERDOG SUPPORT

When they're attacking tumors, T cells of the immune system typically target neoantigens—which are generated by the random mutations accumulated by cancer cells. But relatively little is known about the interplay between T cell responses to distinct neoantigens or how that influences tumor control. Researchers led by Ludwig MIT's Tyler Jacks reported in a September paper in *Cell* their study of these questions in a mouse model of lung cancer. The T cell response in lung tumors, they found, is dominated by neoantigens that most stably bind the MHC protein, which presents the antigenic fragments to T cells. This antigen dominance can result in a failure to generate strong immune responses to subdominant antigens expressed in the same tumor. Further, while those suppressed, subdominant T cells express a protein, TCF1, associated with responses to immune checkpoint blockade (ICB) therapy, they also express proteins associated with T cell dysfunction. Tyler and his colleagues discovered that vaccinating mice with a subdominant neoantigen stimulated the production of highly functional T cells and shrank lung tumors in the mice. The researchers will be examining therapeutic approaches combining this vaccination strategy with ICB therapy.

Stephen Elledge
Ludwig Harvard

EVASIVE MANEUVERS

Researchers led by Ludwig Harvard's Stephen Elledge recently discovered an entirely different mechanism by which tumor suppressor dysfunction contributes to tumorigenesis. The team used CRISPR gene editing to eliminate each of about 7,500 genes, many known to be associated with cancer, in tumor cells. They then examined how the loss of each affects tumor growth by implanting the engineered cells into mice that either had or lacked a functioning immune system. Genetic analysis revealed that mutations to tumor suppressor genes contributed most significantly to tumor growth in mice with intact immune systems. Stephen and his colleagues reported in a September paper in *Science* that mutations to more than 100 tumor suppressor genes—about 30% of all the tumor suppressor genes they evaluated—help tumors evade immune responses. They also showed how the loss of one tumor suppressor, GNA13, helps protect tumor cells from attack by the immune system through the generation of a favorable tumor microenvironment. These findings open the door to understanding the principals of immune evasion and suggest that targeting these escape mechanisms may improve cancer therapies.

Richard Kolodner
Ludwig San Diego

RAD ROLE, RAD REACTION

Base-pair mismatches in DNA that arise from DNA replication errors can contribute to cancer. Eukaryotic DNA Mismatch Repair (MMR), which is essential to suppressing cancer, involves redundant pathways that either employ a DNA snipping enzyme, exonuclease 1 (Exo1), to remove mismatches or involve Exo1-independent pathways to do so. The latter are poorly understood. In a September paper in *Nature Communications*, Ludwig San Diego's Richard Kolodner reported that in Saccharomyces cerevisiae (Baker's yeast) the enzyme Rad27 defines an Exo1-independent pathway that removes mismatches during MMR. Though deletion of Rad27 was known to lead to the rapid accumulation of mutations across the yeast genome, its role in MMR has been controversial. One way to resolve the controversy would be to delete both Exo1 and Rad27 and examine the outcome, but such double mutations proved to be lethal. Richard and his team got around this problem by engineering yeast to encode an Exo1 enzyme that lacks segments—known as SHIP and MIP boxes—essential to MMR but retain parts required for its other life-sustaining functions when Rad27 is also inactive. This double mutant had much stronger MMR defects than either single mutant, demonstrating that Exo1 and Rad27 define redundant MMR pathways. The researchers also reconstituted the reaction involving Rad27 in vitro, offering insight into the mechanism of Rad27-dependent MMR. These findings will guide the search for similar Exo-1 independent MMR pathways in human cells.

Colin Goding
Ludwig Oxford

SNAPS OF NAPPING CELLS

In a June paper in *Nature Communications*, a team led by Ludwig Oxford's Colin Goding and Francesco Neri of Friedrich-Schiller-University in Germany reported their development of a general method for identifying dormant stem cells that is applicable to all cell types, including cancerous ones. The researchers exploited the fact that dormant stem cells have low activity of CDK9, an enzyme that promotes gene expression. They designed a genetically encoded assay for CDK9 activity called Optical Stem Cell Activity Reporter (OSCAR) that is highly fluorescent in dormant stem cells, but not in cells with active CDK9. They showed that the assay could reveal dormant stem cells in time-lapse microscopy of intestinal organoid cultures and in an OSCAR mouse model by fluorescent light-activated cell sorting. The team anticipates that OSCAR may prove to be a useful tool in characterizing dormant cells in both cultured cells and living tissues, including cancers.

George Coukos
Ludwig Lausanne

Melita Irving
Ludwig Lausanne

Fernanda Herrera
Ludwig Lausanne

TEMPERATURE CONTROL

A study led by Ludwig Lausanne's George Coukos, Melita Irving and Fernanda Herrera showed that so-called "cold" tumors that are nearly devoid of immune cells—and therefore unresponsive to immunotherapy—can be turned "hot" with extremely low doses of radiation and the rational use of existing therapies. Researchers have long sought to use high-dose radiation to stimulate anti-tumor immunity, but that is not always an option—for example, when tumors spread into the abdominal cavity, which houses vital organs. To boost the anti-tumor immune responses induced by low-dose irradiation, the researchers combined it with drugs that stimulate dendritic cells, which direct and activate anti-tumor immune responses, and low-dose cyclophosphamide, a chemotherapy that compromises the regulatory T cells that suppress such responses. They also added a combination of anti-CTLA-4 and anti-PD-1 immunotherapies to mobilize a T cell attack on tumors. The researchers reported in *Cancer Discovery* in September that the combination treatment cured 20% of mice and induced regressions in about a third of eight patients with advanced, immunologically cold cancers. Analysis revealed unusual features in the T cells responsible for the cancer-cell killing as well as the dendritic cells essential to that activity. The findings will be applied to the design of various experimental immunotherapies now being developed at Ludwig Lausanne.

