LUDWIG LINK

FEBRUARY 2018

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

LUDWIG LINK
ludwigcancerresearch.org FEBRUARY 2018

LETTER

Good news is the best news to report, and this first Ludwig Link of 2018 does not disappoint.

Aside from the usual slew of awards and distinctions for our stellar scientists, we welcome two new members to Ludwig's Scientific Advisory Committee—W.K. Alfred (Al) Yung of MD Anderson Cancer Center and Victor Velculescu of Johns Hopkins. You can learn a little about them and their work on page 8.

Ludwig scientists have been as prolific as ever on the research front. You'll read here about how breast tumors turn a toxin into an asset for their malignant growth, and a new approach to screening that could improve the early detection of a cancer that's hard to diagnose and even harder to treat. We also have on page 6 a short article on the two-day symposium held at Ludwig Oxford to celebrate the Branch's 10th anniversary. (Read it and you'll discover a talent Director Xin Lu has so far hidden from the Ludwig community.)

Our interview with John Notter—real estate developer, philanthropist, entrepreneur and Chair of Ludwig's Board of Directors—starts on page 19, and we highly recommend it. Finally, we ask our young researchers about their views on growing access to preprints of research papers. See what they think on page 24.

We wish you all a happy and productive new year!

Sincerely,

Rachel Reinhardt
Vice President for Communications

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On the cover: Ludwig Oxford's Lisa Schlicher, left, with Branch alum Katrin Bagola

Web Cavenee
Ludwig Institute

FOR BRAINY DISTINCTION

Web Cavenee, the Ludwig Intsitute's Director of Strategic Alliances in Central Nervous System Cancers, received the Lifetime Achievement Award from the Society for Neuro-Oncology (SNO). Web has made many landmark discoveries in cancer research, but is probably best known for providing the first direct genetic evidence for the existence of tumor suppressor genes. Over the past two decades, he has methodically unraveled the genetics and molecular biology of the brain cancer glioblastoma multiforme (GBM), exploring the mechanisms that drive the growth, invasiveness and drug resistance of GBM tumors. Web is also an architect and leader of GBM AGILE, a pioneering global initiative to accelerate and refine the clinical development of new GBM therapies. The initiative will permit researchers to tailor their treatments to the molecular profiles of GBM tumors and alter treatment approaches midstream as relevant information about patients, the cancer and its treatment come to light. In addition to recognizing Web's extraordinary scientific achievements, SNO noted his mentorship of many leaders in the brain cancer field. Web was the guest of honor at SNO's 22nd Annual Meeting on November 18 in San Francisco.

FOR BREATHTAKING DISCOVERY

The Royal Society has awarded Professor Sir Peter Ratcliffe of Ludwig Oxford the Buchanan Medal for his groundbreaking research on the mechanisms by which cells sense and signal changes in oxygen levels—a capability essential to life and a critical factor in human ailments ranging from cancer to heart disease and stroke. A nephrologist by training, Peter discovered how a master regulator of gene expression that plays a key role in oxygen sensing, hypoxia inducible factor-1, is activated and deciphered the complex signaling networks that orchestrate the hypoxia response. Peter's work continues to explore various aspects of oxygen sensing, including the multiple pro- and anti-tumorigenic effects of the hypoxia pathway and how these processes drive tumor heterogeneity and drug resistance. Established in 1897, the Buchanan Medal is awarded annually by the Royal Society for distinguished contributions to the biomedical sciences. Peter received the medal and the accompanying gift at the Society's Anniversary Day meeting on November 30.

Peter Ratcliffe
Ludwig Oxford

FOR DISSECTING DIVISION

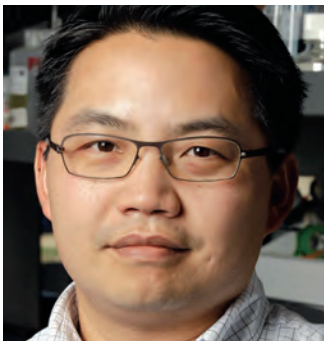
The Women in Cell Biology (WICB) Committee of the American Society for Cell Biology (ASCB) has awarded Ludwig San Diego's Karen Oegema the 2017 Mid-Career Award for Excellence in Research. The award recognized Karen for her exceptional contributions to cell biology. Karen is an expert in high-content phenotypic profiling, which she uses to study cell division mechanisms and how cell-type specific variation in the cell division machinery can be leveraged in cancer therapy. Karen has, evidently, also distinguished herself as a mentor: one of her postdocs, Julie Canman, won the Junior Award for Excellence in Research from WICB. Both received their awards during the 2017 ASCB|EMBO Meeting in Philadelphia on December 5.

