LUDWIG LINK

APRIL 2021

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LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

ON THE COVER

As a lighter take on scientific illustration, this artwork was created to depict Ludwig Harvard Co-director Joan Brugge's study demonstrating that NRF2 hyperactivation, in cooperation with GPX4, maintains the survival of inner matrix-deprived cells within 3-dimensional tumor spheroids by mitigating ferroptosis, the lipid peroxidation-induced non-apoptotic cell death.

The illustration, by Rachel Davidowitz, depicts the fate of inner spheroid cells in the presence or absence of NRF2 hyperactivation. Inner spheroid cells (represented as wooden houses) are vulnerable to lipid peroxidation (fire), compared to outer cells (brick houses). NRF2 hyperactivation (firefighter with water hose) and GPX4 (firefighter with bucket of water) neutralize lipid peroxidation, resulting in the formation of filled spheroid structures. You can read about the study on Page 16.

LUDWIG LINK

ludwigcancerresearch.org APRIL 2021

LETTER

Welcome to the spring issue of Ludwig Link!

This season is said to be all about new beginnings, so it's fitting that Ludwig just launched a new Branch at Princeton University dedicated to the study of cancer metabolism. You can read all about it in here. Ludwig scientists at all the other locations have, meanwhile, given us much else to cover. You'll read about how targeting certain gut bacteria might boost the efficacy of radiotherapy, how a common nutritional supplement could restore the activity of exhausted anti-cancer T cells in tumors—and much, much more.

You'll also see in here a brief report on an engaging virtual Cancer Prevention and Physical Activity Conference Ludwig convened in February in partnership with Cancer Research UK and with support from the Conrad N. Hilton Foundation. The conference was one of several events planned this year to celebrate Ludwig's 50th anniversary.

On a sadder note, we share the loss of four friends of Ludwig—former Ludwig Institute Board members Sir Derek Roberts and Pierre Languetin, Ludwig MIT investigator Angelika Amon and former Scientific Advisor José Baselga.

The interview in this issue is with Ludwig Lausanne's Lana Kandalaft. And we asked Ludwig scientists to tell us how the pandemic changed their perspective on balancing work and personal life. See some select responses in our "Ask a scientist" section.

Happy reading!

Rachel Reinhardt
Senior Vice President for Communications

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A 50th ANNIVERSARY SPLASH

Ludwig Cancer Research announced on its 50th anniversary the newest Branch of the Ludwig Institute for Cancer Research. Based at Princeton University, the Ludwig Princeton Branch will be wholly dedicated to the study of cancer metabolism and the clinical translation of its findings, which will be conducted in partnership with RWJBarnabas Health and Rutgers Cancer Institute of New Jersey and other institutions.

"A more sophisticated understanding of cancer metabolism holds considerable promise for the optimization of cancer prevention and therapy, yet few organizations have assembled a critical mass of experts dedicated exclusively to this promising frontier of research," said Chi Van Dang, scientific director of the Ludwig Institute for Cancer Research. "The Ludwig Princeton Branch will fill that gap."

Ludwig Princeton is directed by Princeton University's Joshua Rabinowitz, and two other scientists have been named founding Members of the Branch: Associate Director Eileen White, of Rutgers University and Yibin Kang, also of Princeton University.

"This new partnership goes to the heart of what Princeton is all about. It draws on Princeton's breadth of excellence in fundamental research to drive real-world breakthroughs at the cutting edge of cancer care," said Princeton University Provost Deborah Prentice.

Altered metabolism is a salient feature of cancer biology, as cancer cells must rewire their metabolic circuitry to sustain their proliferation. Such adaptations not only drive tumor growth, but cripple the anti-tumor immune response and compromise cancer immunotherapy as well. Metabolic dysfunction also causes the wasting disorder known as cachexia that contributes enormously to cancer-related mortality. Yet the metabolic rewiring comes at a cost to cancer cells: it creates biochemical vulnerabilities that can be exploited for cancer prevention and therapy.

The Ludwig Princeton Branch will focus on three main areas of cancer metabolism: metabolic interactions between the tumor and the rest of the body, including how the body supports tumor growth and metastasis, and how tumors induce cachexia; dietary strategies for the prevention and treatment of cancer; and the interplay of host metabolism, the gut microbiome and the anti-cancer immune response.

"Every one of us chooses, day-by-day, what to eat," said Ludwig Princeton Branch Director Josh Rabinowitz. "These choices don't just impact metabolic health, but also immunity and cancer risk. We want to understand the underlying biochemical mechanisms and apply this knowledge to find new ways to prevent and treat cancer."

The Ludwig Princeton team:


Kim Sokoloff

Joshua Rabinowitz


John O'Boyle

Eileen White


Kim Sokoloff

Yibin Kang

FOR ENDURING CONTRIBUTIONS

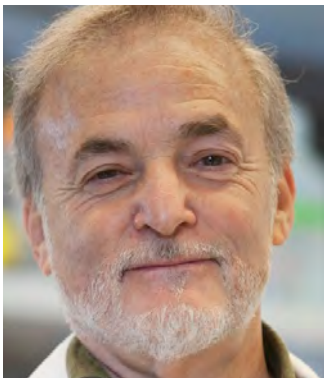
In November, Ludwig Lausanne received a Team Science Award from the Society for Immunotherapy of Cancer for landmark research in basic and tumor immunology. The award recognizes research teams around the world that have made lasting contributions to the field of cancer immunotherapy. Established in 1973 under the leadership of the immunologist Jean-Charles Cerottini, the Lausanne Branch initially led pioneering studies on the development and functional diversification of the immune system's T cells, the underlying mechanisms and dynamics of their responses and their recruitment for cancer immunotherapy. The Branch today, directed by George Coukos, continues that tradition. It has conducted groundbreaking research on individualized immunotherapies—such as dendritic cell vaccines and the engineering and reinfusion of T cells for cancer therapy. Ludwig Lausanne scientists have made significant discoveries on the immune microenvironment of brain and ovarian tumors, the identification of potent patient-specific neoantigens for use in novel immunotherapies and the mechanisms by which cancer metabolism thwarts the immune response. Several Ludwig researchers and alumni were also recognized as members of other teams that received Team Science Awards, including one led by former Ludwig CEO and Scientific Director Lloyd Old.

George Coukos

Ludwig Lausanne

FOR EPIGENETIC RESEARCH

Stephen Baylin, the Virginia and D.K. Ludwig Professor at Johns Hopkins School of Medicine, has been elected Fellow of the American Association for the Advancement of Science. He was recognized for his work on the influence of epigenetic modifications—chemical "marks" made on DNA and its protein scaffolding—on gene expression and cancer progression. More than 30 years ago, Stephen co-discovered cancer-specific changes in the distribution of DNA methylation that aberrantly silence genes in cancer cells. He has since remained at the forefront of the field and has led the development of biomarkers for cancer diagnostics and novel strategies that target epigenetic mechanisms for the treatment of cancer. Stephen recently joined Ludwig Oxford as a visiting professor of cancer epigenetics, where he will advise the Branch on its research in cancer epigenetics and help guide its collaborations in that area. He has also been elected to the American Association of Physicians and is a member of the National Academy of Sciences and co-leader of a Stand Up To Cancer Dream Team for epigenetic therapy.