VECTORIAL REPURPOSING

A preclinical study led by Ludwig Oxford's Benoît Van den Eynde and Carol Leung along with their Oxford colleagues Irina Redchenko and Adrian Hill reported the results of a preclinical study evaluating a prime-boost regimen for cancer vaccination employing the viral vector used in the Oxford/AstraZeneca SARS-CoV2 vaccine and a modified vaccinia Ankara (MVA) vector. The researchers reported in a September issue of the *Journal for ImmunoTherapy of Cancer* that the prime-boost regimen in mice boosted the number of T cells infiltrating into tumors expressing P1A, the murine equivalent of MAGE-type cancer antigens that were identified and validated by Ludwig researchers, including Benoît. Vaccination enhanced responses to anti-PD-1 immunotherapy, reducing tumor size and extending survival of mice compared to anti-PD-1 immunotherapy alone. The researchers also showed that the human version of the prime-boost vaccine regimen—targeting the MAGE-type antigens MAGE-A3 and NY-ESO1—induces strong immune responses. A Phase 1/2a clinical trial of that vaccine regimen in combination with anti-PD-1 immunotherapy and chemotherapy for the treatment of lung cancer has begun, in collaboration with Cancer Research UK, which is sponsoring the trial, and as part of a partnership between Ludwig and Vaccitech plc.

Benoît Van den Eynde
Ludwig Oxford

Carol Leung
Ludwig Oxford

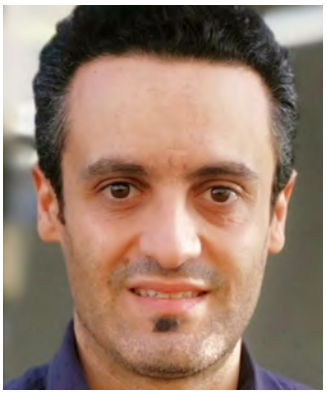
Jens Rittscher
Ludwig Oxford

DIAGNOSTIC RECONSTRUCTION

Measuring and quantifying Barrett's esophagus (BE), a premalignant condition of the lower esophagus, could help improve the timely diagnosis of esophageal cancer. Ludwig Oxford's Jens Rittscher and his University of Oxford colleagues Sharib Ali and Barbara Braden reported in a June paper in *Gastroenterology* an artificial intelligence (AI) system that can be paired with endoscopy to obtain more accurate readings of BE and identify patients at risk of developing cancer. The new system, tested on a 3D printed phantom model and high-definition videos from 131 patients that were scored by expert endoscopists, achieved a 97.2% accuracy in measuring the extent of BE in real time. This technology holds the promise to enable clinicians to assess the risk, the best surveillance interval for patients and the response to treatment more quickly and confidently. The automated process is not only more accurate in measuring the extent of BE, but in providing a complete map of BE, including islands, which is currently not possible. Ultimately, it will be possible to pinpoint the location of an emerging tumor.

Melita Irving
Ludwig Lausanne

George Coukos
Ludwig Lausanne



Evripidis Lanitis
Ludwig Lausanne

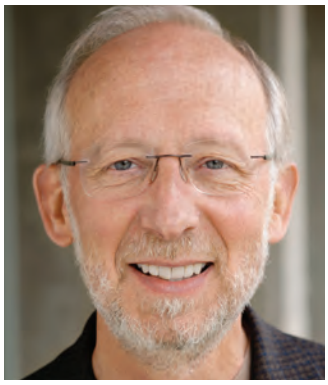
NO CAR ACCESS

Chimeric antigen receptor (CAR)-T cells often fail against solid tumors due to their immunosuppressive microenvironment. A study led by Ludwig Lausanne's Melita Irving, George Coukos and Evripidis Lanitis explored the limitations of second-generation (2G) murine CAR-T cells targeting the vascular endothelial growth factor receptor-2 (VEGFR-2), which plays a central role in the development of new blood vessels that feed tumors. Such CAR-T cells have been shown in previous studies to have limited efficacy as a monotherapy. Melita, George, Evripidis and their colleagues reported in an August paper in the *Journal for ImmunoTherapy of Cancer* that resistance to the therapy stems not from the tumor's suppression of VEGFR-2 expression—a common mechanism of escape—but from its elevated production of VEGF-A, the protein ligand that binds VEGFR-2. They show that VEGF-A undermines the therapy by blocking CAR-T cells' engagement with their target antigen—the first observation of such a mechanism of resistance to CAR-T cell therapy. Administering antibodies to VEGF-A enabled CAR-T control of tumors and boosted persistence of the CAR-T cells in mouse models of melanoma.