Karen Oegema
Ludwig San Diego

Arlene Sharpe
Ludwig Harvard

FOR PIONEERING DISCOVERY

Ludwig Harvard's Arlene Sharpe was one of five scientists honored at the 2017 Warren Alpert Foundation Prize Symposium at Harvard Medical School for transformative discoveries in the field of cancer immunology. These researchers helped illuminate the interplay between cancer and the immune system. Their findings identified mechanisms by which cancers evade the immune system, transformed the understanding of cancer progression and treatment, and led to the development of cancer immunotherapies, most notably checkpoint blockade. Arlene's discoveries helped define the biological functions of the CTLA-4 and PD-1 pathways that inhibit T cell responses. Many tumor cells exploit the PD-1 pathway to evade immune surveillance. The honorees, including former Ludwig MSK Director James Allison, shared a $500,000 prize and were recognized at a day-long symposium on October 5 at Harvard Medical School. The Warren Alpert Foundation, in association with Harvard Medical School, honors "trailblazing scientists whose work has led to the understanding, prevention, treatment or cure of human disease."



Howard Chang
Ludwig Stanford

FOR EPIGENOMIC DISCOVERY

Howard Chang, the Virginia and D.K. Ludwig Professor of Cancer Genomics at Stanford, was elected to the National Academy of Medicine (NAM) in October. His research probes how the chemical—or epigenetic—tagging of DNA and its protein scaffolding affects the fate and function of cells. Such epigenetic control determines which stretches of the genome are expressed at any given time and is essential to every biological process from embryonic development to tumor metastasis. In exploring genome regulation, Howard and his colleagues also discovered long noncoding RNAs and have since extensively characterized their biological roles. Election to the NAM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have "demonstrated outstanding professional achievement and commitment to service."

FOR MICROENVIRONMENTAL STUDIES

Ludwig Lausanne's Johanna Joyce received the Swiss Bridge Foundation Award, which is given to researchers aged 45 or younger to support cutting-edge research that improves our understanding of cancer. The award will help advance Johanna's continuing exploration of the tumor microenvironment, particularly her group's new studies on the role of immune cells known as neutrophils in the microenvironment of brain metastases. Two projects were selected for the Bridge Award this year and each recipient will receive CHF 250,000. A ceremony honoring both recipients was held in Zurich on October 25th. Johanna also received the first Pandolfi Award for Women in Cancer Research, named after Pier Paolo Pandolfi, director of the Cancer Center at Beth Israel Deaconess Medical Center (BIDMC) and an investigator at Ludwig Harvard. She received her award and gave a special lecture at the 10th Annual BIDMC Cancer Symposium in Boston on November 8.

Johanna Joyce
Ludwig Lausanne

Videos of the presentations have been uploaded to the Ludwig intranet. Sign in to view them all.

Oxford Branch Director Xin Lu speaks at the symposium

A DECADE OF LUDWIG OXFORD

Ludwig Oxford celebrated its 10th anniversary in September with a two-day symposium at Keble College, Oxford. Attendees from across Ludwig labs got to share their research and exchange ideas with their peers, and many enjoyed meeting some Ludwig colleagues in person for the first time.

"It's very exciting to see the entire family coming together," said Ludwig Scientific Director Chi Van Dang. Ludwig President and CEO Ed McDermott noted that the symposium provided "an opportunity to strengthen bonds that exist already, and to form new ones."

Ludwig scientists and colleagues gave talks on both basic and translational research. Presentations covered the contributions of amino acid metabolism to tumor immune escape mechanisms and the role of extrachromosomal oncogene amplification in tumor evolution. Cancer cell metabolism and the tumor microenvironment were also hot topics at the symposium. Talks on the subject ranged from discussions of MYC and the metabolic vulnerabilities of cancer to the role p53 plays in adaptations to metabolic stress.

A session on gene regulation and epigenetics included presentations on

the connection of hypoxia to cancer and collecting epigenetic information from circulating tumor DNA. Much of the focus in cancer therapeutics was on immunotherapy, but presenters also discussed stem cell therapy and the improvement of responses to radiotherapy.

Ludwig's presence in the UK dates back to 1971, when the first Branch was established at Royal Marsden in Sutton. Since then, Ludwig Branches have called Cambridge and London home. In 2007, Ludwig formed a new partnership with the University of Oxford, establishing a Branch at the Nuffield Department of Clinical Medicine, within the Medical Sciences Division. Xin Lu has directed the Branch since its inception.

Today, Ludwig Oxford is a thriving scientific enterprise with more than 100 staff members and scientists. The Branch has close ties to the rest of the scientific community at Oxford, including members based at the Target Discovery Institute, and collaborations with many other basic and translational researchers in the broader Oxford community.

The symposium closed with a party at the Weston Library in Oxford, where the crowd was treated to live music and Xin led attendees in Scottish Ceilidh dancing. Xin—not only a dance instructor but an inspiring leader—recalled the team spirit that went into creating the Branch. "My thanks go to all past and present members of Ludwig," she said at the meeting. "It's your party!"

Many researchers at the symposium enjoyed the vibrant scientific discussions they had with colleagues during and after presentations.

Researchers at the meeting relished sharing their data and, in many cases, meeting Ludwig colleagues in person for the first time.

Talks touched on a spectrum of subjects central to cancer research —from cancer metabolism to epigenetics to immunotherapy.