Stephen Baylin

Ludwig Johns Hopkins

In memoriam

JOSÉ BASELGA

Former Scientific Advisor José Baselga, who helped guide the Ludwig Institute's scientific strategy and staffing for ten years before leaving the Scientific Advisory Committee in 2016, died March 22nd from Creutzfeldt-Jakob disease, a rare, degenerative brain disorder. He was 61. At the time of his death, José was executive vice president of oncology research and development for AstraZeneca. José was renowned for his work in developing and testing targeted cancer treatments, particularly against breast cancer. He was also known for his contributions to our understanding of how dysregulation of the PI3K signaling pathway drives the genesis of cancers, and the translation of that understanding into cancer therapies. He was a Fellow of the American Association for Cancer Research and a former President of the organization. He is survived by his wife Silvia and his four children.

Photo courtesy the Roberts family

SIR DEREK ROBERTS

Former Ludwig Institute Board Member Sir Derek Roberts passed away on February 17th, one month shy of his 89th birthday, due to complications from COVID-19. He served on the Board for nearly 14 years before stepping down in 2012. An engineer who was twice provost of University College London, Sir Derek oversaw several successful projects and the university's expansion during his tenure, including its merger with the Institute of Child Health. He was an early pioneer of silicon-based integrated circuit technology, now ubiquitous in electronic devices from PCs to satellites. His professional life was spent primarily in industrial scientific research, first at Plessy—one of Britain's largest electronics manufacturers—developing complex integrated circuits, and subsequently, heading up General Electric's research activities. Elected a Fellow of the Royal Society and of the Royal Academy of Engineering in 1980, he was awarded a Commander of the British Empire in 1988 and knighted in 1995 for services to engineering and education. The following year, he was elected president of the British Science Association. Read an interview with Sir Derek in the November 2012 issue of Ludwig Link.

In memoriam

ANGELIKA AMON

Ludwig MIT investigator Angelika Amon passed away in October from ovarian cancer. A prolific scientist, Angelika pioneered research on the underlying mechanisms and consequences of chromosomal abnormalities, such as aneuploidy, on fundamental processes of cellular life and demonstrated how those dysfunctions contribute to developmental disorders and cancer. Other studies in her laboratory yielded insights into the relationship between stem cell size, function and tissue aging. Angelika described what she loved most about science in 2019, when accepting the Breakthrough Prize in Life Science. "Making a discovery is the best feeling in the world," she said. "It's like Christmas when you were five. The beauty of experimental science is that these eureka moments are often shared with other scientists, and I'm privileged to have experienced this." Angelika was a member of the National Academy of Sciences, the American Academy of Arts and Sciences and the European Molecular Biology Organization. She was also a professor of Biology at MIT, Member of the Koch Institute for Integrative Cancer Research, and was recently named Co-director of the Alana Down Syndrome Center at MIT. Click here for a short video of Angelika speaking about her work.

PIERRE LANGUETIN

Pierre Languetin, a former Ludwig Board Member, passed away in October. A Swiss diplomat and central banker, he joined the Board of Directors of the Ludwig Institute for Cancer Research in 1987 and served with distinction for two decades. Pierre was born on April 30, 1923, in Lausanne and was educated at the University of Lausanne and the London School of Economics. A former trade negotiator, he often represented Switzerland at the Organization for Economic Cooperation and Development and the European Free Trade Organization. In 1976, he began a decade-long stretch as a member of the governing Board of the Swiss National Bank, and was named chairman of its Executive Board in 1985. In addition to his service to the Ludwig Institute, Pierre also served on the boards of numerous organizations, including Sandoz, Paribas Suisse and the Swiss Reinsurance Company.

VIRTUAL CONFERENCE: EXERCISE AND CANCER PREVENTION

When Ludwig Cancer Research and the Conrad N. Hilton Foundation launched a $10 million Cancer Prevention Initiative in 2015, among their stated goals was the promotion of cancer prevention in the scientific and medical community, and support for its incorporation into public policy. A Cancer Prevention and Nutrition Conference, convened in London in partnership with Cancer Research UK in 2018, along with a publication that emerged from the meeting, was a first step in that direction. The second was taken from February 23rd to 25th, 2021, in an international, virtual Cancer Prevention – Physical Activity Conference organized by the same partnership.

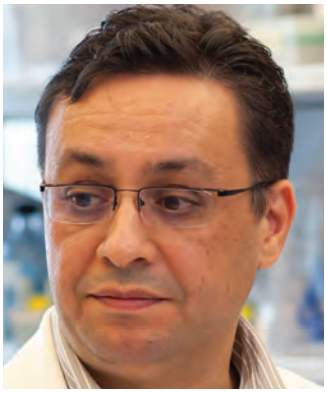
After opening remarks by Scientific Director Chi Van Dang and Ludwig Oxford's Peter Ratcliffe, speakers covered the existing epidemiology on physical exercise and cancer, followed by a session on the molecular and physiological mechanisms that might drive such effects. In the latter session, Ludwig Harvard investigator Rakesh Jain discussed his lab's discovery that exercise normalizes the vasculature of the tumor, improves anti-cancer immune responses and reduces metastasis in mouse models. Memorial Sloan Kettering's Lee Jones, meanwhile, presented his preclinical studies on the significant benefit of exercise on slowing progression of certain types of breast cancer.

The second day covered clinical studies of physical exercise in cancer outcomes and those of interventions that seek to instill healthier behaviors. One speaker, Robert Newton of Edith Cowan University, presented an ongoing study showing that changes in immune factors induced by exercise might slow growth of prostate cancer cells even when men are resting.

Others discussed technical issues in clinical studies of exercise and cancer. Kirsten Rennie of the University of Cambridge, for example, stressed the importance of measuring physical activity independently in free living, pointing to huge differences between self-reports and objective measures of exercise among prostate cancer survivors. On the matter of behavioral interventions, Wendy Wood of the University of Southern California argued that activities reinforced by rewards—even just "fun"—are more likely to establish healthful habits, and discussed why habit, more than rationale, might sustain healthful behaviors.

On the final day, a fascinating session covered the role of the built environment in medical outcomes, with speakers pointing out how little health considerations factor into urban planning decisions. In one particularly engaging talk, Rich Mitchell of the University of Glasgow discussed his studies examining how poverty and the built environment interact with such things as childhood activities and transportation to expose kids to certain foods, tobacco and other factors with lasting consequences for health.

In a concluding Big Ideas session of the conference, Chi noted the pressing need to figure out the mechanistic basis of exercise effects on the pathophysiology of cancer. He raised the intriguing possibility that a mechanistic understanding could also lead to pharmacological interventions with matching effects for patients who can't exercise due to their condition. A poll conducted during this session suggested most attendees agreed that mechanistic studies are the order of the day. This should help guide the research agenda of the field.



