

LUDWIG LINK

DECEMBER 2016

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DECEMBER 2016

LETTER



It's hard to believe this is the last Link of 2016. It's been a whirlwind year, and this closing quarter's newsletter captures that perfectly. Our researchers around the world have been busy, and not just in receiving awards and accolades, or in

helping to ground and guide lofty undertakings like the US Vice President's Moonshot Initiative. They've published some rather splendid research as well.

You'll read about how an international coalition of Ludwig researchers tested out the accuracy and utility of liquid biopsies to predict the likely course of colon cancer after surgery. You will find out how others have examined the macrophages that support brain tumor growth, designed a clever nanosensor to profile tumors and exposed a novel mechanism by which cancer cells evade immune attack that has implications for current research and clinical diagnostics. And that's just a little sample of what's in here.

We share some sad news in this issue too: the death of our longtime board member Steve Bollenbach, whose legendary financial acumen proved of great value to the Board as Ludwig navigated the choppy economic waters of the last several years. We also have in here an interview with Ludwig Oxford Director Xin Lu, and a brief review of a book by a scientist who was diagnosed with an almost certainly deadly cancer. With the guidance of our former Scientific Director, the late Lloyd Old, she and her husband hit the books and took the most extraordinary measures to save her life.

Happy holidays!

Sincerely,

Rachel Steinhardt
Vice President for Communications

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On the cover: Karen Cichowski, Ludwig Harvard

BEYOND-THE-MOON SHOT

In October, Ludwig Stanford scientist Peter Kim was tapped to lead the Chan Zuckerberg Biohub project on infectious disease. The Biohub's mission is to invest in science, technology and human ingenuity to help cure, prevent or manage all diseases by the end of the century. Two projects are on the drawing board: the cell atlas, which will map the functions and location of every cell in the human body, and the infectious disease initiative, which will develop tools to eliminate infectious diseases. In addition to developing new tools to detect infections and new technologies for vaccines, the project will support a rapid response team that can devote scientists and technology to stopping sudden outbreaks, like Ebola. Peter's team will work with the cell atlas group to better understand the interactions between infectious agents and human cells and help validate potential drug targets.



Peter Kim
Ludwig Stanford

IMMUNO-PIONEER

Ludwig MSK's Jedd Wolchok received the 2016 Taubman Prize for Excellence in Translational Medical Science from the University of Michigan's A. Alfred Taubman Medical Research Institute for his groundbreaking work in cancer immunotherapy. He shares the \$100,000 prize with Johns Hopkins' Suzanne Topalian. Jedd has led the clinical development of immunotherapy for melanoma and other types of cancer. His early research led to the FDA approval of ipilimumab, a drug now used as a first-line treatment for patients with advanced melanoma. He also spearheaded efforts to develop immune-related criteria that are now the standard for assessing the effects of immunotherapy on tumors. More recently, Jedd has advanced the use of immunotherapies in combination with each other and other drugs to treat cancer, and has contributed significantly to developing new immunotherapeutic targets and strategies. Jedd and Suzanne gave keynote talks at the Taubman Institute's annual symposium in October. The Taubman Prize recognizes clinician-scientists who have done the most to "transform laboratory discoveries into clinical applications for patients suffering from disease."



Jedd Wolchok
Ludwig MSK

TWICE (MORE) HONORED

Ludwig's Director of Strategic Alliances in Central Nervous System Cancers, Web Cavenee, received the Chinese Government's Friendship Award, the highest recognition bestowed on foreign experts who have contributed to the country's economic and social progress. The ceremonies were held in Beijing in September. Web has been involved in various scientific collaborations with researchers in China for almost two decades. He was cited for his outstanding work in cancer research, prevention and care. Experts from 18 foreign countries received the award this year, honored for their contributions to industry, science and technology, medicine, agriculture, energy, environmental protection and education in China.

Web also received a 2016 Feldman Founder's Award for Adult Brain Tumor Research, recognized for his work coordinating global efforts to accelerate the development of new therapies. He received his award in November at the National Brain Tumor Society's National Gray Gala in Boston. Web is a member of the executive committee for GBM AGILE, a pioneering, adaptive clinical trial investigating new biomarker-directed approaches to treating glioblastoma.



Web Cavenee
Ludwig Institute

A LASKER!

Ludwig Oxford scientist Peter Ratcliffe was awarded the prestigious Lasker Basic Medical Research Award in September for his work on how cells gauge and respond to the availability of oxygen, processes of fundamental importance to sustaining life that also play a role in a variety of diseases and disorders. Many tumors are, for example, profoundly starved of oxygen and the phenomenon is associated with resistance to therapy. Peter shared the award with William Kaelin of the Dana-Farber Cancer Institute and Gregg Semenza of the Johns Hopkins University School of Medicine. Their pioneering work has already contributed to experimental anemia drugs that convince the body it's at high altitude so that it ramps up the production of red blood cells. Peter's lab continues to work toward translating its discoveries into drugs to treat cancer and heart disease. The Lasker award recognizes scientists who have "advanced the potential translation of basic science into addressing unmet medical needs." [Click here](#) to hear Peter's remarks at the award ceremony.



Peter Ratcliffe
Ludwig Oxford

MOON LAUNCH

An advisory panel co-chaired by Tyler Jacks, an investigator at Ludwig MIT, came up with ten recommendations for what Vice President Joe Biden's Cancer Moonshot initiative should do. The suggestions, offered to a task force headed by the VP, aim to accelerate the pace of cancer science as well as translational research and, this being a moonshot, get ten years of work done in five. Big Data weaves through several recommendations, including the creation of a national network to profile tumors and match patients to cutting-edge clinical trials, and a database of 3-D maps that will chart the evolution of human tumors. The panel, which also included Ludwig Harvard Co-director George Demetri, recommended the creation of a translational science network for immunotherapy. Its purpose would be to broaden the number of cancer types and patients suited to the strategy. The National Cancer Institute said it "embraces" the recommendations, and it seems to have begun taking concrete steps toward its goals (see *Solid Progress for a Liquid Biopsy*, page 18).



Tyler Jacks
Ludwig MIT

TITAN OF CHEMISTRY

Chris Walsh, who served as a member of Ludwig's Scientific Advisory Committee (SAC) for five years, stepped down in September. He is a consulting professor to Stanford University's department of chemistry and an advisor to the Stanford ChEM-H institute. He was the Hamilton Kuhn Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School from 1987 to 2013, when he took emeritus status. The author of three books (including the classic *Enzymatic Reaction Mechanisms*), Chris has left a lasting mark on several subfields of the life sciences. But he is probably best known for advancing our understanding of the mechanisms of enzymatic activity, antibiotic resistance and the biosynthesis of antibiotics. His research laid the groundwork for the burgeoning field of chemical biology, which has transformed drug discovery. "I think the great 'Aha!' moments are when you take things from very different fields, or disparate observations, and put them together in a way no one else has before," he said in a short film made upon his receipt of the prestigious Benjamin Franklin Medal. Chris, it appears, has had more than his fair share of such moments. He is an elected member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. The Institute is deeply grateful to Chris for the experience, wisdom and judgment he brought to the discussions and deliberations of the SAC.