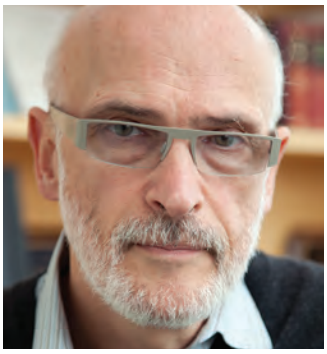
NEW ADVISORS

Ludwig appointed W.K. Alfred Yung and Victor Velculescu to its Scientific Advisory Committee (SAC) in August. A clinical oncologist, researcher and cancer survivor, Al is a professor of neuro-oncology and cancer biology and the Margaret and Ben Love chair of clinical cancer care at MD Anderson, where he is a member of the executive committee of the MD Anderson Moon Shot program. He also advised the National Cancer Moonshot Initiative led by former Vice President Joe Biden. Al's research has long focused on developing new therapeutic approaches to treating glioblastoma multiforme (GBM). In 1997, he and his colleagues discovered that the PTEN gene is frequently deleted or mutated in GBM and that this often drives progression of the brain tumor. More recently, his lab has explored the targeting of the PI3 kinase pathway to treat GBM. He is a member of the executive committee of GBM AGILE, a global collaboration to test and develop new brain cancer treatments, and a special advisor to the CEO of the National Brain Tumor Society. Earlier in his career, Al led the study that paved the way for FDA approval of temozolomide (Temodar) for GBM and the registration study that preceded FDA approval of the drug bevacizumab (Avastin) for recurrent GBM.

Victor is co-director of cancer biology and professor of oncology and pathology at the Johns Hopkins Kimmel Cancer Center. Victor helped pioneer the global analysis of cellular gene expression—or transcriptomics—and completed the first such analysis of a eukaryotic cell. In collaboration with Ludwig Johns Hopkins researchers, he performed the first sequence analysis of the coding genome in human cancers, identifying key genes and pathways dysregulated in breast, colorectal, brain, ovarian and pancreatic cancers. These studies broadly illuminated the mutational landscape of malignancies and have shaped the design of new therapies and our current understanding of cancer initiation and evolution. Victor and his colleagues have also developed technologies for detecting and sequencing vanishingly rare traces of DNA shed by cancer cells. Such technologies, known as liquid biopsies, are among the most exciting developments in cancer research and promise to revolutionize the diagnosis and treatment of many malignancies. Victor has been a director on the board of the American Association of Cancer Research and is a co-founder of Personal Genome Diagnostics, a company that develops technologies to identify and characterize unique genomic alterations in human cancers.

W.K. Alfred Yung
Ludwig Scientific Advisory Committee

Victor Velculescu
Ludwig Scientific Advisory Committee



Alexander Rudensky
Ludwig MSK

DEADLY HEALING

Alexander Rudensky and his colleagues reported in *Cell* a couple of years ago the discovery of a novel function of regulatory T cells (Tregs), one mechanistically distinct from their vitally important suppression of immune responses. Tregs, they discovered, support the repair of tissue, a function mediated by a protein named amphiregulin. In October, Alexander and his colleagues reported in the *Journal of Experimental Medicine* that amphiregulin production by Tregs and other types of T cells that flood into tumors also contributes significantly to lung cancer progression. They show in their paper that the loss of amphiregulin across T cell types has no effect on the immune function of the T cells in mice. But such loss does significantly retard the growth of transplanted lung tumors. Amphiregulin produced by T cells appears to act on other noncancerous cells present within the tumor's microenvironment—including immune cells, such as macrophages, and noncancerous epithelial cells—to promote tumor growth.

LEMONS TO LEMONADE

Rapidly proliferating cancer cells generate vast quantities of ammonia, a toxic, nitrogenous byproduct of metabolism. Ordinarily, ammonia is sent to the liver, detoxified and discarded as urine. But tumors have poor blood supply, so ammonia tends to accumulate in them. Now a team led by Ludwig Harvard investigator Marcia Haigis has discovered that breast tumors not only tolerate the noxious stuff but have come to depend on it to a notable extent. Their study, reported online in *Science* in October, reveals that ammonia in the microenvironment of tumors feeds the protein synthesis essential to cancer cell proliferation. This, it turns out, is because breast tumors adapt to recycle the toxic byproduct as a component of amino acids—primarily glutamate, but also others like aspartate and proline. Around 20% of the cellular glutamate pool in breast cancer cells contains such recycled nitrogen. Inhibiting glutamate dehydrogenase, an enzyme key to this nitrogen scavenging, stunts breast tumors in mice. Providing ammonia boosts their growth. Marcia and her team are now investigating the possible therapeutic applications of their discovery.

Marcia Haigis
Ludwig Harvard

LASTING SYNERGY

Jedd Wolchok
Ludwig MSK

A team led by Ludwig MSK's Jedd Wolchok reported in an October *New England Journal of Medicine* study that the long term survival of patients with previously untreated advanced melanoma is better when they're treated with nivolumab alone or a combination of the checkpoint blockade antibodies nivolumab and ipilimumab than it is with ipilimumab alone. The treatment involves an infusion of two different antibodies that, in distinct ways, release the brakes the body imposes on the immune system's cytotoxic T cells, boosting their ability to seek and destroy malignant cells. Specifically, ipilimumab and nivolumab block the inhibitory checkpoints CTLA-4 and PD-1, respectively. In this study, 58% of patients given the combination therapy were alive three years later, while 52% given nivolumab alone and 34% of those who got ipilimumab alone were alive at that time point. The study was not powered to detect a difference between the two nivolumab-containing arms but subset analyses showed numerically higher survival for the combination, especially in patients with tumors having low PD-L1 expression. The combination therapy is associated with significant side effects: 59% of patients receiving it had serious (Grade 3 or 4) treatment-related adverse events. But the analysis also found that discontinuing combination therapy after a median of three doses did not compromise its long-term benefits.