Taha Merghoub
Ludwig MSK

Sadna Budhu
Ludwig MSK

Jedd Wolchok
Ludwig MSK

IMMUNE REVIVAL

Phosphatidylserine (PS) is a small molecule mainly found at high levels on the outer membrane of dying cells, from where it is known to promote an immunosuppressive microenvironment in tumors through its interaction with its receptors. A study led by Ludwig MSK researchers Taha Merghoub, Sadna Budhu and Jedd Wolchok published in *Cell Reports* in January found expression of PS on live tumor-infiltrating immune cells rises after a single dose of radiation delivered to melanoma tumors in mice. The researchers found that PS-blockade with the antibody mch1N11 enhanced the effects of radiotherapy and extended survival of the mice. The effect was accompanied by an increase in the proportion of pro-inflammatory macrophages and an increase in the recruitment and activation of T cells in tumors. Adding anti-PD-1 checkpoint blockade immunotherapy to the mix further enhanced T cell activation, responses to radiotherapy and survival of the mice. The researchers also showed that immune cells in the blood of melanoma patients who have received radiotherapy similarly express higher levels of PS. These findings suggest that patients could benefit from the concurrent blockade of PS and PD-1 in combination with radiotherapy.

GUT REACTION

In a study published in the *Journal of Experimental Medicine* in January, Ludwig Chicago Co-director Ralph Weichselbaum and Yang-Xin Fu of the University of Texas Southwestern Medical Center showed how certain gut bacteria can reduce the efficacy of radiotherapy. They identified two families of bugs—*Lachnospiraceae* and *Ruminococcaceae*—that interfere with radiotherapy in mice and described how the short-chain fatty acid butyrate, a metabolic byproduct of these bacteria, undermines the therapy. The antibiotic vancomycin decreased the abundance of butyrate-producing gut bacteria and enhanced antitumor responses following radiotherapy in mice. Previous studies led by Ralph and Yang-Xin have shown that radiation activates a signaling pathway in dendritic cells that primes other immune cells—killer T cells—to attack tumors. This pathway, controlled by a protein named STING, ramps up the dendritic cells' production of immune-stimulating factors known as type-1 interferons (IFN-I), which boost T cell activation. In this study, they show that butyrate inhibits a step of the biochemical signaling cascade that links STING activation to the production of IFN-I. The researchers suggest that the highly selective targeting of butyrate-producing gut microbiota may augment the radiotherapy sensitivity of tumors and improve patient responses.

Ralph Weichselbaum
Ludwig Chicago

TAPS AND MORE

Chemical, or epigenetic, modifications made to the DNA base cytosine play an important role in the regulation of gene expression across the genome. The base is chemically modified with four chemically and functionally distinct "marks", with 5-methylcytosine (5mC) being the most common and most frequently disordered in cancer. The others are 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5-fC) and 5-carboxycytosine (5caC). The Ludwig Oxford laboratory of Chunxiao Song reported in 2019 a sensitive, cost-effective and efficient method for the whole-genome sequencing of 5mC named TET-assisted pyridine borane sequencing (TAPS). Now the gold standard of such technologies, TAPS was at the heart of a biotech spin-off that was bought late last year by Exact Sciences, which will use the method in novel cancer diagnostics. In January, researchers led by Chunxiao and his University of Oxford colleague Ahmed Ahmed reported in *Nature Communications* an expanded toolkit for the direct and quantitative sequencing of all four cytosine epigenetic marks—a new version of TAPS for 5mC (named TAPSβ) and brand new methods for the other three.

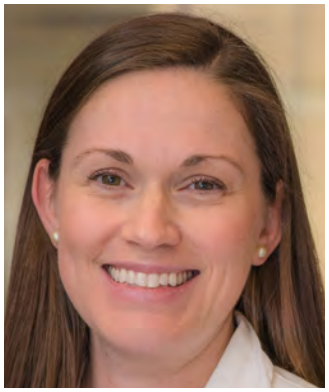
Chunxiao Song
Ludwig Oxford

STOP SIGNAL

During cell division, protein cables called microtubules latch on to a copy of every chromosome at a structure called the kinetochore and pull one of each to opposite poles of the dividing cell. In healthy cells, this choreographed segregation of chromosomes is monitored by a "spindle checkpoint" that halts cell division if even one kinetochore is not firmly attached to a microtubule, ensuring that chromosomes are equally distributed to each daughter cell. In a January paper in *Science*, Ludwig San Diego's Arshad Desai, Pablo Lara-Gonzalez and colleagues detailed the mechanism by which the checkpoint is generated by the association of two proteins, Cdc20 and Mad2. Using a visual probe that tracks one of the proteins, the team detailed how Cdc20 and Mad2 are geometrically constrained at the kinetochore, held in a particular position by phosphorylation events that prime their interaction, and how their enzymatic substrates are locally delivered to them to generate the wait signal. The findings help explain why that signal is generated at kinetochores and not elsewhere in the cell, thereby ensuring that no chromosome is left behind.

Arshad Desai
Ludwig San Diego

Pablo Lara-Gonzalez
Ludwig San Diego



Jennifer Guerriero
Ludwig Harvard

TARGET: TNBC

Triple negative breast cancers (TNBC) bearing mutations to their BRCA genes can be treated with a class of drugs known as PARP inhibitors, but the benefits of this therapy are often fleeting. Since PARP inhibitors can also help stimulate anti-tumor immune responses, researchers are already examining their combination with immunotherapy to improve outcomes. In a December paper in *Nature Cancer*, a team led by Ludwig Harvard investigator Jennifer Guerriero exposed a potential challenge to such strategies—and offered a possible solution. PARP inhibitors, the researchers showed, can also promote an immune-suppressive tumor microenvironment (TME), pushing immune cells known as macrophages in the TME into an immunosuppressive state through the reprogramming of their lipid metabolism. These immunosuppressive macrophages express high levels of the CSF-1 receptor, which is essential to their survival. Jennifer and her colleagues demonstrated that treating mice bearing BRCA-deficient TNBC tumors with a combination of PARP inhibitors and CSF-1R blocking antibodies extended survival of the animals. The effect was mediated primarily by activation of cancer-targeting killer T cells in the less immunosuppressive TME. The authors suggest that combining PARP inhibition with CSF-1R inhibition could be a promising therapeutic strategy for BRCA-deficient TNBCs.