BIOMARKER FOR SUCCESS

CAR-T therapies targeting the CD19 molecule have been approved for treating blood cancers. Though many patients respond well, about half eventually relapse because cancer cells remove the CD19 target from their surfaces. A team led by Ludwig Stanford's Crystal Mackall and her Stanford colleague David Miklos examined the roots of CAR-T escape in lymphoma patients and tested a strategy to overcome that resistance. They reported in a July paper in *Nature Medicine* that lymphoma cells too escape CAR-T targeting by reducing CD19 expression. Most notably, their analysis of lymphoma patients revealed that those whose cancers express fewer than 3,000 CD19 molecules per cancer cell are most likely to relapse—establishing a valuable method to select patients for CAR-T therapy. The researchers also devised CAR T-cells that simultaneously target CD19 and another antigen, CD22, and tested them in 38 patients with B cell acute lymphocytic leukemia and large B cell lymphoma. All leukemia patients initially responded, while just 13 of 21 lymphoma patients did. But a good number in both groups ultimately relapsed because the CAR-T cells were preferentially targeting the CD19 molecule, which lymphoma cells removed from their surfaces. The researchers aim to develop bispecific CAR T-cells that target CD22 and CD19 with equal vigor.

◀ **Crystal Mackall**
Ludwig Stanford



Don Cleveland ▶
Ludwig San Diego

Ofer Shoshani ▶
Ludwig alum

DEADLY INSTABILITY

A study led by Ludwig San Diego's Don Cleveland and his former postdoc Ofer Shoshani along with Floris Foijer of the University of Groningen found that inducing random chromosome instability (CIN) events in mice for as little as one week suffices to trigger harmful chromosomal patterns in cells that spur the formation of tumors. Reported in *Genes & Development* in July, the findings confirm a nearly 120-year-old hypothesis, proposed by the German biologist Theodor Boveri, that aneuploidy—an abnormal number of chromosomes—drives tumorigenesis. The researchers transiently overexpressed the gene for polo-like kinase 4 (Plk4) in mice, inducing the production of cells in the animals with unequal numbers of chromosomes. Just one week of such overexpression induced aggressive T cell lymphomas often characterized by cells with triplicates of chromosomes 4, 5, 14 and 15. The team showed that the generation of aneuploidy is an early event in cancer initiation, and that transient CIN events can drive tumorigenesis regardless of whether p53—a major tumor suppressor that is frequently mutated in human cancer—is inactivated. The findings are of high relevance to people receiving aneugens, chemotherapies that cause chromosome instability and aneuploidy, suggesting that they might be at risk for secondary cancers induced by therapy.

DUAL ATTACK

A study led by Ludwig Stanford's Irv Weissman published in July in the *Proceedings of the National Academy of Sciences* preclinically validated a potential combination therapy for breast cancer. Irv and his colleagues showed that targeting a protein named CD47 in a mouse model of HER2+ breast cancer increases the efficacy of trastuzumab (Herceptin)—a standard treatment for this malignancy—even when the cancer is resistant to the antibody therapy. Irv and his colleagues have previously shown that CD47 transmits a "don't eat me" signal to the immune system's macrophages, that several cancers express the protein for immune escape and that blocking that signal can stimulate a potent macrophage assault on tumors in mouse models of various cancers. They also helped develop an anti-CD47 antibody therapy (magrolimab) that is now in clinical development. Trastuzumab, meanwhile, works in part by recruiting another type of immune cell, the natural killer cell, to attack breast cancer cells. Irv and his team showed in this study that combining trastuzumab and magrolimab also engages macrophages in the antitumor attack. The dual therapy significantly inhibited tumor growth in mouse models of HER2+ breast cancer—including those resistant to trastuzumab—and improved survival compared to either treatment alone.

Irv Weissman
Ludwig Stanford

Ash Alizadeh
Ludwig Stanford

Maximilian Diehn
Ludwig Stanford

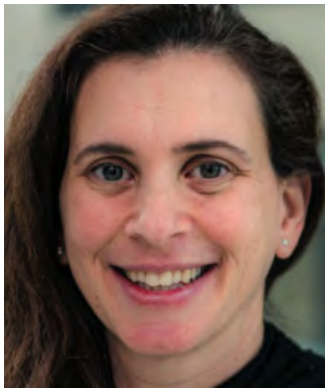
RESIDUAL DANGER DETECTOR

An accurate and rapid detection of minimal residual disease (MRD) after therapy could significantly improve management of diverse tumor types treated with curative intent. For example, standard therapies fail to cure 30-40% of patients with diffuse large B-cell lymphoma (DLBCL). In a July paper in *Nature Biotechnology,* Ludwig Stanford's Ash Alizadeh and Maximilian Diehn and colleagues reported their development and assessment of a highly sensitive liquid biopsy technology— PhasED-seq (phased variant enrichment and detection sequencing)—for MRD detection in DLBCL and other tumor types. The new method uses multiple somatic mutations in individual DNA fragments to improve sensitivity, and the study showed it to be 40-100 times more sensitive than competing ctDNA detection approaches. In studying nearly 700 specimens from over 200 patients during therapy, PhasED-Seq detected nearly twice as many cases of MRD in patients with DLBCL as did a single nucleotide variant (SNV)-based ctDNA method. Applied to a group of 19 DLBCL patients who had completed all induction therapy with curative intent, PhasED-Seq detected MRD in every patient who relapsed, compared to a detection rate of just 40% using the alternative method. The team also used proof-of-concept studies in lung and breast cancers to highlight the promise of the method in other solid tumors.