Chris Walsh
Ludwig Scientific Advisory
Committee

IN MEMORY OF STEPHEN BOLLENBACH



The Ludwig Institute lost a valued colleague and Board member in October with the passing of Stephen Bollenbach. Steve joined the Board in 2010 armed with a wealth of executive experience. As chief executive officer of Hilton Hotels—the first person outside of the Hilton family to hold the position—he engineered the company’s international expansion. Prior to that, he had served as CFO for the Trump Organization and the Walt Disney Co., where he helped create a media powerhouse that now includes theme parks, movie studios and television networks. Between those stints, he was CFO of the Holiday Corporation, which runs Holiday Inn motels. Impressive for someone who, as a teenager, spent summers scooping ice cream at Disneyland. Early in his

career, Steve worked for a decade with the Institute’s founder Daniel K. Ludwig, attending to his investments in the financial services industry and some of his other interests. Outside the boardroom—Steve sat on the boards of several companies, including Time Warner and Macy’s—he was an avid traveler who loved to ski, drive sports cars, golf and collect wine. He also established the Bollenbach Family Scholarship, which sends 15 deserving and financially strapped students each year to college. “Steve’s calm counsel and financial acumen brought valuable perspective to the Ludwig Board,” said John Notter, Chairman of the Board and a longtime friend. “He was a true leader. He will be missed.”



Alexander Rudensky
Ludwig MSK

TO SUPPRESS A KILLER

Regulatory T cells play a critical role in suppressing inflammation and autoimmunity, but they are also hijacked by tumors to squelch immune attack. A [study](#) led by Ludwig MSK Director Alexander Rudensky and published in November in *Nature Immunology* illuminates a key requirement for the function of these cells (called Treg cells). The researchers showed that the receptor for an immune factor known as interleukin-2 (IL-2) is required for the function of Treg cells and explored the role it plays in their activity. Using an elegant genetic approach, they determined that IL-2 receptor signaling is both required and sufficient

for Treg cell-mediated suppression of helper T cells. But the receptor protein itself appears to play an additional and necessary role in the suppression of cytotoxic T cell activity: It sequesters IL-2 from these cells, which also require the factor to function optimally. The researchers showed that Treg cells have a dual role in inflammation-associated gastrointestinal cancers. They limit the formation of precancerous lesions but promote tumor growth in later stages of the disease. The results hold clues to new strategies for cancer prevention, and to the development of new drugs for treating GI cancers and an array of autoimmune diseases.



Rickard Sandberg
Ludwig Stockholm

MOM GENES, DAD GENES

A [study](#) led by Ludwig Stockholm's Rickard Sandberg, sheds light on why identical twins can appear different even though their genes are identical and why many genetic disorders vary so much in their manifestation. Applying single-cell sequencing technology developed in Rickard's lab, the researchers examined how and to what degree our cells utilize each copy—or allele—of each inherited gene pair, one of which comes from each parent. Because alleles have slight differences in their DNA sequence, variations in the expression of each can

have functional consequences in tissues. But it has been unclear whether the “choice” of which allele a cell should express is carried through as cells generate clonal descendants—or if the pick is made independently in each cell over and over again. Rickard and his team reported in November in *Nature Genetics* that the expression of each allele fluctuates dynamically from cell to cell, regardless of their clonal antecedents. As few as 0.5% to 1% of genes are fixed into expressing just one of the alleles.

HOARDING RESOURCES

Many tumors produce high levels of enzymes that degrade the amino acid tryptophan to evade attack by T cells of the immune system, which require this amino acid for their activity. But it has long been unclear how tumor cells ensure their own access to this important nutrient. A team of researchers led by Ludwig investigator Vincenzo Cerundolo and including Executive Vice President for Research Bob Strausberg showed in a [paper](#) published in November in *Cancer Research* that tumor cells accomplish this by stepping up their production of proteins that import amino acids into the cell—especially a type named SLC1A5. The study provides insights into the poor prognosis of patients whose tumors co-express tryptophan-degrading enzymes and SLC1A5.



Vincenzo Cerundolo
Ludwig Oxford



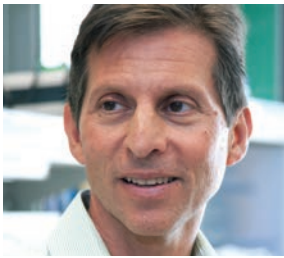
Bob Strausberg
Ludwig Institute

FOREIGN AGENTS

Macrophages are typically described as roving cells of the immune system that gobble up invading pathogens and cancer cells, helping to initiate and perpetuate protective immune responses. While true, macrophages also take on unique properties and functions in various organs and tissues (see *Grit in the Filter*, page 15). Certain subtypes even play a vital role in various tumors, where they support the proliferation and metastasis of cancer cells. Like other immune cells, macrophages are largely generated by stem cells in bone marrow—except those of the brain, called microglia, which replicate themselves. Brains are, in fact, ordinarily devoid of bone marrow-derived macrophages (BMDMs). Less clear is whether this holds true in brain tumors as well. Ludwig Lausanne's Johanna Joyce and her colleagues published a November [study](#) in *Cell Reports* showing that BMDMs indeed infiltrate brain tumors. They also found that the genomes of these cells, while partly reprogrammed by tumors to perform supporting functions, are already primed to do so when they arrive. They also report the discovery of a biomarker—the protein CD49D—which is not expressed by microglia and can be used to distinguish them from BMDMs.



Johanna Joyce
Ludwig Lausanne



Paul Mischel
Ludwig San Diego

UNDONE BY A NEED

Ludwig San Diego's Paul Mischel and his team, in collaboration with colleagues at The Scripps Research Institute, have identified a metabolic vulnerability in the incurable brain cancer glioblastoma (GBM), which is shaped by the brain's microenvironment and might be exploited for therapy. In a [paper](#) published in November in *Cancer Cell*, they report that the GBM tumors re-engineer existing metabolic pathways to ramp up the import of cholesterol made by other cells in the brain while disabling the normal feedback systems that keep

cholesterol levels in the cell in check. They demonstrate that these adaptations render GBM tumors exquisitely sensitive to an experimental drug for metabolic disease named LXR-623, which accumulates in the mouse brain. This drug activates the Liver X Receptor (LXR), potentially killing tumor cells by depleting them of cholesterol, while sparing non-cancerous cells, including astrocytes. The drug also dramatically shrank GBM tumors from human patients that were implanted in mice, significantly prolonging their survival.

MAPPING THE ISLET

Using a technology developed in his lab, Ludwig Stockholm's Rickard Sandberg led a study of genome expression in key cells of the human pancreas in partnership with the pharmaceutical company AstraZeneca. These cells, some of which differ in very subtle ways, play critical roles in controlling the body's metabolism and their dysfunction contributes to diabetes, obesity and other metabolic syndromes. Profiling the "transcriptomes"—the global expression of genes—in thousands of individual islet cells of the pancreas, Rickard and his colleagues found that less studied islet cells, such as δ and γ cells, might influence insulin-producing β cells in a manner so far unexplored. For example, leptin receptors were found on δ cells, which indicates that these cells integrate not only



Rickard Sandberg
Ludwig Stockholm

local but also systemic signals. The [study](#), published in October in *Cell Metabolism*, also provides a resource of cell-type specific gene expression programs in the human pancreatic islets and shows how gene expression differs between healthy individuals and those with diabetes.