THE IMMUNOLOGIC X-FACTOR

The liver X receptor β (LXRβ) is a nuclear receptor that plays a key role in the regulation of lipid and cholesterol metabolism and inflammatory immune responses. Yet its precise role in T cell biology has thus far been unclear. In a December Brief Definitive Report in the *Journal of Experimental Medicine*, a team led by Ludwig MSK's Alexander Rudensky and Clarissa Campbell revealed that the loss of LXRβ in a mouse model leads to a severe deficiency of T cells accompanied by the spontaneous activation of effector T cells. Studies of chimeric mice with mixed populations of LXRβ-deficient T cells and normal T cells showed that the receptor is needed for T cell fitness, and that its loss especially compromises regulatory T cells (Tregs), which suppress effector T cells and protect tumors from anti-cancer immune responses. LXRβ deficiency, Alexander and his colleagues show, profoundly compromises Treg function. Indeed, the loss of just one copy of the LXRβ gene in Tregs suffices to induce early and fatal autoimmune disease in mice. The researchers argue these findings suggest the receptor could be a prime target for immunological therapies.

Alexander Rudensky
Ludwig MSK

Clarissa Campbell
Ludwig MSK

FUEL GAUGE

Sick animals often lose their appetites. Though this behavior is widely observed across species, its consequences on the effector T cells battling infection was not clear. In a December paper in the *Proceedings of the National Academy of Sciences*, Ludwig MSK Director Alexander Rudensky and colleagues showed that starvation during infection decreases the number of effector T cells in mice through mechanisms governed by the cells' Farnesoid X Receptor (FXR), a nuclear receptor also involved in liver responses to fasting and refeeding. That loss of effector T cells, they showed, could be reversed by the provision of the sugar glucose, supporting the sugar's availability as a determinant of effector T cell survival. Deletion of FXR in T cells prevented their loss during starvation, altered their utilization of fuel from glucose to other nutrients and improved their fitness. It also caused weight loss in the mice. The study, supported by the Ludwig-Hilton Cancer Prevention Initiative, identified a mechanism by which the host scales immune responses in reaction to nutrient availability, and showed that FXR is the sensor in T cells that triggers those responses.

AN ESSENTIAL INEFFICIENCY

Cancer cells burn sugar using an inefficient metabolic pathway known as fermentation, which captures much less energy as ATP and which most healthy cells—except rapidly proliferating ones, like activated T cells of the immune system—use mainly when starved of oxygen. A study led by Ludwig MIT's Matthew Vander Heiden and published in December in *Molecular Cell* examined why this is the case. Matthew and his colleagues show that fermentation, or aerobic glycolysis, helps cells regenerate large quantities of NAD+, a chemical essential to the synthesis of some large molecules like DNA that all cells need to divide. Inhibiting fermentation and forcing cancer cells to make ATP, the currency of cellular energy, through aerobic respiration slowed their growth. When those cells were then additionally treated with a drug that stimulates NAD+ regeneration, however, their proliferative frenzy was restored. Cancer cells, it appears, need NAD+ more than they do ATP. When ATP abounds, aerobic respiration slows down, and so does mitochondrial NAD+ regeneration. Cancer cells and activated T cells, the researchers demonstrate, maintain high levels of NAD+ by employing the less efficient generator of ATP: fermentation. The findings suggest drugs that force cancer cells into aerobic respiration or inhibit NAD+ production could be useful as cancer therapies.

Matthew Vander Heiden
Ludwig MIT

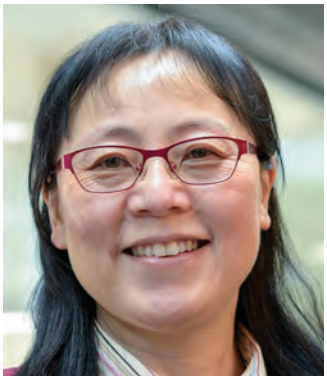
Don Cleveland
Ludwig San Diego

SHATTERED SOURCES

Circles of DNA unassociated with chromosomes, extrachromosomal DNAs (ecDNA) encode multiple copies of cancer genes and drive tumor evolution, growth and drug resistance. Identifying where ecDNA comes from has been an important challenge of cancer research. In December, a team led by Ludwig San Diego's Don Cleveland and Peter Campbell of the Sanger Center reported in *Nature* that ecDNAs are formed by chromothripsis—or the shattering and shuffled reassembly of chromosomes. While earlier work led by Don and Peter had established that chromothripsis of missegregated chromosomes can produce the complex genome rearrangements found in many tumors, the researchers now report that chromothripsis drives the evolution of gene amplification in cancer through production of ecDNA, including the induction of drug resistance through the generation of ecDNAs carrying a gene that inactivates an anticancer drug. They showed that once formed, ecDNA undergoes successive rounds of chromothripsis to spawn additional rearranged ecDNAs that drive increased drug resistance by further amplification of genes responsible for the resistance. The study lays the groundwork for combination therapy in which a chemotherapeutic drug is paired with another drug that prevents the DNA fragments created by chromosomal shattering from closing to form ecDNA circles.

STRUCTURAL SOLUTION

The poison arsenic is a well-worn device of crime novels. But in low doses it can also be a useful treatment for acute promyelocytic leukemia. Building on the latter theme, a study led by Ludwig Oxford Director Xin Lu and Min Lu of the Shanghai Institute of Hematology performed a screen for drugs that could reactivate mutant forms of the p53 tumor suppressor and found that arsenic compounds—including arsenic trioxide—rescued some structural defects in p53. Although p53, called the "guardian of the genome," is the most frequently mutated gene in human cancer, efforts to devise drugs that reactivate the mutated protein have generally come up short. This is due to the large variety of p53 mutations, their diverse effects and a lack of sites on the p53 protein that can be easily targeted by drugs. However, over half of all p53 mutations cause structural alterations that affect p53 activity. These mutants were the focus of the study reported in *Cancer Cell* in December. For some of the structural mutations, arsenic trioxide was also able to reactivate the tumor suppressor function of p53 in experimental models. It is now being tested in a phase I clinical trial in patients with p53-mutated blood cancers.



Xin Lu
Ludwig Oxford

LIQUID CRYSTAL DYSFUNCTIONS

Loss of function of the RNA-binding protein TDP-43 is seen in neurodegenerative diseases, such as ALS, Huntington's disease and Alzheimer's disease. A study led by Ludwig San Diego's Don Cleveland reported online in *Science* in December that RNA-binding deficient TDP-43—which is produced by neurodegeneration-causing mutations or biochemical modifications to the protein—drives TDP-43 de-mixing into liquid spherical shells with liquid cores in the nuclei of neurons. Don and his colleagues named these structures anisosomes and identified the major components of the liquid core to be HSP70 family chaperones, whose activity, powered by the molecule ATP, maintains the liquidity of shells and cores. In animal studies, inhibiting the proteasome—which degrades proteins—within neurons to mimic the aging-related decline in its activity induced the formation of TDP-43-containing spherical shells. The shells convert into aggregates when ATP levels drop. These findings suggest the TDP-43 aggregation seen in neurodegenerative diseases may have its origins in anisosomes. The study also explains the peripheral neuropathy caused by bortezomib, a proteasome inhibitor used to treat multiple myeloma. The researchers showed that anisosomes form in sensory neurons in bortezomib-treated mice and rats and are thus likely to form in multiple myeloma patients who develop peripheral neuropathy.