THINGS NATURAL KILLERS LIKE

Natural killer (NK) cells are versatile immune cells that play a critical role in suppressing and controlling cancer. Rather than targeting specific antigens, as do B and T cells, these agents of the innate immune system determine the fate of their cellular targets by detecting a panel of molecules and molecular patterns on their surfaces. A team led by Ludwig Harvard's Constantine Mitsiades and Michal Sheffer explored the molecular features on tumor cells that are recognized by NK cells. The researchers measured the responsiveness of hundreds of barcoded tumor cell lines to NK cells and applied CRISPR-based gene editing screens to identify genes involved in shaping NK cell responses. They reported in a *Nature Genetics* paper in July that tumor cells sensitive to NK cell targeting have mesenchymal-like gene expression signatures and express genes involved in chromatin remodeling complexes. They also display high levels of B7-H6, which is known to activate NK cells, and low levels of certain antigen presentation genes. Notably, signatures associated with sensitivity to NK cells are also linked to poor responses to checkpoint blockade immunotherapy in clinical samples. The study offers important clues for the future development of NK cell-based immunotherapies.

Constantine Mitsiades
Ludwig Harvard



Michal Sheffer
Ludwig Harvard

Sangeeta Bhatia
Ludwig MIT

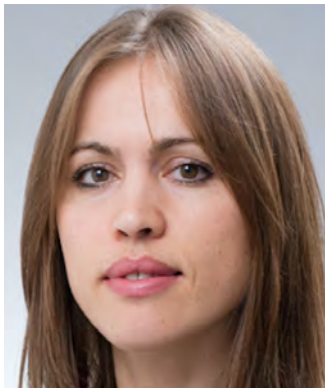
NANO DOUBLE DUTY

Researchers led by Ludwig MIT's Sangeeta Bhatia devised a diagnostic nanoparticle that can reveal the presence of tumors through a urine test and double as an imaging agent, pinpointing where the tumors are located. Their work was reported in a July paper in *Nature Materials*. Sangeeta's lab has for several years been developing diagnostic nanoparticles coated with peptides that are selectively cleaved by enzymes known as proteases, including matrix metalloproteases, which are specifically expressed by cancer cells as they shape their environment and metastasize. When the particles enter a tumor, the peptides are snipped off by the proteases and excreted in the urine, where they can be detected via fluorescence. But it's one thing to detect a tumor, quite another to locate where it's growing. To equip their nanodetectors with that capability, Sangeeta and her colleagues added to them a radioactive tracer, copper-64, and coated them with a peptide that favors acidic environments, which are common in tumors. The peptides insert themselves into cell membranes in such environments, generating a strong signal for PET imaging. The technology could prove useful for cancer diagnostics and monitoring of patients for cancer recurrence.

THE STING PARADOX

Approximately 10% of ovarian cancers are characterized by inherited mutations in the *BRCA1* and *BRCA2* genes. Researchers led by Ludwig Lausanne's George Coukos and Denarda Dangaj Laniti explored the role of a double stranded DNA-sensing protein named STING, found in the cytoplasm of cells, in both driving immunoreactivity and promoting immune resistance in ovarian tumors with mutated BRCA genes. They reported in a July paper in *Cell Reports* that ovarian cancer cells with mutated BRCA genes induce inflammatory signals by activating STING and type 1 interferons (IFN), drawing T cells into such tumors. On the other hand, STING activation caused by the accumulation of double stranded DNA in the cytoplasm also promotes expression of VEGF-A, a critical regulator of blood vessel growth that drives tumor progression and immune evasion. In fact, the genetic loss of STING reduced VEGF-A expression and angiogenesis and increased T cell infiltration into tumors, an effect that could be mimicked by treatment with anti-VEGF-A antibodies. Combining an anti-VEGF-A antibody therapy with PARP inhibitors—which exacerbate double stranded DNA accumulation in BRCA-mutated cells—coupled with dual immune checkpoint blockade, suppressed *BRCA*-deficient ovarian tumors in mice. This suggests a new strategy for treating tumors with BRCA mutations or related deficiencies.