IDENTITY ON THE BALANCE

Macrophages come in two distinct flavors, known as M1 and M2. The former engulf and kill cancer cells, while the latter, which otherwise help with healing, can provide a variety of services that help tumors thrive and metastasize. Researchers are, of course, rather interested in figuring out how to convert M2 macrophages in tumors into M1s. In a September paper in *Nature Immunology*, Ludwig Lausanne's Ping-Chih Ho and his team report that α-ketogluterate—a key metabolite in the reactions that generate energy for the cell, and a precursor to the amino acid glutamate—can play a critical role in this dynamic. Levels of glutamate relative to succinate, another metabolite involved in energy production (and one that promotes inflammation) can influence whether macrophages assume an M1 or M2 form. A high α-ketogluterate/succinate ratio drives the generation of M2s, while a low ratio favors M1s. This suggests that the well characterized biochemical processes that control α-ketogluterate and succinate production could be targeted for cancer immunotherapy.

Ping-Chih Ho
Ludwig Lausanne

Jacqueline Lees
Ludwig MIT

Michael Hemann
Ludwig MIT

EXPORT CONTROL

In a study published in October in *Cancer Cell*, researchers at MIT led by Jacqueline Lees, the Virginia and D.K. Ludwig Professor of Cancer Research, and Michael Hemann of Ludwig MIT, reported a potential new drug target for the brain cancer glioblastoma multiforme (GBM). Jacqueline and her colleagues show how an enzyme expressed at high levels in GBM cells, PRMT5, is involved in a special type of gene splicing of importance to cancer cell proliferation and survival. The enzyme promotes the removal of noncoding elements of gene sequences (known as introns) from messenger RNA transcripts. But PRMT5 is especially important in snipping out introns deliberately retained in RNA transcripts to control their expression; as long as they're there, the transcript can't be exported out of the nucleus for protein synthesis. These retained introns, the researchers show, primarily regulate transcripts encoding proteins that drive cell proliferation—which are abundant in cancer cells. They also demonstrate that an existing PRMT5 inhibitor stalls the growth of cultured GBM cells and brain tumors implanted under the skin of mice. However, it does not work as well in tumors located in the mouse brain because it fails to traverse the blood-brain barrier. Jacqueline and her colleagues hope to develop inhibitors that will.

AXIS OF EVIL

Ludwig Lausanne's Camilla Jandus and her colleagues reported in a September paper in *Nature Communications* a novel cellular axis of immune evasion that is exploited by cancer cells. This rather complicated axis involves immune cells known as group 2 innate lymphoid cells (ILC2s), which are abundant and activated in patients diagnosed with acute promyelocytic leukemia (APL). The cells respond to a metabolite known as prostaglandin D2 (PGD2), and to a protein named B7H6, both of which are made in quantity by APL cells. Both molecules prompt ILC2s to secrete an immune factor known as interleukin-13 (IL-13)—which, in turn, switches on monocytic myeloid-derived suppressor cells (M-MDSCs). These cells dramatically inhibit the immune system's killer T cells, which would otherwise attack the leukemic cells. Targeting each of the molecules involved in this axis restored anti-cancer immunity and extended the survival of leukemic mice. Notably, antibodies against IL-13 and inhibitors of PGD2 are already in clinical use, while antibodies that block B7H6 are in clinical development. Most important—while APL is, fortunately, a curable cancer—there's evidence that this newly discovered immunosuppressive axis also operates in other cancers that are currently untreatable.

Camilla Jandus
Ludwig Lausanne

Michelle Monje
Ludwig Stanford

TUMOR TIMEOUT

High grade gliomas are extremely aggressive and difficult to treat. In a September *Nature* paper researchers led by Ludwig Stanford's Michelle Monje reported that the growth of many gliomas might be stalled by cutting off their access to neuroligin-3, a protein released by firing neurons. The team extracted tumor cells from patients with high-grade gliomas and inserted them into the brains of mice lacking the gene that produces neuroligin-3. In these mice, none of the tumors grew for four and a half months, until some evolved to circumvent the dependency. This did not happen with patient-derived breast cancer brain metastases that had been transplanted into the brains of the same mice. Exposure to neuroligin-3, they found, activates multiple signaling pathways and drives the expression of genes involved in cell division–a finding that underscores how important the microenvironment is to tumor growth. Michelle and her colleagues also discovered that a protein-snipping enzyme called ADAM10 triggers the release of neuroligin-3. Inhibiting ADAM10 with two agents, one of which is already in human trials, disrupted neuroligin-3 release and inhibited the growth of gliomas in the mouse model. Though the strategy arrests rather than destroys gliomas, it could be used as an adjunct treatment along with other therapies.