Don Cleveland
Ludwig San Diego

TIRED TIL RECHARGE

Ludwig Lausanne's Ping-Chih Ho and his colleagues reported in *Nature Immunology* in October a novel mechanism by which the harsh microenvironment of the tumor enervates tumor-infiltrating T lymphocytes (TILs). They also showed that a common nutritional supplement, nicotinamide riboside (NR), could revive the anti-tumor activity of the TILs. Starved of oxygen and essential nutrients in tumors, TILs adjust metabolic processes to compensate, in part by making more mitochondria (the energy generators of the cell). Meanwhile, prolonged and fruitless stimulation by cancer antigens pushes TILs into an exhausted state. Ping-Chih and his team found that exhausted TILs are packed with dysfunctional mitochondria, mainly because the TILs can't remove damaged ones. This, they showed, is a cause, not a consequence, of exhaustion. NR has been shown by Ludwig Lausanne researchers and others to improve mitochondrial fitness, so Ping-Chih and his colleagues examined whether it might rescue TILs from terminal exhaustion. Their cell culture experiments showed that NR improved the mitochondrial fitness and function of T cells in conditions resembling those of the tumor. More notably, dietary supplementation with NR stimulated the anti-tumor activity of TILs in mouse models of melanoma and colon cancer. When combined with checkpoint blockade immunotherapies, it also significantly inhibited the growth of tumors in the mice.

◀ **Ping-Chih Ho**
Ludwig Lausanne

Wenbin Lin ▶
Ludwig Chicago

PERSONAL NANOVACCINE

Ludwig Chicago investigator Wenbin Lin and his colleagues reported in *Science Advances* in October their design and preclinical evaluation of a combined nanotechnology-based radiotherapy strategy that effectively generates a personalized cancer vaccine within the body. It revolves around nanoparticles named nanoscale metal-organic frameworks (nMOFs) developed in Wenbin's lab that amplify the cell-killing free radicals generated by radiotherapy, boosting its effects. Wenbin's team adapted their nMOFs to carry an adjuvant, a substance that stimulates vaccine-induced immune responses. The adjuvant, known as a CpG oligonucleotide, drives the maturation of the immune system's dendritic cells, which activate and direct cytotoxic T cells toward cancer cells. In mouse models of pancreatic and colon tumors, which tend to harbor few viable cytotoxic T cells and so resist immunotherapy, irradiating tumors treated with the nMOFs caused a release of the CpG adjuvant and the shedding of cancer antigens and molecular danger signals by dying cells. This drove dendritic cell maturation and activation, which stimulated anti-tumor T cells and caused regression of treated tumors. When combined with anti-PD-L1 checkpoint blockade immunotherapy, the treatment elicited immune responses against untreated tumors as well—and an 83% cure rate in mice implanted with the immunosuppressive colon cancer.

RESCUED FROM ROS

Cancer-associated mutations are known to stabilize the transcription factor, NRF2, that controls the expression of genes involved in cellular antioxidant defense systems, which shield DNA and other vital molecules from highly reactive molecules called reactive oxygen species (ROS). In a *Molecular Cell* paper published in October, Ludwig Harvard Co-director Joan Brugge and colleagues reported their analysis of how NRF2 contributes to cancer cell growth and survival in experiments using lung cancer spheroid models—cultured, three-dimensional mimics of tumors. Their studies showed that its hyperactivation is required for both proliferation and survival of spheroid cultures, though distinct signaling pathways control each outcome. A pathway mediated by mTOR supports proliferation. As for survival, NRF2 activity protects cancer cells within the spheroid that are deprived of contact with the extracellular matrix from a type of programmed cell death known as ferroptosis, which is mediated by ROS. But when cells lack NRF2, a critical suppressor of ferroptosis, GPX4, and related proteins are expressed at high levels. Joan and her team show that inhibiting both NRF2 and GPX4 leads to the death of cancer spheroids. The results reveal a vulnerability in tumors dependent on NRF2 hyperactivation that might be targeted for the development of novel cancer therapies.

◀ Joan Brugge
Ludwig Harvard

Ash Alizadeh ▶
Ludwig Stanford

Maximilian Diehn ▶
Ludwig Stanford

DIRECT-ON PREDICTIONS

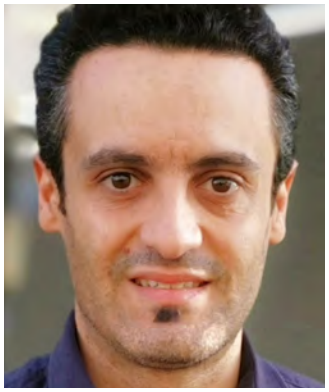
Immune checkpoint inhibitors like anti-PD-1 antibodies improve survival in advanced non-small cell lung cancer (NSCLC). However, conventional imaging often can't identify which patients treated with these agents will benefit from such therapy. In a *Cell* paper published in October, a team led by Ludwig Stanford's Ash Alizadeh and Maximilian Diehn and Matthew Hellmann of Memorial Sloan Kettering Cancer Center reported a method to accurately predict early in treatment which patients with NSCLC are likely to benefit from PD-1 checkpoint blockade. Called DIREct-On, (for Durable Immunotherapy Response Estimation by immune profiling and ctDNA-On treatment), the method incorporates three types of biomarkers to predict treatment responses: the level of mutation in tumors, changes in levels of circulating tumor DNA (ctDNA) and levels of circulating cytotoxic T cells. DIREct-On benefits from the noninvasive measurement of biomarkers not only before but during treatment as well. In preliminary studies, it accurately predicted progression-free survival from blood samples collected after one treatment cycle and was more precise than use of any of the three variables alone. Combining all three resulted in the prediction of durable clinical benefit with a sensitivity of 94% and specificity of 89%. DIREct-On could help physicians quickly determine whether anti-PD-1 immunotherapy should be continued, modified or stopped.

CARTS OF MICE

Chimeric antigen-receptor (CAR)-T cell therapy involves taking a patient's peripheral blood T cells and engineering them with a receptor that redirects them to attack their tumor. Though such therapies have been approved for blood cancers, their application to solid tumors has proved challenging, in part because the microenvironments of solid tumors suppress immune responses. Meanwhile, due to technical difficulties associated with developing mouse CAR-T cells, new CAR therapies have typically been preclinically evaluated using human CAR-T cells in mice that lack an immune system. The CAR-T cells are thus not challenged in the context of inhibitory immune infiltrates in tumors. In November, Ludwig Lausanne's Melita Irving, George Coukos, Evripidis Lanitis and colleagues reported in the *Journal of Experimental Medicine* a method to overcome that difficulty involving, among other things, the sequential use of three immune factors known as interleukins (IL-2, 7 and 15) in the cultivation of mouse CAR-T cells. The team also developed "4th generation" (4G) CAR-T cells engineered to co-express the IL-15 protein, which stimulates T cell proliferation and survival, and showed that their CAR-T cells were superior in persistence, fitness and efficacy in a mouse model of melanoma. Notably, the 4G CAR-T cells reprogramed the tumor microenvironment by activating tumor-targeting natural killer cells and causing a decline in M2 macrophages that can suppress anti-cancer responses.