George Coukos
Ludwig Lausanne

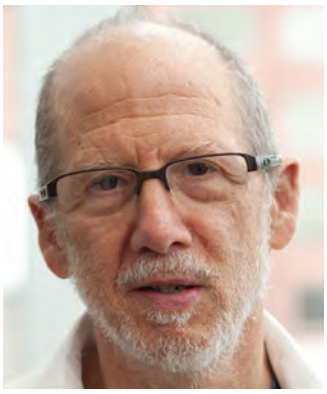


Denarda Dangaj Laniti
Ludwig Lausanne

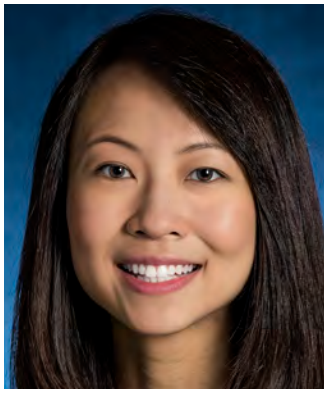
Colin Goding
Ludwig Oxford

UNUSUAL SUPPRESSOR

The major oncogenes that drive melanoma are well known, and researchers have also characterized many of the mutations that affect the activity of tumor suppressors like PTEN in the cancer. But less is known about how the levels of tumor suppressor affect total tumor suppressor activity in this cancer. A study led by Ludwig Oxford's Colin Goding and Lionel Larue of the Institut Curie, in France, identified BRN2 as a noncanonical tumor suppressor that regulates PTEN levels whose partial insufficiency can drive melanoma. The authors showed previously that BRN2 is a key transcription factor that lies downstream of three melanoma-associated signaling pathways to control gene expression, and that *in vitro* and in xenograft experiments BRN2 controls melanoma migration and invasiveness. The researchers reported in *Nature Communications* in June using mice in which BRN2 is specifically inactivated in mouse melanocytes that loss of BRN2 increases melanoma initiation, and that low levels of BRN2 promote metastatic dissemination. This is the first time that the function of BRN2 in melanoma initiation and metastasis has been demonstrated in an animal model engineered to develop melanoma. The authors also reported that BRN2 loss or low levels are linked to worse prognoses in melanoma.



Bert Vogelstein
Ludwig Johns Hopkins



Yuxuan Wang
Ludwig Johns Hopkins

Jeanne Tie
Ludwig alum

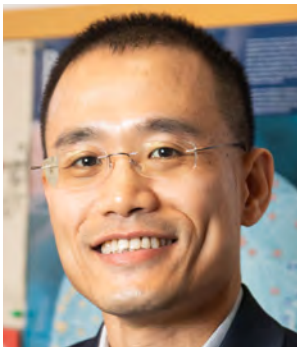
Peter Gibbs
Ludwig alum

RECURRENCE RISK GAUGE

A May paper in *PLOS Medicine* led by Ludwig Johns Hopkins' Bert Vogelstein and Yuxuan Wang and Ludwig alumni Jeanne Tie and Peter Gibbs reported that detecting circulating tumor DNA (ctDNA) in patients' blood after surgery, or following adjuvant chemotherapy, is associated with a very high risk of recurrence and death in patients with resectable colorectal liver metastases (CRLM). An initial study from Bert's group published in *Nature Medicine* in 2008 showed that ctDNA detection after surgery or chemotherapy was successful in predicting eventual cancer relapse in 18 patients with colorectal cancer. In the latest study, which recruited 54 patients with CRLM, the researchers found that patients with detectable ctDNA after surgery had an 83% recurrence risk compared to only 31% in those with undetectable ctDNA after surgery. Similarly, ctDNA predicted for recurrence after adjuvant chemotherapy: All 8 patients with detectable postoperative ctDNA who failed to clear their ctDNA following adjuvant chemotherapy experienced recurrence, while 2 of 3 patients whose ctDNA became undetectable after chemotherapy remained disease-free. The authors suggest ctDNA monitoring could be incorporated into routine surveillance to identify patients who are most likely to experience a recurrence after definitive treatment for CRLM. Prospective clinical trials to test this hypothesis are now underway.

Josh Rabinowitz
Ludwig Princeton

Eileen White
Ludwig Princeton



Yibin Kang
Ludwig Princeton

MEETING THE FOUNDERS

As part of its Scientific Insights Webinar series, Ludwig Communications hosted on September 22nd a panel discussion with the founding Members of Ludwig Princeton—Director Josh Rabinowitz, Associate Director Eileen White and Yibin Kang—moderated by Ludwig Institute Scientific Director Chi Van Dang. After thanking the leadership of Princeton University, RWJ Barnabas Health System and Rutgers University for their support in launching the Princeton Branch, Chi asked each of the researchers to introduce themselves and discuss their research plans at Ludwig Princeton. (For more on each of the founding Members, check out their profiles in the 2021 Research Highlights Report.)

Josh highlighted his interest in exploring dietary interventions for cancer therapy, while Eileen discussed investigating cachexia, the frequently deadly wasting disorder associated with advanced cancers, and the interplay of metabolism and antitumor immunity. Yibin, meanwhile, discussed harnessing Ludwig support to vet a hypothesis he has formulated about pro-survival genes playing a pivotal role in cancer metastasis, and to study the influence of diet on the tissue microenvironment of specific organs and the role such changes play in cancer metastasis.

Guided by Chi's questions, the subsequent conversation covered matters ranging from technological gaps in the field of cancer metabolism to previous collaborations between the founding Members of Ludwig Princeton to how the researchers plan to explore the influence of diet on anti-tumor immunity and the tumor microenvironment. Josh also said Ludwig Princeton plans to soon recruit at least three additional Members and discussed the expertise—such as tumor immunology and computational biology—they're most interested in bringing into the Branch.