THE CELL AS CRYSTAL BALL

Ludwig Chicago Co-director Ralph Weichselbaum published in an October [issue](#) of *Scientific Reports* a new method and risk model to assess how aggressive a bladder cancer is likely to be. Ralph and his colleagues showed that an excess of one relatively rare subtype of bladder tumor cells—the basal tumor cell (BTC)—in early stage cancers suggests a poor prognosis for the disease. In more advanced, invasive tumors, however, it is the ability of BTCs from such tumors to take hold and grow when injected into immune-deficient mice that indicates poorer outcomes, which may be an indirect

measure of the ability to form tumors. Analyzing the global expression of genes in BTCs, the researchers also identified a potentially new biomarker for bladder cancer: CDC25C, a protein that drives cell division. Notably, this association disappeared in patients who had received chemotherapy. A test for CDC25C could therefore help determine whether any bladder cancer patient is likely to benefit from chemotherapy—provided the marker is validated in larger studies. Further, with a method to isolate and grow BTCs, researchers can begin to look for unique ways to target these stem-like cancer cells.



Ralph Weichselbaum
Ludwig Chicago



Sangeeta Bhatia
Ludwig MIT

A NANONOSE FOR TUMORS

Ludwig MIT scientist Sangeeta Bhatia and her collaborator, Polina Anikeeva Professor in the Department of Materials Science and Engineering at MIT, have designed a nanosensor that can profile tumors and may predict how they respond to certain therapies. The system, described in an October [issue](#) of *Nano Letters*, detects the activity of protein-snipping enzymes, called proteases, that cancer cells use to remodel their surroundings as they spread. Tumors, especially aggressive ones, often express certain combinations of proteases in abundance. Once injected into the tumor

site, the nanosensors, each coated with a heat-sensitive material, are activated by a targeted, alternating magnetic field that is harmless to tissue. This treatment heats up the particles, destroying the coat and exposing small proteins that are known to be digested by a class of proteases expressed by the cancer cells. Upon digestion, the nanosensors become smaller protein fragments that are excreted via the urine, where they can be easily detected in less than an hour. Sangeeta, Polina and their trainees successfully tested the system in a pair of mouse models of colon cancer.

A GENTLER DECIMATION I

It might be possible to prepare patients for bone marrow transplants without having to expose them to toxic radiotherapy and chemotherapy. Researchers led by Ludwig Stanford investigator Hiro Nakauchi and Satoshi Yamazaki of the University of Tokyo [reported](#) in October in *Science* that a diet deficient in the essential amino acid valine can effectively deplete blood stem cells in mice. Human blood stem cells in the laboratory were similarly affected by a lack of valine, suggesting the approach may work in us as well. The effects of a valine-deficient diet were relatively benign—certainly compared to chemotherapy or radiotherapy—and the depletion it induces appears to be relatively specific to blood stem cells. If stem cells that generate leukemia are also vulnerable to valine deficiency, the method suggests a potential dietary intervention for these blood cancers. The experimental method complements other Ludwig Stanford work, in which antibodies were used to clear out blood stem cells from mice (see story at right). How valine deficiency depletes blood stem cells remains unknown and a focus of inquiry at Hiro's lab.



Hiro Nakauchi
Ludwig Stanford

A GENTLER DECIMATION II

Candidates for bone marrow transplants must first undergo chemotherapy or radiotherapy to kill their own population of blood stem cells. The procedure is risky and can be fatal for some patients. But a less toxic bone marrow transplant just might be on the horizon. A team led by Judith Shizuru of Ludwig Stanford [reported](#) in August in *Science Translational Medicine* a new technique, tested in mice, for depleting blood stem cells from a recipient in preparation for a bone marrow transplant. It relies on the use of a pair of antibodies. The first targets a cell surface protein called c-kit, which is a primary marker of blood stem cells. The second antibody blocks a cell surface protein called CD47, which prompts the immune system's macrophages to gobble up the stem cells. Together, they show, the antibodies deplete blood stem cells in immune-deficient mice. This clears the way for blood stem cells transplanted from a donor to take up residence in the bone marrow and generate a new immune system.



Judith Shizuru
Ludwig Stanford

BLOOD ANCESTRY

A team co-led by Ludwig Stanford scientist Ravi Majeti defined chromatin accessibility—which determines whether genes are made available for expression—and captured the full profile of expressed genes in the pathways of differentiation that give rise to 13 distinct types of blood cells from hematopoietic stem cells. The [paper](#), published in October in *Nature Genetics*, profiles the key genomic regulators of this process and captures elements of DNA sequence linked to a

variety of blood diseases. The researchers also describe the relationship between chromatin accessibility, the regulation of genes and the accumulation of mutations in acute myeloid leukemia. They find that HOX factors, which are master regulators of gene expression, are aberrantly expressed in many malignancies and contribute significantly to the evolution of cellular characteristics that generate leukemic cells.



Ravi Majeti
Ludwig Stanford

CANCER'S SCISSORS

Certain types of macrophages in tumors help cancer cells thrive by supporting their proliferation, generating blood vessels to feed them and aiding their metastasis. Enzymes that snip other proteins and are produced by macrophages as well as cancer cells play an important role in these processes. However, it hasn't been clear how one type of these scissors, cysteine cathepsin proteases, are regulated and released into the tumor microenvironment. Ludwig Lausanne researcher Johanna Joyce and

her team described in a September *Cell Reports* [study](#) that an immune factor, interleukin (IL)-4, synergizes with two others (IL-6 and IL-10) to activate the unfolded protein response (UPR) pathway. Within the macrophage, this induces the cooperative activation of two signaling proteins known as STAT3 and STAT6, which activates a biochemical sensor known as IRE1 α . Critically, the researchers show that targeting this sensor impairs tumor progression and invasion in mouse models.



Johanna Joyce
Ludwig Lausanne

MOM GENES TO BABY GENES

A team led by Ludwig San Diego's Bing Ren, and John Dahl and Arne Klungland of the University of Oslo developed a novel technique to map specific chemical (or "epigenetic") modifications made to the protein packaging of DNA using a small population of cells. Such epigenetic marks play a central role in the regulation of the genome's expression and are extensively reordered in cancer cells. The researchers applied their method to probe how an epigenetic mark known as H3K4me3 controls gene expression in the earliest stage of embryonic development—a period known as the maternal-to-zygotic transition (MZT). In this phase, control of embryonic development shifts from pre-existing maternal gene products to the products of genes encoded by the early embryo, or zygote. Bing and his colleagues [reported](#) in September in *Nature* that large segments of the immature egg cell's genome, representing some 22% of the whole, are heavily marked by H3K4me3. These domains dramatically decrease in size in 2-cell embryos to launch the major wave of synthesis of zygotic gene products. Their mapping technique, named μ ChIP-seq, allowed them to work with far fewer cells than permitted using earlier techniques for such experiments.