Melita Irving
Ludwig Lausanne

George Coukos
Ludwig Lausanne



Evripidis Lanitis
Ludwig Lausanne

GOING VIRAL

Targovax, a company developing immune activators for combination therapy in solid tumors, completed part 1 of its two-part, open label phase 1 trial evaluating the combination of the oncolytic virus ONCOS-102 and the checkpoint blockade durvalumab, a PD-L1 inhibitor, for colorectal cancer (CRC) and platinum-resistant ovarian cancer that has spread to the peritoneum—the membrane that lines the inner wall of the abdomen. ONCOS-102 is an experimental cancer therapy comprised of an engineered adenovirus that replicates specifically inside cancer cells, leaving healthy cells unharmed. The trial met the pre-defined efficacy threshold in the CRC cohort at week 24 and the second part of the CRC expansion cohort is now open for recruitment. The treatment did not meet that threshold for the ovarian cancer cohort, which is now closed. The trial was designed with a dose-escalation phase assessing three different dosing levels, followed by an expansion phase. The study is sponsored by Ludwig and led by Ludwig MSK's Dmitriy Zamarin. CRC is a challenging disease to treat, with a response rate to immune checkpoint inhibitor monotherapy of less than 5%. The researchers are betting immune activation by ONCOS-102 will sensitize these tumors to immune checkpoint inhibition and improve the response rate.

LANA KANDALAFT

ASSOCIATE DIRECTOR OF CLINICAL TRANSLATION, LUDWIG LAUSANNE

Can you tell us about what excites you most in your work right now?
We're pretty unique here at the Ludwig Lausanne Branch, in that there are not many translational programs around the world like ours. I have an amazing team to work with in developing cancer vaccines and other immunotherapy products for our patients. And right now, we are in an excellent position to deliver some innovative products to them. Our work is very gratifying because we are able to see our technologies being implemented in clinical protocols and witness first-hand how a treatment is working and whether it is benefitting an individual patient.

You've done a lot of research on ovarian cancer. How optimistic are you about near-term opportunities for immunotherapy treatments for this kind of cancer?
While we don't have immunotherapy for ovarian cancer as yet, we have a lot of promising leads. I think the challenge is going to be defining exactly which patients may get the best results from different approaches. There are a couple of studies out whose results are encouraging and indicate we need combination therapies along with chemotherapy to produce a better response. Chemotherapy and PARP inhibitors are viable combination partners for immunotherapy and combining checkpoint inhibition with other drugs may lead to some new options for patients. But none of these combinations are standard of care right now. Now the more that we understand the tumor microenvironment and its influence on a

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> It’s a different ballgame when you interact with patients and their husbands or mothers or sisters … part of my attachment to ovarian cancer stems from my personal experience with patients.
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patient’s response to therapy, the more we’ll be able to understand how various combination therapies work and which ones might work best.

My interest is in vaccines, and I have a paper out right now with my colleagues here Alexandre Harari and Cheryl Chiang at the Ludwig Lausanne Branch on a personalized cancer vaccine strategy that recognizes the importance of T cells for controlling ovarian cancer. Some interesting early data have come out that may lead us in directions that we want to go, but larger studies need to be done to validate the findings. Vaccines are not the cure, however. It’s my hope that they will eventually be integrated into the standard of care, but they will not be the definitive cure for ovarian cancer.

What worries you the most about developing these therapies?
First of all, they are difficult to develop, and the difficulty is the technology—choosing the right antigen, choosing the right TCR (T cell receptor). The T cells themselves are difficult to handle. Number two, in order to ramp up production, you have to have the infrastructure to actually manufacture these products. Producing them and getting them to patients is complex and very challenging. While it took us quite a few years to build, the Center of Experimental Therapeutics (CTE) has two GMP manufacturing facilities: the Tumor Processing Facility and the Cellular Manufacturing Facility. Just as CAR T-cell therapy has been approved for standard of care for some cancers, I believe these new immunotherapies will be as well. And third, once we’ve developed these therapies there are some big questions to answer. How will the world adapt? Will pharma make use of all the good technology we’ve developed and run with it? Will every hospital in every country and in every city have the infrastructure in-house to treat its patients? Will these therapies eventually become part of the standard of care? We have a lot of hurdles to overcome, but I’m confident they are all doable.

Given all these challenges, what is it about ovarian cancer that drives you?
It’s what’s called the silent killer because it’s a very tough cancer to detect and by the time a woman receives a diagnosis, the disease is quite advanced, at either Stage III or IV. I started working on it at the Ovarian Cancer Research Center at the University of Pennsylvania with George Coukos and found it very challenging to treat. The disease landscape is such that the cancer bounces back in 85% of women who undergo the standard of care, which is surgery followed by chemotherapy. I think

there is a watchful waiting period with this disease where a vaccine could be given to women in remission to prevent recurrence.

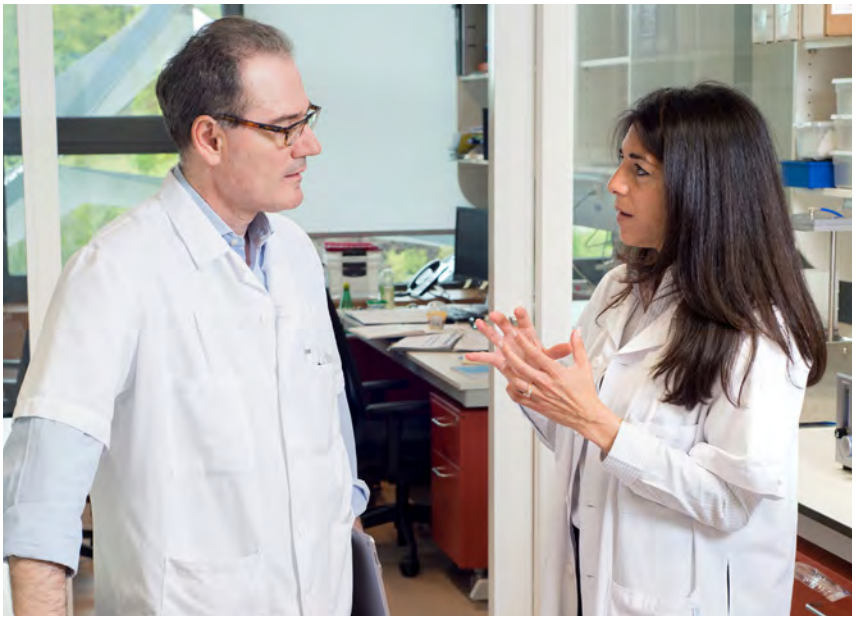
But it might have been my exposure to patients when I was at Penn that changed my mentality and the way I approach this disease. It's a different ballgame when you interact with patients and their husbands or mothers or sisters or other close relatives. And I think part of my attachment to ovarian cancer stems from my personal experience with patients, many of whom have become friends.