At the end of the webinar, Chi opened the virtual floor to questions from the audience, which were moderated by Rachel Reinhardt, senior vice president for communications. Many of the questions had to do with collaboration, with Ludwig Lausanne Director George Coukos and Ludwig Harvard Co-director George Demetri asking how research partnerships might be established between Ludwig locations. As it happened, Yibin had a specific idea for a partnership with George's lab to explore the targeting of sarcomas using a small molecule drug developed in his laboratory. Eileen spoke about an incipient partnership with researchers at the Ludwig Lausanne Branch whose antibody technologies could be useful to her work on tumor immunology and cachexia. Josh mentioned his conversations with Peter Sorger, among the leaders of the Ludwig Tumor Atlas project (see page 23) and his interest in adding metabolic information to the project's high dimensional imaging of the tumor microenvironment.

The webinar closed with Chi assuring researchers that the Ludwig Institute is ready and sufficiently resourced to "catalyze" what he called "cogent" collaborations. The webinar remains available for viewing on the Ludwig Cancer Research website.

TREG REVIVAL

Ludwig MSK's Alexander Rudensky and his team discovered in 2003 that the regulator of gene expression FOXP3 controls the induction and maintains the identity of regulatory T cells (Tregs). Tregs generally tamp down immune responses once an infection has been dealt with and are actively recruited by tumors to suppress anticancer immune responses. Genetic disabling of FoxP3 leads to fatal autoimmunity in mice, characterized by every known type of inflammatory response, all stemming from the loss of Tregs. But it has long been unclear whether Tregs can persist and effectively exert their function in a disease state, in which their activity is compromised or their target immune cells have become impervious to their influence. In a study published in the August issue of *Nature Immunology*, Alexander and postdoc Wei Hu showed that Tregs can indeed persist and function in diseased states. They engineered Foxp3-deficient mice capable of restoration of FoxP3 expression and Treg function on demand and showed that the aberrant immune activation and severe autoimmune disease could be efficiently and durably reversed by Treg cells and that a single pool of Tregs can provide long-term protection against inflammation and autoimmunity.

Alexander Rudensky
Ludwig MSK

Wei Hu
Ludwig MSK

NEW FRONTIER

Tumors are an ecosystem of cancer cells cooperating with noncancerous cells, including those of the immune system, vasculature and connective tissue—all of which play important roles in the growth and dissemination of malignancies. Cancer researchers, including many across the Ludwig community, have been probing these dependencies to find vulnerabilities to target for cancer therapy and biomarkers to guide diagnosis, prognosis and treatment. The Ludwig Tumor Atlas is one such effort. Based at the Ludwig Center at Harvard, the project includes researchers at nine Ludwig-affiliated laboratories in the U.S. and Switzerland. Its member labs are applying high-dimensional imaging methods developed by Ludwig Harvard researchers in combination with single-cell genomics and molecular profiling technologies to determine precisely how tumor and immune cells interact, and how those interactions determine responsiveness to the latest generation of immunotherapies. Projects underway at Ludwig Harvard, Lausanne, MIT and Chicago are exploring the microenvironmental factors that drive drug resistance and examining the immune landscape and its influence on immunotherapies for melanoma and pancreatic, ovarian and prostate cancers. You can learn more about the project and opportunities to join the collaborative effort on the recently launched Ludwig Tumor Atlas website.

What is your most important scientific goal for the next year?

As a junior investigator, my primary scientific goal for this year is to characterize the metabolic phenotype of autophagy deficiency. This involves collaborating with various labs at Rutgers Cancer Institute and Princeton University. Additionally, I plan to submit my first manuscript as a PhD candidate.

MARIA IBRAHIM
Ludwig Princeton

What's your biggest challenge in attaining that goal?

My biggest challenge in attaining this goal is twofold. The first is expanding my knowledge in various topics, specifically in the field of metabolism, which will help direct the project. Second, to sharpen my oral and written communication skills to prepare for presentations and publications.

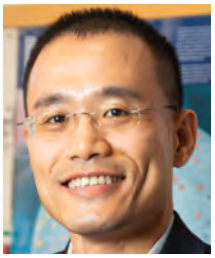
We will do a deep dive into the complexity of the immune microenvironment in human triple-negative breast cancer, trying to understand which features are associated with response to immunotherapy. We have a particular interest in pathways that render tumor cells resistant to T cell-mediated cytotoxicity, such as the integrin αvβ6 – TGFβ – SOX4 pathway we recently reported. Our working hypothesis is that resistance is shaped by gradients of cytokine signaling in the tissue, and we aim to discover pathways that enable switching between tumor-promoting and immuno-stimulatory pathways.

KAI W.
WUCHERPFENNIG
Ludwig Harvard

The multiple layers of complexity are clearly the biggest challenge, but complexity also makes this interesting and fun. We try to peel the layers by asking concrete questions, for example focused on specific cytokine pathways.

Ask a scientist

We would like to systemically define the bone metastatic niche at single cell resolution and analyze the impact of diet and other external factors on the composition and properties of metastatic niches.



YIBIN KANG
Ludwig Princeton

We are in the process of developing appropriate diet models in collaboration with Josh Rabinowitz and Eileen White groups at the Princeton Branch, and integrating single cell data analysis workflow in collaboration with computational biology groups at Princeton. Meanwhile, we are also improving the methods to label the niche cell populations in different proximity to metastatic tumor nodules.