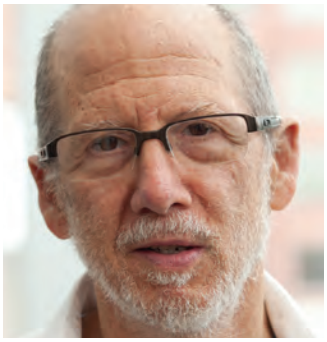
BETTER TOGETHER

Breast tumors are routinely analyzed for the presence of the estrogen and progesterone receptors (ER and PR), which are biomarkers for patient prognosis and response to endocrine therapies. However, there is some debate about whether to target PR with activating or inhibiting drugs, or to combine these drugs with antiestrogen therapies, like tamoxifen. A study led by Ludwig Chicago Co-director Geoffrey Greene and published in September in *Oncotarget* found that the two receptors not only communicate with each other in breast tumor cells, but that the specific inhibition of both results in significant regression of ER+/PR+ tumors in a preclinical animal model. PR comes in two isoforms, PRA and PRB, which are variably expressed in breast tumor cells. Geoffrey and his team show that both forms of PR recognize similar but distinct DNA sites to differentially reprogram estrogen activity to either support or suppress tumor progression. Activation of PRA induces malignant processes and gene expression programs that correlate with poorer patient survival, and PR antagonists inhibit the growth of breast tumors expressing higher levels of PRA. The study suggests that combinations of ER antagonists with PR antagonists should be considered as possible therapies for ER+/PR+ breast cancers.

Geoffrey Greene
Ludwig Chicago

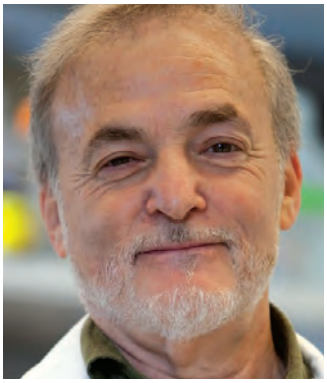
IN SANGUIS VERITAS

The fourth leading cause of cancer death in the United States, pancreatic cancer, frequently presents no symptoms before reaching an advanced stage, which largely accounts for its lethality. Convenient tests to detect the disease early could significantly improve patient survival, and liquid biopsies—which detect rare molecular markers and DNA shed by tumors into the blood—could be the answer. In a September paper in the *Proceedings of the National Academy of Sciences*, researchers led by Ludwig Johns Hopkins Co-director Bert Vogelstein and Anne Marie Lennon, a colleague at the university, reported that screening for both DNA and protein markers is twice as accurate at detecting early stage pancreatic cancer as the use of DNA markers alone. Searching for just the mutated KRAS gene—a common driver of pancreatic tumors—the researchers identified 30% of 221 patients with early stage cancer. When the team looked only for the protein biomarker CA19-9 in the blood of this cohort, they found it in 49% of the patients. But when they combined KRAS mutations, CA19-9 and three other protein biomarkers in a test, they accurately identified pancreatic cancer in 64% of the patients.



Bert Vogelstein
Ludwig Johns Hopkins

TIMING IS EVERYTHING



Stephen Baylin
Ludwig Johns Hopkins

A team of researchers led by Ludwig Johns Hopkins Stephen Baylin reported in a September paper in *Cancer Cell* that redistribution of chemical tags on DNA (epigenetic marks), which control gene expression, could be among the earliest triggers of lung cancer induced by cigarette smoke. The team mimicked the effect of tobacco smoke on cultured bronchial cells by bathing them in a liquid form of cigarette smoke daily for 10 to 15 months—comparable to smoking one to two packs of cigarettes a day for 20 to 30 years. Within three months the cells had a two- to four-fold spike in an enzyme that suppresses the expression of certain genes. This was followed by a two- to three-fold increase in another that silences tumor suppressor genes by marking cytosine, a base in their coding DNA sequence, with a molecule known as a methyl group. This epigenetic methylation continued to influence gene expression 10 and 15 months later. When Stephen and his team mutated the KRAS gene, which often drives lung cancers, the smoke-exposed cells only became cancerous if the methylation had already occurred, typically after 10 months of smoke exposure. Previous studies have shown that the abnormal DNA methylation they detected is partially reversed after ten years of no smoking.

WEIGHTY MATTERS

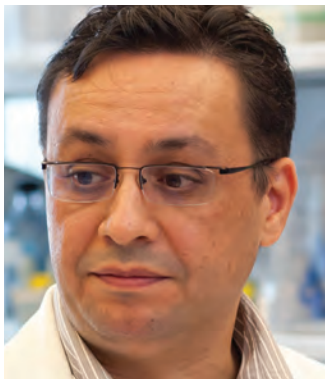
According to an October report from the Centers for Disease Control and Prevention, overweight- and obesity-related cancers now account for an estimated 40% of all US cancer cases. The link between obesity and cancer risk is clear. Less clear is how one leads to the other. A team led by Ludwig Lausanne's Johanna Joyce reported in a paper published in *Nature Cell Biology* in August that obesity significantly alters the immune cell landscape of the lungs in a manner that promotes metastasis of breast cancer to that organ. Their studies in a mouse model of breast cancer showed that obesity induces an abnormal accumulation of immune cells known as neutrophils in the lungs of mice that supports increased metastasis of breast cancer cells to the site. The effect is dependent on the immune factors IL5 and GM-CSF, which promote inflammation. Notably, Johanna and her team found that weight loss is sufficient to reverse the metastatic effect and reduce levels of both factors in mice and in humans.