Lana with Ludwig Lausanne's Alexandre Harari, left, and Director George Coukos.

Can you tell us what you find most stimulating about the research environment at Ludwig Lausanne?
At Ludwig we are really very lucky. The leadership has set a specific direction for the organization, and everyone on the team has a shared sense of purpose, and we are all working towards one goal. Or, as I like to say, we're all drumming to the same beat. Our focus is on translational science—primarily tumor immunology and the design and development of novel immunotherapies. I admit it can be daunting in terms of career development because not every member can become their own PI or have their own lab or run their own Branch. But at the end of the day, we're all working on something that will eventually get to our patients and hopefully make a difference.

What has it enabled you to do that you could not do previously?
Prior to coming here, I worked with George at Penn developing immune therapies for ovarian cancer patients. It was a small operation focused on vaccines. It was difficult because we didn't have a Good Manufacturing Practice (GMP) facility and had to outsource everything. Here in Lausanne, we built a department that has it all. We're one of the largest immunotherapy centers in Europe, and we have it all right here—the researchers, the doctors and the patients. Within the CHUV's Department of Oncology, we created the CTE, which I run with a staff of 140. We have a clinical investigation unit to run our clinical trials and two GMP manufacturing facilities for cancer immunotherapies. Without these resources, we could not have achieved what we are achieving right now.

Your training has been very international. What perspective does that provide for you?
That you can be whoever you want to



Lana with Ludwig Lausanne Director George Coukos.

be wherever you are. It doesn't matter if you're in India, Spain, the U.S. or Switzerland. All it takes is the right mindset and the right attitude. Every new venue presents a different challenge. Each institution has a lot to offer. You have to adapt, as each has its own mission and its own way of doing things. There are new languages to learn, new cultures to embrace and new techniques to learn. But since I left home at such a young age, I was able to adapt quite easily and absorb everything around me like a sponge. And bottom line, science is science, whether you are working in the U.S. or Switzerland.

What is the most effective/best way for scientists to use social media to engage, communicate and interact?
Honestly, I don't know. It's very important to communicate about your work and share it with others, but I have to admit I lack the time right now to even think about using social media. I would need the support of a very good communications team to even start.

What would our readers be surprised to know about you?
I'm aware that people perceive me as a workaholic, and I know they think that I have no private life. But I do. I am a mother with two amazing boys. I'm a very good cook and have even mastered a Lebanese lamb dish that my dad said was even better than my mother's. Music is a big part of my life. I wrote my entire PhD thesis to Jon Bon Jovi's music—played very loud. And since moving to Switzerland, I have fallen in love with the mountains and ski touring. It's my new passion. Exhausting, but so beautiful.

Would you share a story that led to you choosing your field of work?
It was in Cardiff, Wales, where I was working on my PhD in pharmaceutical drug delivery. I had just started a course in pharmaceutical biology that was interesting, but I couldn't see a real-world application. One evening when I was sitting at the bench next to my computer, I came across a paper written by Doug Hanahan and Bob Weinberg entitled The Hallmarks of Cancer. I said to myself, "Ah, Lana, this is what you need to do. You need to deliver drugs to cancer. This is what you must do." So I immediately started looking into postdoc opportunities at the National Cancer Institute in Bethesda. That was a turning point in my life. When I came to Lausanne in 2012, and first saw Doug Hanahan, I was so excited and thrilled to

actually meet him that I know my face turned completely red. I kept saying to myself, Doug Hanahan is here, and it was his amazing paper that really touched me and changed my life.

When you're not wearing your many science hats, what other activities are you involved in?
I'm at a stage in my life where my role as a mother has changed. I have a different connection with my two sons, who are now 10 and five years old, than I did when they were younger. While I encourage them to be independent, they will often bike alongside me when I run. I still play a lot of tennis and in winter we ski a lot on the weekends. Opera is not my thing, sports are. And I watch a lot of movies with the boys and, of course, listen to music.

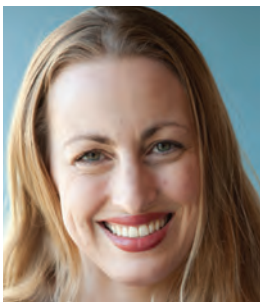
What kind of music do you listen to?
I'm into French rap because it's what my kids are listening to, and I want to be cool. I also listen to a lot of oldies because growing up, my dad was always playing them. But it's definitely the music from the 80's that gets me pumped up. It's great music to run to.

There has been a lot of discussion in the media lately about women in science. What has been your experience as a female scientist? How do you see your role in helping to mentor women?
Again, I have been very lucky in that I have always worked in an environment where the leadership has been nothing but supportive of women. The field of science is challenging as it is, and it doesn't really matter whether you are male or female, everyone is working towards the same goal. Here at the CHUV, women are well represented as 69% of the employees are female, and many are in leadership positions.

> "Since I left home at such a young age, I was able to adapt quite easily and absorb everything around me like a sponge. And bottom line, science is science, whether you are working in the U.S. or Switzerland."

My role as a mentor is very important to me, and I often wish I had more time to devote to it. I am often approached by young women who want to know how I was able to achieve what I did, what my life is like, and ask whether a life outside the lab possible. Mentoring the younger generation is key to helping them reach the next level. I had one very talented female postdoc who came to work for me and over the years received a number of promotions, and ultimately became a key member in our department here at the CHUV. She now works in the pharmaceutical industry. One day, she came to me and said, "Lana, you didn't just give me a job, you gave me a career." That touched me deeply and reinforced how important it is to mentor and inspire the next generation.

How has the pandemic changed your perspective on balancing your work and personal life?



Prior to the pandemic, I had a system and support structure that allowed me to balance my work in the lab and the clinic with caring for and spending good time with my husband and our four children. That system of balance disappeared when the pandemic hit and schools shut down. My husband (who is also in academic medicine) and I have been doing 100% work and 100% childcare at the same time, all the time it seems. To cope with this new unbalanced reality, I have been learning to say "no" more to work commitments, to reset my expectations of what I can accomplish every day, and to seek and cherish those rare quiet and un-interrupted moments when I can think creatively about an experiment or write a paper. It has been hard. But the extra time with my children and a chance to take a break from frequent academic travel has been really wonderful, and my ability to multi-task has improved to a new level.

MICHELLE MONJE DEISSEROTH
Ludwig Stanford

Prior to the pandemic, research was the center of my life, and I had to travel frequently for scientific meetings. I see now that my mindset was not sustainable, especially on maintaining my personal life, as well as supporting the development of my lab members. After the shocking experience and a 'valuable' reset happened in 2020, I realize that work-life balance is key to sustaining my research motivation and appreciate the fact that everyone in my lab is heading to our goal in their own way. Although this pandemic is sad in many ways, I do feel that it brings positive changes for our research and training culture.

PING-CHIH HO
Ludwig Lausanne

This pandemic has brought a general sense of uncertainty and disorientation. The possibility to go to conferences and build a good network is still missing, and I fear this will have a negative impact on my career. However, I will do my best and fight to keep my research and progress going even in this tough period.