Bing Ren
Ludwig San Diego

JEKYLL OR HYDE, DEPENDING

Dichotomies can lend a sense of order to the messy business of biology. On the other hand, they don't always reflect biological reality. Take the Jekyll and Hyde of cancer, the tumor suppressor and its antithesis, the oncogene: We've known for some time that p53—reputedly a tumor suppressor—can simultaneously play either role in cancer. A team of researchers led by Ludwig Oxford's Sebastian Nijman and Barbara Mair recently added another character to this list of ambivalent proteins. They [reported](#) in September in *PLOS Genetics* that a gene often mutated in breast cancer, GATA3, can play either role depending on how precisely it is mutated—one type of mutation results in a gain of activity, while another leaves it inactive. The authors show that the two types of mutations have vastly different effects on cancer cell biology and patient survival. Their findings also suggest a personalized therapeutic approach that might improve survival for patients with the activating mutations.



Sebastian Nijman
Ludwig Oxford



Barbara Mair
Ludwig Oxford



Mads Gyrd-Hansen
Ludwig Oxford

SNIPPING AWAY A SIGNAL

A team of researchers led by Ludwig Oxford's Mads Gyrd-Hansen took us a step further in unraveling the basic regulatory mechanisms that control innate immune signaling. In a [paper](#) published in September in *Molecular Cell*, they demonstrate that a protein called SPATA2 is crucial for the regulation of ubiquitination—the process of linking the small ubiquitin protein into polymeric chains to generate intracellular signals. A protein complex named LUBAC, which tacks ubiquitin together in chains to

generate so-called Met1-linked ubiquitin chains, is central to the transmission of signals that underlie the body's frontline defenses to pathogens. However, uncontrolled signaling via ubiquitin can also promote chronic inflammation—which can drive the development of tumors. Mads and his colleagues show how SPATA2 brings together two proteins that, working in concert, snip units of ubiquitin from ubiquitin chains assembled by LUBAC and so dampen its inflammatory signals.



Calle Heldin
Ludwig Uppsala

THE GUARDIAN'S COUSIN

Everybody's heard about p53. It is, after all, the "Guardian of the Genome", a protein mutated in roughly half of all cancers. Thing is, p53 has relatives, and those relatives are nothing to sneeze at either. Take p63, a cousin to said Guardian and a master regulator of gene expression in skin cells. Its role in cancer has, however, proved difficult to discern. Trouble is it both suppresses and promotes tumors, depending on how it's expressed as a protein—and it is expressed in a number of different ways (known as isoforms). A team led by Ludwig Uppsala Director Calle Heldin explored, in collaboration with Kohei Miyazono's team at Tokyo University, how a truncated

isoform named Δ Np63 drives the progression of tumors in tissues that line inner body cavities, or epithelia. In a [paper](#) published in August in *Science Signaling*, Calle and his team show that signaling through the transforming growth factor- β (TGF- β), and the ubiquitous driver of cancer cells, Ras, boosts the expression of genes controlled by Δ Np63. They report this isoform of p63 boosts the migration and invasion of breast and squamous cancer cells in culture and in mice. They also found that high levels of Δ Np63 expression in a variety of cancers result in a relatively poor patient prognosis if the p53 encoded by tumor cells is mutated as well.

GRIT IN THE FILTER

Bundles of biomolecules made of antigens, antibodies and a set of defensive proteins of the body known as complement can get lodged in the nooks and crannies between cells. These gritty pollutants can cause an inflammatory immune reaction called type III hypersensitivity that injures tissue and can promote autoimmune disease. The kidney, with its fine blood filtration systems, is a prime site for such immunologic mayhem. In an August [Cell](#) study, a team of researchers led by Ludwig MSK scientist Frederic Geissmann reported a new anatomical unit found in the filtering mechanism of the kidney that appears to play a co-starring role in type III hypersensitivity. This unit consists of an endothelial cell that lines kidney blood vessels and an immune cell known as a tissue-resident kidney macrophage. Frederic and his colleagues showed that, on an ordinary day, this unit monitors the routine transport of proteins and detritus ranging from 20 to 700 nanometers in size. When the specialized macrophage encounters an immune complex, however, it initiates a signaling cascade that culminates in the recruitment of other immune cells that batter local tissue, especially if the complex contains DNA or RNA fragments. The study identifies a basic mechanism by which immune complexes induce damage to the kidneys.



Frederic Geissmann
Ludwig MSK

T CELL REVIVAL

Chronic viral infections and tumors can, quite literally, tire out the immune system. The phenomenon manifests as the so-called “exhaustion” of T cells, a state, it was believed, that precludes the formation of “memory” T cells. These special forces of the body’s defenses recognize and swiftly relaunch assaults on old enemies, making us immune to bugs we’ve met before. Turns out old views about exhaustion and memory T cells might have been a tad too glum. A team of Ludwig Lausanne scientists led by Werner Held published a [report](#) in August in *Immunity* describing a memory-like T cell population that, though apparently exhausted, drives a blossoming of anti-viral T cells in response to immunotherapy. These cells, they report, are marked by their production of a protein named Tcf1 that controls gene expression. Now that they can be identified and isolated, this new subset of T cells may represent a plum target for immunotherapies designed to boost immune responses not only to chronic infections but also to cancer.



Werner Held
Ludwig Lausanne

AN ASPP IN THE BRAIN

The ASPP family of proteins must be the workaholics of the cell's molecular society. They collectively regulate, among other things, the shape and polarity of cells and the activity of p53, the so-called guardian of the genome—which is mutated in at least half of all cancers. Their malfunction contributes not only to various types of cancer but, as a previous study by Ludwig Oxford Director Xin Lu and her team found, may also underlie a rare kind of heart failure. The researchers [reported](#) in

July in *Cell Death & Differentiation* that a deficiency in one member of this family, the tumor suppressor ASPP2, also appears to underlie the central nervous system dysfunctions associated with 1q41q42 microdeletion syndrome. This rare developmental disorder is characterized by severe developmental delay, intellectual disability and predisposition to seizures. The discovery sheds new light on the development of the human brain.



Xin Lu
Ludwig Oxford

TWO'S BETTER'N ONE

More than two-thirds of breast cancers contain both estrogen and progesterone receptors. The estrogen receptor is one of the standard markers pathologists use to determine if a breast tumor is hormone sensitive and a target for endocrine therapy. Progesterone receptors, meanwhile, have traditionally been used as a diagnostic only to confirm that the estrogen receptor protein is active. Until now. Ludwig Chicago Co-director Geoff Greene and his team [report](#) in a June *Science Advances* that when activated individually, each receptor interacts with different sets of binding sites in the cell's chromosomes, and that when both are activated at the same time, the progesterone receptor alters how and

where estrogen receptors contact the cell's DNA. Estrogen has been shown to activate genes that stimulate the growth of breast tumors. Geoff and his colleagues show that when progesterone is added along with estrogen, the opposite happens. They also show in a mouse model of breast cancer that combination therapy with an experimental progesterone receptor inhibitor (CDB4124) and tamoxifen, an approved estrogen receptor inhibitor, results in a 70% regression of transplanted tumors. Conversely, tumors stopped growing but did not perceptibly regress in mice treated with either drug alone. These results suggest that combination therapies that target both receptors might have clinical utility.