Johanna Joyce
Ludwig Lausanne

ECOLOGICAL DIVERSITY

A team of researchers led in part by Ludwig MSK's Alexandra Snyder and including Taha Merghoub examined the metastatic tumors of a woman with high-grade serous ovarian cancer who had received multiple regimens of chemotherapy. After therapy was stopped, some of her tumors were regressing, while others continued to grow. Their analysis, published in August in *Cell*, details the distinct tumor microenvironments that can be found in a single cancer patient. Alexandra and her colleagues show that, unlike the patient's progressing tumors, regressing and stable metastases were infiltrated by helper and killer T cells that recognized specific cancer antigens and retained a memory of their identity that can be measured in the blood. They also expressed immune factors and signaling molecules that stimulate immune responses. Cells of the progressing tumors, meanwhile, engaged immunosuppressive signaling pathways, like the Wnt pathway. The findings explain in part the varied responses of metastatic lesions following therapy. An engaging video abstract of the study, written, scored and narrated by Alexandra and the patient herself, is available on YouTube.

Alexandra Snyder
Ludwig MSK



Taha Merghoub
Ludwig MSK

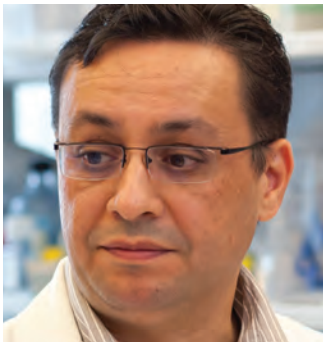
Frank Furnari
Ludwig San Diego

A NEFARIOUS CROSSTALK

Cancer cells mutate and diversify rapidly as tumors evolve, and all that cellular heterogeneity contributes in a variety of ways to drug resistance. This is certainly true of glioblastoma multiforme (GBM), which invariably evades drugs that target the enzymatic activity of a signaling protein known as the EGF receptor (EGFR). When overactive, EGFR drives a number of cancers. In a paper published in advance online in July in *Genes & Development*, a team led by Ludwig San Diego's Frank Furnari reported a novel way in which different subtypes of cells in GBM tumors that either express the normal form of the EGFR or a mutant known as EGFRvIII interact to induce such resistance. They report that EGFRvIII cells in GBM tumors secrete a signaling molecule known as IL-6, which activates—in both those cells and in cells expressing the normal EGFR—a signaling cascade mediated by a protein called NF-κB. This cascade induces the expression of survivin, a protein that promotes cell survival, dulling the sensitivity of GBM tumors to EGFR inhibiting drugs. Frank and colleagues show that both NF-κB and survivin are found at high levels in tumors derived from patients. They also report that the pharmacological inhibition of survivin expression by a class of drugs currently under development restores, in the culture dish and in mice, the sensitivity of GBM tumors to EGFR inhibitors.

Sadna Budhu
Ludwig MSK

Jedd Wolchok
Ludwig MSK



Taha Merghoub
Ludwig MSK

TOUCH CONTROL

A team of researchers led by Ludwig MSK's Sadna Budhu, Jedd Wolchok and Taha Merghoub reported in *Science Signaling* in August the mechanism by which regulatory T cells (Tregs) suppress the anti-tumor activity of killer T cells in melanoma tumors. The team developed three dimensional cultures of murine melanoma tumors for their experiments and showed that their cultures, grown in a gel, recapitulate Treg-mediated immune suppression of killer T cells seen in mouse models of these tumors. Further experiments and intravital-microscopic imaging revealed that this suppression requires close proximity or direct contact between killer T cells and Tregs. It also depends on the Tregs having an immune factor called TGF-β bound to their surfaces. The researchers found that the interactions of Tregs with killer T cells is associated with lower amounts of enzymes these cells use to kill target tumor cells. This interaction also increases expression of the PD-1 receptor—a surface protein that renders them non-functional when activated. This suggests that drugs that block Treg access to TGF-β—a number of which are already in development—could significantly boost the efficacy of cancer immunotherapies.

UNFOLDING INSIGHT

Every time a cell divides, it needs to replicate its 46 chromosomes and partition one copy to each daughter cell. Errors in this chromosome partitioning process lead to aneuploidy—an improper number of chromosomes—which is a hallmark of most cancers. In an August issue of *The EMBO Journal*, a team led by Ludwig San Diego's Kevin Corbett describes how a key checkpoint pathway controlling chromosome partitioning is turned on and off by the oncogene TRIP13. The researchers combined X-ray crystallography, cross-linking mass spectrometry, and functional assays in collaboration with Ludwig San Diego's Don Cleveland, to reveal the molecular details of how TRIP13 disassembles a protein complex called the "mitotic checkpoint complex". They discovered that TRIP13 partially unfolds one checkpoint complex protein, MAD2, to release it from its binding partners and re-set the protein for a new round of checkpoint complex assembly. Because disruption of the TRIP13 gene predisposes patients to cancer, even though many cancers also show a high-level of TRIP13 overexpression, a molecular understanding of this enigmatic protein's function is key to determining its contributions to cancer. This work, part of an ongoing collaboration between the Corbett and Cleveland labs, uncovers a key piece of that puzzle.