Therapy-resistant carcinoma cells often display heightened vulnerability to inducers of ferroptosis—an iron-dependent form of cell death driven by oxidative modifications of membrane phospholipids. I plan to investigate whether treatment of metastatic breast cancers with various ferroptosis-inducing drugs in combination with immune checkpoint inhibitors yields long lasting, anti-tumor responses.

WHITNEY HENRY
Ludwig MIT

The identification of tumor-targeting, small molecule inhibitors that can induce ferroptosis *in vivo* has been an ongoing challenge in the field. So far many of the available GPX4 inhibitors (which are potent ferroptosis inducers) suffer from poor bioavailability and are unsuitable for *in vivo* application.

This year, I will be expanding my research group in new scientific directions, pushing the boundaries to develop novel epigenetic technologies for deepening our understanding of cancer biology and for cancer detection and monitoring in the clinic.

CHUNXIAO SONG
Ludwig Oxford

The biggest challenge—but also excitement—in attaining that goal is to invent new chemical biology methods that could overcome the innovation bottleneck and push the field forward.

Ask a scientist

T cell leukemia and T cell lymphomas, collectively called T cell cancers, affect ~100,000 patients each year. A significant percentage of these patients die from the disease. My goal is to develop a new therapy against T cell cancers to provide the patients with additional treatment options.

SUMAN PAUL
Ludwig Johns Hopkins

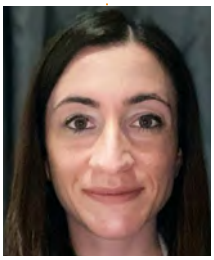
The challenge is to make the therapy kill the T cell cancers while sparing the healthy T cells, as the healthy T cells are required for our immune system. Therefore, we are designing the therapy to recognize genetic variations present only in T cell cancers and not in healthy T cells.

My main scientific goal for 2022 is to identify a targetable sensitivity in endocrine therapy-resistant, estrogen receptor-positive breast cancer. I also hope to publish a manuscript of my findings and finish up my PhD training by the end of this year.

ROSEMARY HUGGINS
Ludwig Chicago

The biggest challenge to achieving this goal will be roadblocks in experiments, such as the need to adjust methods and optimize protocols. I expect some experiments may be delayed (or alternative options will need to be found) due to continued supply chain issues and lab material shortages.

Cancer initiation and development is related to a gradual accumulation of driver gene mutations conferring a survival and proliferation advantage. My goal this year is to begin to identify specific mutations called "mutational signatures" that may be used as a novel biomarker for tumor diagnosis and treatment guidance.



ANTONELLA D'AMORE
Ludwig Oxford

Only a minimal fraction of all mutations in the genome can be considered cancer drivers. Thus, the biggest challenge will be to identify and discern these events. To achieve this, I am lucky to benefit from a strong network of clinicians, bioinformaticians and wet lab scientists in the Ludwig community.

Ask a scientist

The application of adoptive T cell transfer to solid tumors has been limited by a lack of specific and targetable antigens. My goal is to develop new T cell therapies targeting driver gene mutations that are presented as mutant peptides in HLA molecules on the surface of cancer cells.

BRIAN MOG
Ludwig Johns Hopkins

Targeting driver gene mutations is challenging because there are very few mutant peptide-HLA molecules on the surface of each cancer cell. This low antigen density limits the therapeutic effects of T cells. We are designing strategies to maximize T cell activation against the low levels of mutation-derived antigens on cancer cells.

Over 24 years ago, we rescued women with metastatic breast cancer receiving high dose chemo with purified (and therefore cancer-free) hematopoietic stem cells (HSC), extending median survival time from 26 to 120 months, and curing 33%. We now intend to run a larger clinical trial of this treatment protocol. In addition, after the existing HSCs have been eliminated with chemotherapy and upon HSC engraftment, we will test if the remaining chemoresistant macrophages support treatment then with anti-CD47 antibody combinations, e.g. with Herceptin for Her2+ cases, to eliminate the relatively small number of breast cancer cells that might remain. Hopefully other Ludwig investigators will think of what therapies they have, e.g. CAR T or TILs, that do not add to the chemotoxicity but will likely do better with a much reduced tumor burden.

IRV WEISSMAN
Ludwig Stanford

The greatest challenge is that we need clinicians to conduct the trial, but most oncologists don't distinguish between rescue with cancer-free HSC and cancer-contaminated mobilized blood.

Required reading

Click on the title to read an abstract of the study

Ludwig Harvard

Proceedings of the National Academy of Sciences
2021 November 9

Dendritic cell paucity in mismatch repair-proficient colorectal cancer liver metastases limits immune checkpoint blockade efficacy.

Ho WW, Gomes-Santos IL, Aoki S, Datta M, Kawaguchi K, Talele NP, Roberge S, Ren J, Liu H, Chen IX, Andersson P, Chatterjee S, Kumar AS, Amoozgar Z, Zhang Q, Huang P, Ng MR, Chauhan VP, Xu L, Duda DG, Clark JW, Pittet MJ, Fukumura D, Jain RK.