Geoffrey Greene
Ludwig Chicago

EARLY WARNING SYSTEM

Ludwig researchers in Australia and the US, showed that ctDNA—fragments of tumor DNA circulating in the blood—can be used to gauge the risk of colorectal cancer recurrence and the efficacy of chemotherapy following surgery. The [study](#), led by Bert Vogelstein, co-director of the Ludwig Center at Johns Hopkins, and Jeanne Tie and Peter Gibbs, Ludwig investigators at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Victoria, Australia, was published in *Science Translational Medicine* in July. The researchers, working with colleagues in both countries, analyzed DNA in tumor samples from 230 patients with stage II colorectal cancer and devised personalized assays to detect ctDNA in each patient. Twenty of the patients tested positive for ctDNA after

surgery to remove their tumors. Of these patients, 80% experienced a relapse within two years. Only 10% of those who tested negative for ctDNA relapsed. The team found that two of six patients who tested positive after surgery switched to negative after receiving chemotherapy. This is exciting because it suggests ctDNA tests might someday help physicians determine who should—and should not—be given chemotherapy after surgery for stage II colon cancer. Serial analysis of ctDNA creates the exciting possibility of a real time marker of the effectiveness of the administered chemotherapy and a new paradigm for performing clinical trials in an adjuvant setting.



Bert Vogelstein
Ludwig Johns Hopkins



Peter Gibbs
Ludwig WEHI



Jeanne Tie
Ludwig WEHI

STICKY BUSINESS

A [study](#) led by Pierre van der Bruggen of Ludwig Brussels uncovered one of the mechanisms by which tumor cells thwart attack by killer T cells of the immune system. He and his team described in a July issue of *Nature Communications* how a protein named galectin, which is overproduced and secreted by many types of cancer cells, stops activated T cells from triggering their attack. Galectin gums up a protein known as LFA-1 on the surface of T cells that have infiltrated tumors and are primed and ready to attack. LFA-1 is essential for clearing a passage out of the T cell for toxic granules and cytokines in the final stage of the strike. Detaching galectin from human tumor-infiltrating T cells, Pierre's team found, restored the ability of these T cells to kill cancer cells. The findings indicate that assessing the function of tumor-infiltrating T cells by measuring the intracellular production of cytokines, rather than their release, is likely to generate false positives of T cell function. They also suggest that drugs that counter galectin could potentially boost immunotherapies.



Pierre van der Bruggen
Ludwig Brussels

SOLID PROGRESS FOR A LIQUID BIOPSY

Personal Genome Diagnostics (PDGx), a biotech founded in 2010 by Ludwig Johns Hopkins' Luis Diaz and his colleague Victor Velculescu, has lately blazed quite a trail in the world of molecular diagnostics. The company partnered with Takeda Pharmaceuticals to present data at the 2016 Precision: Lung Cancer World R&D Summit supporting the feasibility of liquid biopsies for genomic testing in lung cancer. The study profiled DNA from 12 relapsed small cell lung cancer (SCLC) patients and identified genetic alterations known to be associated with SCLC, as well as those that are not. PDGx then launched its product, PlasmaSELECT 64, which the company says can use liquid biopsies to identify clinically actionable and functionally important mutations across multiple cancer types. All this appears to have impressed the genomics giant Illumina, which inked a partnership with the biotech to develop two diagnostic tests to characterize tumor DNA from tissue or blood samples that will run on Illumina's sequencing instruments. It also, apparently, impressed the folks over at the US Cancer Moonshot initiative, who picked PGDx as a participant in their Blood Profiling Atlas, which will develop an open, high-quality database for liquid biopsies.



Luis Diaz
Ludwig Johns Hopkins

SMARTER SURVEILLANCE

PapGene, Inc., founded by Ludwig Johns Hopkins scientists Bert Vogelstein, Kenneth Kinzler, Luis Diaz, Nickolas Papadopoulos and Shibin Zhou, was awarded a Fast-Track Small Business Innovation Research contract from the National Cancer Institute of the National Institutes of Health to commercialize a test for recurrent bladder cancer. The fourth-leading cause of cancer death among men, bladder cancer has a relatively high rate of recurrence, making it one of the most expensive cancers to manage on a per-patient basis. A noninvasive molecular test for recurrent bladder cancer surveillance has the potential to improve patient outcomes while decreasing the cost of care. The \$2.2 million grant will be allocated in two phases. The first phase will determine the accuracy and clinical validity of the test. The second will test its clinical efficacy, and begin the regulatory approval process.

TESTING A TARGETED STIMULUS

Agenus, a biotech company that has licensed therapeutic antibodies to several distinct immune-oncology targets from Ludwig Cancer Research, announced the first dosing of a patient in its phase 1/2 clinical trial of INCAGN01876, a monoclonal antibody that targets GITR. Developed initially by Ludwig MSK, INCAGN01876 activates GITR, a receptor that stimulates cytotoxic T cells to target diseased and cancerous cells. Agenus has initiated a clinical trial of a second immune-oncology antibody INCAGN01949, also developed through the Ludwig collaboration, this time targeting OX40. The trials will evaluate the safety and optimal dosing of INCAGN01876 and INCAGN01949 in patients with advanced or metastatic solid tumors, including advanced endometrial adenocarcinoma—a gynecological cancer of the uterine walls—melanoma, non-small cell lung cancer and renal cell carcinoma.

Agenus is developing INCAGN01876 and INCAGN01949 in collaboration with Incyte Corporation.

UNDOING A MALIGNANT DEFENSE

Ludwig spin-off iTeos announced the start of a phase 1 clinical trial of its lead IDO1 inhibitor, PF-06840003/EOS200271, as a single agent for the treatment of brain cancer. Many human tumors express IDO, an enzyme that deprives infiltrating T cells of a vital amino acid, suppressing their ability to kill cancer cells. IDO inhibition is meant to boost the immune surveillance of tumors and the induction of anti-tumor immune responses. The dose-escalation study is being conducted by Pfizer to establish the safety, maximum tolerated dose and a recommended dosage for subsequent trials. The study will also evaluate early biomarkers of activity.

SUSSING OUT SUPPRESSORS

Ludwig spin-off Seramatrix received CLIA approval for a test to measure myeloid-derived suppressor cells (MDSC) in cancer patients. MDSCs are potent suppressors of immune responses. Their presence in tumors is associated with poor patient outcomes and can compromise immunotherapy. Developed at the Ludwig Center at MSK and licensed by Seramatrix in 2013, the test is already widely used by several of the leading companies developing immuno-oncology therapies. The CLIA certification makes it available to clinical oncologists, who can use it to predict how patients will respond to immunotherapy. Ludwig MSK's Jedd Wolchok, who chairs Seramatrix's Scientific Advisory Board noted that clinicians can now use the blood test to help select and optimize therapies for their patients.