Rakesh Jain
Ludwig Harvard

Kevin Corbett
Ludwig San Diego

Don Cleveland
Ludwig San Diego

DIVERGENT ROADS

A study led by Rakesh Jain of Ludwig Harvard and published in *Science* in July upends the established model for the spread of colorectal cancers: that they invariably move from the primary tumor to nearby lymph nodes and from there to distant organs. Rakesh and his team applied a genotyping assay they've developed to more than 200 tissue samples from 17 patients to trace the pathways of their cancer metastases. The researchers found that both the lymph node and distant metastases in 35% of patients had developed from the same cells in the primary tumor. In the remaining 65%, however, cells from distant metastases differed from those in the lymph nodes but matched different cell types within the primary tumor. Their findings indicate that colorectal cancer spreads in at least two distinct ways—via the local lymph nodes and, separately, directly out of the primary tumor. It also suggests that lymph node metastases may be more than just a waystation for migrating cancers; they may, in fact, indicate the presence of an especially aggressive primary tumor. The team is investigating whether the two patterns of metastasis result in different outcomes for patients.

GOING VIRAL

Dmitriy Zamarin
Ludwig MSK

Patients are being enrolled in a Ludwig sponsored phase I/II clinical trial combining virus-based cancer immunotherapy with checkpoint blockade. The study led by Ludwig MSK investigator Dmitriy Zamarin, is investigating the safety and the biologic and anti-tumor activity of ONCOS-102, an engineered human adenovirus (a relative of the cold virus) designed to induce systemic, anti-tumor responses. The virus, which is being developed by the biotech company Targovax, has been engineered to express GM-CSF, an immune stimulating factor, and to selectively infect tumor cells. It will be administered in combination with the checkpoint blockade antibody durvalumab in patients with ovarian cancer or colorectal cancer. Preclinical research by Zamarin and others has shown that broad anti-tumor activity may be induced with the combination of an oncolytic virus and checkpoint blockade therapy. The hope is that viral infection, GM-CSF expression and checkpoint blockade will synergize in their effects to provoke a vigorous anti-tumor immune response.

GREEN LIGHT

The biopharmaceutical company Mersana Therapeutics is enrolling patients into its phase 1b clinical study of its antibody-drug conjugate XMT-1536 in epithelial ovarian cancer and non-squamous non-small cell lung cancer (NSCLC), as well as a number of other tumor types after the U.S. Food and Drug Administration cleared the company's investigational new drug application. XMT-1536 is an antibody-drug conjugate, which boosts the cell-killing potential of monoclonal antibodies. The antibody targets a protein called sodium-dependent phosphate transport protein 2b (NaPi2b), which is present in 75% to 90% of non-squamous, NSCLC and epithelial ovarian cancers. The clinical trial will evaluate the drug's safety and preliminary signs of efficacy in patients with NaPi2b-positive tumors. The humanized antibody originated from the Ludwig New York Branch and was subsequently licensed to Ludwig start-up Recepta Biopharma. Following further preclinical development by Recepta, the antibody was licensed to Mersana for use with Mersana's second generation Dolaflexin drug conjugation platform.

JOHN NOTTER

LUDWIG'S CHAIR OF THE BOARD

You came to the United States from Switzerland when you were 7 years old. Why did your family emigrate, and where did they settle?
It was the middle of World War II and my father, who was a chef, couldn't find any work. He had friends in the U.S. so it was a no brainer to emigrate. My mother and I followed a year later. It was a very difficult trip. We came to the U.S. through Portugal where we lived in a little room for about three or four months before we were able to get passage on a ship going to the U.S. Like many refugees who came at that time, we first settled in the Bronx, in New York City.

Was arriving here a huge culture shock for you?
It was more than a culture shock. I spoke Swiss German so everyone thought I was German. So you can imagine how difficult it was living in the Bronx in the middle of the war. Needless to say, I learned English very quickly. I even changed my name to John from Hans so that I would have an American name. My father worked as a chef at a hotel in Manhattan and in those days, you had to work the split shift, which meant he worked the breakfast shift, the lunch shift and the dinner shift with time off in the afternoon. So, he was gone for 14 to 16 hours every day. A few years later, when I was about 11, we moved from the Bronx to New Jersey where my mother and father became managers of the Swiss Hall. It was a community with a lot of foreigners—mostly Italian, German and Swiss and I felt more at home. It was tough to find workers in 1946, so I started washing dishes. I was still a kid and had to stand on a wooden box to reach the

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> … when you work hard as a kid, you appreciate everything you have. When everything is handed to you, you don’t have the sense of appreciation that you should.
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sink. I can still recall those days. And I have to say that when you work hard as a kid, you appreciate everything you have. When everything is handed to you, you don’t have the sense of appreciation that you should.