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September 16 Epub

The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation.

Martin TD, Patel RS, Cook DR, Choi MY, Patil A, Liang AC, Li MZ, Haigis KM, Elledge SJ.

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July 12 Epub

Genome-scale screens identify factors regulating tumor cell responses to natural killer cells.

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Ludwig Johns Hopkins

PLoS Medicine
2021 May 3 eCollection

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Tie J, Wang Y, Cohen J, Li L, Hong W, Christie M, Wong HL, Kosmider S, Wong R, Thomson B, Choi J, Fox A, Field K, Burge M, Shannon J, Kotasek D, Tebbutt NC, Karapetis C, Underhill C, Haydon A, Schaeffer J, Ptak J, Tomasetti C, Papadopoulos N, Kinzler KW, Vogelstein B, Gibbs P.

Ludwig Lausanne

Nature Biotechnology
2021 November 15
Online ahead of print

Sensitive identification of neoantigens and cognate TCRs in human solid tumors.

Arnaud M, Chiffelle J, Genolet R, Navarro Rodrigo B, Perez MAS, Huber F, Magnin M, Nguyen-Ngoc T, Guillaume P, Baumgaertner P, Chong C, Stevenson BJ, Gfeller D, Irving M, Speiser DE, Schmidt J, Zoete V, Kandalaft LE, Bassani-Sternberg M, Bobisse S, Coukos G, Harari A.

Cancer Cell
2021 November 4 Epub

Myeloid antigen-presenting cell niches sustain antitumor T cells and license PD-1 blockade via CD28 costimulation.

Duraiswamy J, Turrini R, Minasyan A, Barras D, Crespo I, Grimm AJ, Casado J, Genolet R, Benedetti F, Wicky A, Ioannidou K, Castro W, Neal C, Moriot A, Renaud-Tissot S, Anstett V, Fahr N, Tanyi JL, Eiva MA, Jacobson CA, Montone KT, Westergaard MCW, Svane IM, Kandalaft LE, Delorenzi M, Sorger PK, Färkkilä A, Michielin O, Zoete V, Carmona SJ, Foukas PG, Powell DJ Jr, Rusakiewicz S, Doucey MA, Dangaj Laniti D, Coukos G.

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2021 October 22 Epub

Tumor-induced reshuffling of lipid composition on the endoplasmic reticulum membrane sustains macrophage survival and pro-tumorigenic activity.

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Nature Cancer
2021 October 18

Compensatory CSF2-driven macrophage activation promotes adaptive resistance to CSF1R inhibition in breast-to-brain metastasis.

Klemm F, Möckl A, Salamero-Boix A, Alekseeva T, Schäffer A, Schulz A, Niesel K, Maas RR, Groth M, Elie BT, Bowman RL, Hegi ME, Daniel RT, Zeiner PS, Zinke J, Harter PN, Plate KH, Joyce JA, Sevenich L.

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2021 September 3
Online ahead of print

Low Dose Radiotherapy Reverses Tumor Immune Desertification and Resistance to Immunotherapy.

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2021 August

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Lanitis E, Kosti P, Ronet C, Cribioli E, Rota G, Spill A, Reichenbach P, Zoete V, Dangaj Laniti D, Coukos G, Irving M.J

Required reading

Click on the title to read an abstract of the study

Cell Reports
2021 July 20

Cell-autonomous inflammation of BRCA1-deficient ovarian cancers drives both tumor-intrinsic immunoreactivity and immune resistance via STING.

Bruand M, Barras D, Mina M, Ghisoni E, Morotti M, Lanitis E, Fahr N, Desbuisson M, Grimm A, Zhang H, Chong C, Dagher J, Chee S, Tsianou T, Dorier J, Stevenson BJ, Iseli C, Ronet C, Bobisse S, Genolet R, Walton J, Bassani-Sternberg M, Kandalaft LE, Ren B, McNeish I, Swisher E, Harari A, Delorenzi M, Ciriello G, Irving M, Rusakiewicz S, Foukas PG, Martinon F, Dangaj Laniti D, Coukos G.

Ludwig MIT

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2021 October 20 Epub

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Nature Communications
2021 September 28

Measuring kinetics and metastatic propensity of CTCs by blood exchange between mice.

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2021 September 16

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Burger ML, Cruz AM, Crossland GE, Gaglia G, Ritch CC, Blatt SE, Bhutkar A, Canner D, Kienka T, Tavana SZ, Barandiaran AL, Garmilla A, Schenkel JM, Hillman M, de Los Rios Kobara I, Li A, Jaeger AM, Hwang WL, Westcott PMK, Manos MP, Holovatska MM, Hodi FS, Regev A, Santagata S, Jacks T.

Nature Materials
2021 July 15 Epub

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Ludwig MSK

Nature Immunology
2021 August 23 Epub

Regulatory T cells function in established systemic inflammation and reverse fatal autoimmunity.

Hu W, Wang ZM, Feng Y, Schizas M, Hoyos BE, van der Veeken J, Verter JG, Bou-Puerto R, Rudensky AY.

Ludwig Oxford

Cell Reports 2021
November 9

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Required reading

Click on the title to read an abstract of the study

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