Our leader in Oxford

Why did you choose to pursue a career in science?

I don't think I chose it so much as it was thrust upon me. I grew up during China's Cultural Revolution and in the late sixties, Chairman Mao issued a call for the "Down to the Countryside Movement," in which young students from the city were sent to live in the countryside. Having been brought up in an urban area, I didn't have the skills or stamina for intensive agricultural labor, and knew I'd never survive. So at the age of 13, I decided to study the violin and practiced every day for at least three hours. I hoped it would give me a skill that could be exchanged for food. But I was one of the lucky ones and right after I graduated from high school, the colleges and universities reopened and I was able to sit for the exams. You'll remember that schools and universities had been closed as the Cultural Revolution began heating up in the mid-sixties, and it wasn't until 1977 that the first nationwide university entrance examination was held. I chose science with no particular interest in the subject but, after the first biology course, I realized that I really loved it.

What do you consider your most important discovery so far?

Identification of the ASPP family of proteins and its importance in regulating p53, which is a primary target for mutation in a diverse range of cancers. There are three family members—ASPP1, ASPP2 and



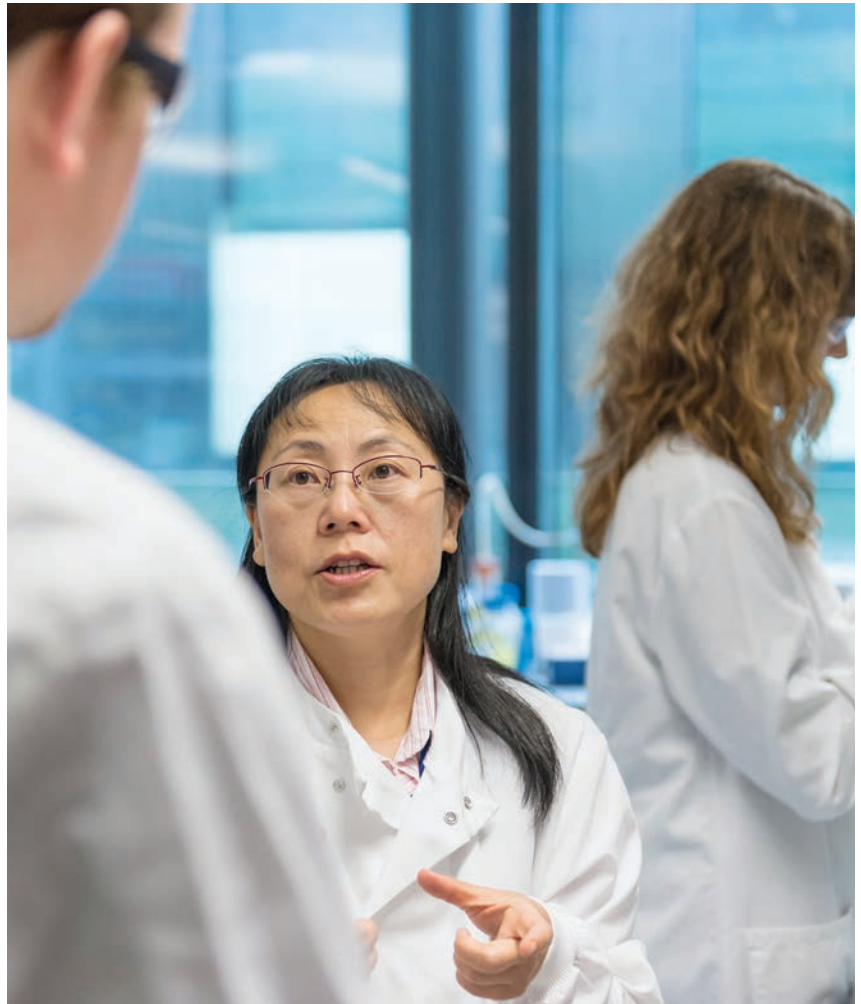
iASPP, and all bind to p53. ASPP1 and ASPP2 activate p53 and iASPP inhibits it. Since all three play important roles in tumor development and response to therapy, we're investigating the ASPPs as potential biomarkers and targets for anti-cancer therapies. Through the identification and characterization of the evolutionarily conserved ASPP family of proteins, our lab was one of the first to show how to selectively activate p53 to kill cancer cells. We now know that the ASPPs have other important functions, including in the heart and brain.

Does this research have real-world applications?

Yes. For example, one of our discoveries provides a clue as to why some healthy people, even high-performance athletes, suffer completely unexpected heart failure. When we were looking at how iASPP might be involved in the growth of tumors, we found that mice that lack this gene died prematurely of sudden cardiac death. Our studies showed that iASPP has a previously unknown role in controlling desmosomes—one of the main structures that help to “glue” heart muscle cells together. Mice lacking iASPP were prone to arrhythmogenic right ventricular cardiomyopathy (ARVC), a genetic, progressive heart condition that in humans mainly affects young adults. We have also found that deletion of ASPP2 is implicated in a neurodevelopmental disorder.

What do you find most exciting about your work?

Discovery. It's what drives science and scientists. For proteins to function correctly they need to be in the correct part of the cell, but nearly half of proteins that enter the nucleus don't have an identifiable nuclear localization signal. When we were looking at how the ASPP proteins get into the nucleus of the cell, it led us to the discovery of a protein code that defined a new nuclear import pathway we named RaDAR, which turns out to be the second most common mechanism we know of by which proteins are imported into the nucleus. Interestingly, the most frequently mutated site in p16 in melanoma



creates a RaDAR code, enabling the mutant protein to enter the nucleus. Right now, we're also looking at ways to exploit this pathway and study its implications in human disease.

Do you still have links with China?

I have a collaborative grant from Cancer Research UK (CRUK) with the Chinese Academy of Medical Sciences. I also helped CRUK establish its China Fellowships program and am a founding member of international review committees of the Chinese Academy of

Sciences and the Tsing Hua University and Peking University Schools of Life Sciences. I was also a Chair of the UK Chinese Life Science Society, which promotes collaborations between China and the UK in the life sciences. Right now my group is working with colleagues in China to identify the molecular causes of esophageal and stomach cancers—with a focus on cancer-causing pathogens—to improve treatment efficacy and develop cancer prevention strategies.

Are there any significant differences in cancer incidence between Asia and the Western world?

Gastric cancer is more common in Asia than the Western world; it is the second most common cancer in China. The largest contributor is a type of bacteria called *H. pylori*. It's a risk factor for gastric cancer and very prevalent throughout Asia. CagA is a protein produced by *H. pylori* and CagA-positive *H. pylori* induces gastric cancer by suppressing p53. It does this by hijacking the activating function of the tumor suppressor ASPP2 and triggering degradation of p53, one of our body's main defense mechanisms against tumor cell development. Our work on the role of ASPP proteins in tumor suppression pathways could lead to novel therapeutic strategies for prevention of this cancer.