FRANCESCA ALFEI
Ludwig Lausanne

With hours limited by the shift system, I have found I am able to achieve more than I expected by being more efficient, whilst the extra time at home has highlighted the indispensable nature of interests outside of work. I have also learned not to worry about things that you have no control over.

MICHAEL McCLELLAN
Ludwig Oxford

For me, the pandemic has emphasized the importance of having firm boundaries between work and personal time. Home-schooling whilst in a lab meeting, responding to emails whilst shushing a crying baby, cramming in lab time then rushing home for childcare, etc. This is not conducive either to good research or to good parenting. In the future I will be very grateful to work and to parent at separate times and with my full focus.

ALICE NEAL
Ludwig Oxford

I've realized that achieving a work-life balance is not just a worthwhile goal—it is vital for mental and physical health and future success. I've learned that mastery of work-life balance comes down to how well we can prioritize the aspects of our lives that we most enjoy, whether professional or personal.

SEAN PITRODA
Ludwig Chicago

Ludwig Chicago

Journal of Experimental Medicine 2021 January 26

Suppression of local type I interferon by gut microbiota-derived butyrate impairs antitumor effects of ionizing radiation.

Yang K, Hou Y, Zhang Y, Liang H, Sharma A, Zheng W, Wang L, Torres R, Tatebe K, Chmura SJ, Pitroda SP, Gilbert JA, Fu YX, Weichselbaum RR.

Science Advances 2020 October 2

Nanoscale metal-organic frameworks for x-ray activated in situ cancer vaccination.

Ni K, Lan G, Guo N, Culbert A, Luo T, Wu T, Weichselbaum RR, Lin W.

Ludwig Harvard

Nature Cancer 2020 December 14

Targeting immunosuppressive macrophages overcomes PARP inhibitor resistance in BRCA1-associated triple-negative breast cancer

Mehta AK, Cheney EM, Guerriero JL.

Molecular Cell 2020 October 30 Epub

3D Culture Models with CRISPR Screens Reveal Hyperactive NRF2 as a Prerequisite for Spheroid Formation via Regulation of Proliferation and Ferroptosis.

Takahashi N, Cho P, Selfors LM, Kuiken HJ, Kaul R, Fujiwara T, Harris IS, Zhang T, Gygi SP, Brugge JS.

Ludwig Lausanne

Journal of Experimental Medicine 2020 November 6

Optimized gene engineering of murine CAR-T cells reveals the beneficial effects of IL-15 coexpression.

Lanitis E, Rota G, Kosti P, Ronet C, Spill A, Seijo B, Romero P, Dangaj D, Coukos G, Irving M.

Nature Immunology 2020 October 5 Online ahead of print

Disturbed mitochondrial dynamics in CD8+ TILs reinforce T cell exhaustion.

Yu YR, Imrichova H, Wang H, Chao T, Xiao Z, Gao M, Rincon-Restrepo M, Franco F, Genolet R, Cheng WC, Jandus C, Coukos G, Jiang YF, Locasale JW, Zippelius A, Liu PS, Tang L, Bock C, Vannini N, Ho PC.

Ludwig MIT

Molecular Cell 2020 December 22 Online ahead of print

Increased demand for NAD+ relative to ATP drives aerobic glycolysis.

Luengo A, Li Z, Gui DY, Sullivan LB, Zagorulya M, Do BT, Ferreira R, Naamati A, Ali A, Lewis CA, Thomas CJ, Spranger S, Matheson NJ, Vander Heiden MG.

Ludwig MSK

Cell Reports 2021 January 12

Targeting phosphatidylserine enhances the anti-tumor response to tumor-directed radiation therapy in a preclinical model of melanoma.

Budhu S, Giese R, Gupta A, Fitzgerald K, Zappasodi R, Schad S, Hirschhorn D, Campesato LF, De Henau O, Gigoux M, Liu C, Mazo G, Deng L, Barker CA, Wolchok JD, Merghoub T.

Journal of Experimental Medicine 2020 December 29

Nuclear receptor LXRβ controls fitness and functionality of activated T cells.

Michaels AJ, Campbell C, Bou-Puerto R, Rudensky AY.

Proceedings of the National Academy of Sciences USA 2020 December 14 Epub

FXR mediates T cell-intrinsic responses to reduced feeding during infection.

Campbell C, Marchildon F, Michaels AJ, Takemoto N, van der Veeken J, Schizas M, Pritykin Y, Leslie CS, Intlekofer AM, Cohen P, Rudensky AY.

Ludwig Oxford

Nature Communications 2021 January 27

Subtraction-free and bisulfite-free specific sequencing of 5-methylcytosine and its oxidized derivatives at base resolution.

Liu Y, Hu Z, Cheng J, Siejka-Zielińska P, Chen J, Inoue M, Ahmed AA, Song CX.

Cancer Cell 2020 December 7 Online ahead of print

Arsenic Trioxide Rescues Structural p53 Mutations through a Cryptic Allosteric Site.

Chen S, Wu JL, Liang Y, Tang YG, Song HX, Wu LL, Xing YF, Yan N, Li YT, Wang ZY, Xiao SJ, Lu X, Chen SJ, Lu M.

Ludwig San Diego

Science 2021 January 1

A tripartite mechanism catalyzes Mad2-Cdc20 assembly at unattached kinetochores.

Lara-Gonzalez P; Kim T; Oegema K; Corbett K; Desai A

Science 2020 December 17 Online ahead of print

HSP70 chaperones RNA-free TDP-43 into anisotropic intranuclear liquid spherical shells.

Yu H, Lu S, Gasior K, Singh D, Vazquez-Sanchez S, Tapia O, Toprani D, Beccari MS, Yates JR 3rd, Da Cruz S, Newby JM, Lafarga M, Gladfelter AS, Villa E, Cleveland DW.

Nature 2020 December 23 Epub

Chromothripsis drives the evolution of gene amplification in cancer.

Shoshani O, Brunner SF, Yaeger R, Ly P, Nechemia-Arbely Y, Kim DH, Fang R, Castillon GA, Yu M, Li JSZ, Sun Y, Ellisman MH, Ren B, Campbell PJ, Cleveland DW.

Ludwig Stanford

Cell
2020 October 1
Epub ahead of print

Noninvasive early identification of therapeutic benefit from immune checkpoint inhibition

Nabet BY, Esfahani MS, Moding EJ, Hamilton EG, Chabon JJ, Rizvi H, Steen CB, Chaudhuri AA, Liu CL, Hui AB, Almanza D, Stehr H, Gojenola L, Bonilla RF, Jin MC, Jeon YJ, Tseng D, Liu C, Merghoub T, Neal JW, Wakelee HA, Padda SK, Ramchandran KJ, Das M, Plodkowski AJ, Yoo C, Chen EL, Ko RB, Newman AM, Hellmann MD, Alizadeh AA, Diehn M.

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