Are women gaining ground in science professions?

In China we have a saying: 'women hold up half the sky'. So gender bias has never



been a big part of my life. Both my parents were doctors and, growing up, I never saw any difference in the way men and women were treated. The director of the Cancer Institute, Chinese Academy of Medical Sciences—China's most prestigious cancer institute, where I got my Master's degree—was a woman, and half the principal investigators were as well. In fact, when I came to the UK, I was rather surprised that the number of female scientists was very low compared to China in the 1980s. In the UK, there are now a lot of positive steps being taken through the Athena SWAN Charter, which encourages and recognizes commitment to advancing the careers of women in higher education and research. We need the very best scientists, male and female, to drive forward discoveries, and right now there aren't enough women making it to the highest levels.

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One of our discoveries provides a clue as to why some healthy people, even high-performance athletes, suffer completely unexpected heart failure.

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If you could be present at one scientific discovery, which one would it be?

Penicillin. It's truly a miracle drug and one of the greatest advances in therapeutic medicine. Prior to 1940, there was no effective treatment for infections like pneumonia, tuberculosis or rheumatic fever. People could develop blood poisoning from a cut or scratch and many would die. It's strange to think that my career followed penicillin's path from its discovery at St. Mary's Hospital in London, where I started my work with Ludwig, and then on to Oxford, where its therapeutic potential was recognized.

What do you like to do when you aren't working?

Sleep. But visiting art museums and galleries is a close second. When you think about it, art and science are very similar. They both try and answer big questions. Art is seen as creative and emotional; science, as methodical and rational. Both are a means of investigation—one in a laboratory, the other in a studio. Both involve long hours, tedious work and often it seems like nothing is working or coming out the way we hoped. But the end result—a breakthrough scientific discovery or great work of art—are both exciting, and very rare accomplishments.

You started the Ludwig Oxford Branch at the University of Oxford approximately nine years ago. What makes this a great location for the Branch's research?

The Oxford campus has grown to be one of the largest biomedical research centers



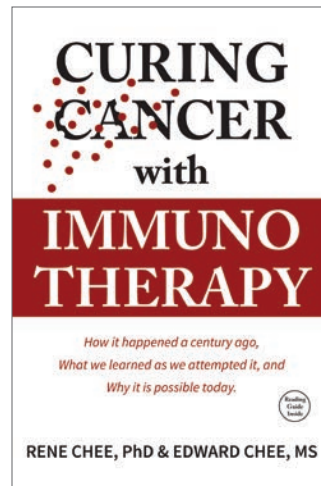
in Europe, and it is a vibrant and stimulating place to work. Recent additions include the neighboring Kennedy Institute for Rheumatology, which houses many leading immunologists, the Target Discovery Institute and the nearly-completed Big Data Institute. In terms of cancer research in particular, being in Oxford is great because it is one of the three major centers of research designated by Cancer Research UK, and the Biomedical Research Centre here facilitates fantastic clinical links. Oxford is also a perfect environment for students and postdocs to develop their careers. The whole university is within cycling distance, so there are no practical barriers to them visiting and working with other institutes. The Oxford college system also brings together people from different disciplines and offers extra support and opportunities.

BOOK REPORT

Rene Chee had been married barely a year and was working as a post-doctoral researcher in Lucy Shapiro's Stanford laboratory when the young bacteriologist discovered that the strange pains and neurological symptoms she'd been suffering for several months were caused by a golf ball-sized tumor pressing against her jaw. Diagnosed with advanced synovial sarcoma, Rene was put on a debilitating course of surgery, radiation and chemotherapy beginning in early 2008. But aware that her cancer was almost certain to recur (the tumor was advanced and burst open during surgery) she and her husband Edward began exploring unconventional therapies, trying out a number of them on Rene.

This was how they stumbled on Coley's toxins. Fielded more than a century ago by the New York physician William Coley, the treatment was the first immunotherapy ever recorded. Trouble was the toxins—actually, dead bacteria—are not approved as a therapy in the US. In any case, their oncologist was dubious and understandably declined to give Rene the therapy. But Lucy, who is a scientific advisor to Ludwig, got Rene and Edward in touch with Ludwig's former CEO Lloyd Old, who thenceforth became their advisor, friend, tutor and guide as they explored the nascent field of immuno-oncology. Lloyd had Rene's tumor sample analyzed and, finding that it expressed the NY-ESO-1 protein, saw to it that she received a cancer vaccine Ludwig and CRI were developing against that antigen. He also wanted her to receive the checkpoint inhibitor ipilimumab, which was in clinical development at the time. But she failed to qualify for the trial. That was when Lloyd told the couple it was time to try Coley's toxins.

Rene and Edward traveled to Mexico to get the bacteria and the initial treatments. Over the next couple of years, Rene received more than 200 infusions of the bacteria,



many delivered by Edward, and took other measures to excite an immune response against her tumors. Long story short: thanks to their informed persistence, Rene, who had a life expectancy considerably less than five years at diagnosis, remains alive and well today.

If you're interested in the long story, check out their book, *Curing Cancer with Immunotherapy*. Dedicated to Lloyd Old and another physician to whom they owe thanks, Ravin Agah, the book engagingly details their journey from devastation through desperation to apparent victory against an almost certainly lethal cancer. It also serves as a brief guide to others dealing with cancer who wish to take extraordinary measures to stay alive, and as a sort of Intro to Immunotherapy for nonscientists. The pair have included small, more technically detailed boxes and references for physicians and scientists who wish to delve deeper.

In a letter to Lucy, Rene and Edward called their book “a heartfelt tribute to Dr. Old,” who died in 2011. “Without him,” they wrote, “immunotherapy would not be where it is today. And without you helping us get in touch with him, [Rene] most likely wouldn't be alive today.”

If you could change one thing about how science works today, what would it be and why?



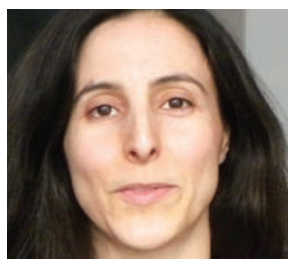
Limited funding and scarcity of permanent employment demand that scientists spend a disproportionate amount of time and resources pursuing their own sustainability. As a result, scientists are required to push quick and fashionable research projects, often neglecting significant and important questions.

DANIEL HIRSCHHORN-CYMERMAN
Ludwig MSK



I would change funding system because the current grant-based system is broken. One possible scenario would be to combine stable federal funding with a peer-reviewed grant system to encourage young scientists and the most competitive laboratories. This may improve the situation of young scientists, offering them support and stability.

NIKOLAI KHODAREV
Ludwig Chicago



Transparency is a key ingredient of good science and some processes should be available and open to the whole scientific community: editorial revision of manuscripts, funding decisions, negative data and protocol handicaps and evaluation of candidates. While science forums have helped, there is still a lot more to be done to make science more objective and efficient.

MONICA GORDON-ALONSO
Ludwig Brussels

Required reading

Ludwig Brussels

Nature Communications 2016 July 22

A major secretory defect of tumour-infiltrating T lymphocytes due to galectin impairing LFA-1-mediated synapse completion.

Petit AE, Demotte N, Scheid B, Wildmann C, Bigirimana R, Gordon-Alonso M, Carrasco J, Valitutti S, Godelaine D, van der Bruggen P.

Ludwig Chicago

Scientific Reports 2016 October 24

Basal tumor cell isolation and patient-derived xenograft engraftment identify high-risk clinical bladder cancers.

Skowron KB, Pitroda SP, Namm JP, Balogun O, Beckett MA, Zenner ML, Fayanju O, Huang X, Fernandez C, Zheng W, Qiao G, Chin R, Kron SJ, Khodarev NN, Posner MC, Steinberg GD, Weichselbaum RR.

Science Advances 2016 June 24
Genomic agonism and phenotypic antagonism between estrogen and progesterone receptors in breast cancer.

Singhal H, Greene ME, Tarulli G2, Zarnke AL, Bourgo RJ, Laine M, Chang YF, Ma S, Dembo AG, Raj GV, Hickey TE, Tilley WD, Greene GL.

Ludwig Johns Hopkins

Science Translational Medicine 2016 July 6

Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer.

Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, Silliman N, Tacey M, Wong HL, Christie M, Kosmider S, Skinner I, Wong R, Steel M, Tran B, Desai J, Jones I, Haydon A, Hayes T, Price TJ, Strausberg RL, Diaz LA Jr, Papadopoulos N, Kinzler KW, Vogelstein B, Gibbs P.

Ludwig Lausanne

Cell Reports 2016 November 9 (Epub ahead of print)

Macrophage ontogeny underlies differences in tumor-specific education in brain malignancies.

Bowman RL, Klemm F, Akkari L, Pyonteck SM, Sevenich L, Quail DF, Dhara S, Simpson K, Gardner EE, Iacobuzio-Donahue CA, Brennan CW, Tabar V, Gutin PH, Joyce JA.

Cell Reports 2016 September 13

STAT3 and STAT6 signaling pathways synergize to promote cathepsin secretion from macrophages via IRE1 activation.

Yan D, Wang HW, Bowman RL, Joyce JA.

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T Cell factor 1-expressing memory-like CD8(+) T cells sustain the immune response to chronic viral infections.

Utzschneider DT, Charmoy M, Chennupati V, Pousse L, Ferreira DP, Calderon-Copete S, Danilo M, Alfei F, Hofmann M, Wieland D, Pradervand S, Thimme R, Zehn D, Held W.

Ludwig Melbourne

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Ludwig MIT

Nano Letters 2016 October 12

Magnetically actuated protease sensors for in vivo tumor profiling.

Schuerle S, Dudani JS, Christiansen MG, Anikeeva P, Bhatia SN.

Ludwig MSK

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An essential role for the IL-2 receptor in Treg cell function.

Chinen T, Kannan AK, Levine AG, Fan X, Klein U, Zheng Y, Gasteiger G, Feng Y, Fontenot JD, Rudensky AY.

Cell 2016 August 11

Immune monitoring of trans-endothelial transport by kidney-resident macrophages.

Stamatiades EG, Tremblay ME, Bohm M, Crozet L, Bisht K, Kao D, Coelho C, Fan X, Yewdell WT, Davidson A, Heeger PS, Diebold S, Nimmerjahn F, Geissmann F.

Ludwig Oxford

Cancer Research 2016 November 1

Nutritional stress induced by tryptophan-degrading enzymes results in ATF4-dependent reprogramming of the amino acid transporter profile in tumor cells.

Timosenko E, Ghadbane H, Silk JD, Shepherd D, Gileadi U, Howson LJ, Laynes R, Zhao Q, Strausberg RL, Olsen LR, Taylor S, Buffa FM, Boyd R, Cerundolo V.

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Elliott PR, Leske D, Hrdinka M, Bagola K, Fiil BK, McLaughlin SH, Wagstaff J, Volkmar N, Christianson JC, Kessler BM, Freund SM, Komander D, Gyrd-Hansen M.

PLoS Genetics 2016 September 2

Gain- and loss-of-function mutations in the breast cancer gene GATA3 result in differential drug sensitivity.

Mair B, Konopka T, Kerzendorfer C, Sleiman K, Salic S, Serra V, Muellner MK, Theodorou V, Nijman SM.

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Zak J, Vives V, Szumska D, Vernet A, Schneider JE, Miller P, Slee EA, Joss S, Lacassie Y, Chen E, Escobar LF, Tucker M, Aylsworth AS, Dubbs HA, Collins AT, Andrieux J, Dieux-Coeslier A, Haberlandt E, Kotzot D, Scott DA, Parker MJ, Zakaria Z, Choy YS, Wiczkorek D, Innes AM, Jun KR, Zinner S, Prin F, Lygate CA, Pretorius P, Rosenfeld JA, Mohun TJ, Lu X.

Ludwig San Diego

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An LXR-cholesterol axis creates a metabolic co-dependency for brain cancers.

Villa GR, Hulce JJ, Zanca C, Bi J, Ikegami S, Cahill GL, Gu Y, Lum KM, Masui K, Yang H, Rong X, Hong C, Turner KM, Liu F, Hon GC, Jenkins D, Martini M, Armando AM, Quehenberger O, Cloughesy TF, Furnari FB, Cavenee WK, Tontonoz P, Gahman TC, Shiao AK, Cravatt BF, Mischel PS.

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Broad histone H3K4me3 domains in mouse oocytes modulate maternal-to-zygotic transition.

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Ludwig Stanford

Nature Genetics 2016 October
Lineage-specific and single-cell chromatin accessibility charts human hematopoiesis and leukemia evolution.

Corces MR, Buenrostro JD, Wu B, Greenside PG, Chan SM, Koenig JL, Snyder MP, Pritchard JK, Kundaje A, Greenleaf WJ, Majeti R, Chang HY.

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Depleting dietary valine permits nonmyeloablative mouse hematopoietic stem cell transplantation.

Taya Y, Ota Y, Wilkinson AC, Kanazawa A, Watarai H, Kasai M, Nakauchi H, Yamazaki S.

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Hematopoietic stem cell transplantation in immunocompetent hosts without radiation or chemotherapy.

Chhabra A, Ring AM, Weiskopf K, Schnorr PJ, Gordon S, Le AC, Kwon HS, Ring NG, Volkmer J, Ho PY, Tseng S, Weissman IL, Shizuru JA.

Ludwig Stockholm

Nature Genetics 2016 November
Analysis of allelic expression patterns in clonal somatic cells by single-cell RNA-seq.

Reinius B, Mold JE, Ramsköld D, Deng Q, Johnsson P, Michaëlsson J, Frisén J, Sandberg R.

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Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes.

Segerstolpe Å, Palasantza A, Eliasson P, Andersson EM, Andréasson AC, Sun X, Picelli S, Sabirsh A, Clausen M, Bjursell MK, Smith DM, Kasper M, Ämmälä C, Sandberg R.

Ludwig Uppsala
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