What cause or causes are you interested in, and why?
I support a broad range of charities that benefit the young and the old and focus on where the money will make a real difference. I’m a firm believer that equality can be achieved through education. Without a good education, the prospects for needy kids are diminished. Last year, I paid half the tuition for 18 promising students, all of whom were the first in their family to go to college. I also donated this year to the Boys and Girls Club in Thousand Oaks, California. On the other end of the spectrum, I support the House of Hope, a residential care facility for the elderly, and Senior Concerns, which provides support services to the elderly and their families.

What drives you in your work?
I like to create. I don’t enjoy the status quo. I didn’t just quit because I’m over 65. I am always involved in something new. I still love seeing a new building go up in Westlake Village. Many people that I worked with over the years just stopped, but me, I want to stay actively involved in different ventures. A lot of people are given an opportunity but they don’t embrace it. That’s not me. I like the variety of projects—Westlake, Ludwig Cancer Research, Hilton. Part of my drive might stem from having worked with Mr. Ludwig because he involved me in so many different industries.

Who has been your most significant role model or inspiration in life?
There are a couple of people I can think of. One would be Bob Ahmanson, whose uncle was the founder of H.F. Ahmanson & Co., an insurance and savings and loans corporation based in Los Angeles. I started my career at the Home Savings of America, which at that time and for many years after, was the largest savings and loan association in the US. Bob hired me when I was in my mid-20s and by the time I was 28, I was president of one of their subsidiary banks. Mr. Ludwig was another one. I wanted to get into international finance and Bob Ahmanson said it wouldn’t happen at Home Savings, so I started looking for another job and connected with Mr. Ludwig who was a major shareholder in a string of savings and loan companies. He asked me to take one over that was failing in Woodland Hills, California, and see if I could turn it around. I agreed but on one condition—if I were successful, he would give me an opportunity to get involved in international finance. It was and I will say that Mr. Ludwig was a man of his word.

How did you become involved in Mr. Ludwig's other ventures?
After the successful turnaround of the savings and loan, I received a phone call from Mr. Ludwig telling me that he needed me to be on a plane tomorrow to Australia. And I was like, what? I eventually took control of all his Australian operations, which included coal mines and shipping. I also started an insurance company and a savings and loan there. I even built a golf course. This led to my involvement in the salt mines in Mexico, shipbuilding in Japan and petroleum refineries in Florida and Panama. It's hard to believe sometimes that Mr. Ludwig gave someone in his early 30s that much responsibility. But he did. And it worked out fine for both of us. I guess, maybe I was in the right place at the right time with the right person because it was a period of time that I was able to develop many different interests and it is why today I embrace every new challenge that comes along.

How did you become chairman of a major hotel chain?
In the late fifties, Mr. Ludwig bought two hotels—one in Bermuda and one in the Bahamas, neither of which was doing very well. But both countries were known as "flag of convenience" countries, which allowed him to reduce operating costs. I eventually became the chairman of Princess Hotels International and built the Acapulco Princess in Mexico and the Southampton Princess in Bermuda. It was through my involvement in the hotel business that I came to know Barron Hilton and eventually sat on the board of directors of the Hilton Hotels

Corporation and served as chairman of the audit committee. Today I'm still very involved with him and the Hilton Foundation.

Was it difficult to constantly juggle all these responsibilities?
In every industry, it all comes down to numbers. Whether it's the hotel business or the shipping business, numbers are the driving force. To be successful, you have to spend time and energy on what will drive the business forward. I can hire people to dig coal. I can hire people to build ships. I leave the day to day running of the business to others. It's not what I'm interested in. The challenge for me is the financing—raising the money to build a new hotel or a new ship or a golf course. All my time and energy are spent looking at a business from a macro perspective. Should we build more rooms? Should we build different types of structures? Where should we put it? That's what I'm interested in.

Which of your philanthropic endeavors are you most proud of?
I would have to say being involved in the creation of the Ludwig Institute for Cancer Research.

How did you come to be involved?
The Ludwig Institute for Cancer Research was my idea. It's my baby. It was around 1969-1970 and, since Mr. Ludwig had no children, we were trying to figure out what to do with his international holdings and who to leave them to. I suggested we establish the Ludwig Institute for Cancer Research. Since I'm a Swiss citizen, we were able to locate the financial office in Zurich. A law was passed in Switzerland that allowed Mr. Ludwig to become a controlling shareholder. There are 50 shares, 49 of which are held by the Ludwig Institute Charitable Trust and one that is held by the Swiss government with the stipulation that the charitable nature of the organization would never change. That's the key.

Which aspects of cancer research interest or excite you the most?
As we were starting up the Institute, I went to see Benno Schmidt who was the chairman of the board of Memorial Sloan Kettering to find out who might be a good scientist to head it up. Lloyd Old was the first to come on board. He was doing something new in the field of immunology. And it was pretty much Lloyd who kept the Institute together through the initial trials and tribulations. I wish he were alive today because, clearly, it's one of the areas in cancer research that has the most promise. Ups and downs, of course, but certainly in the long run, the most promise. The other area that excites me is prevention. Preventing the disease is a lot more effective than curing it. Prevention isn't being funded by pharma because the pharmaceutical companies are more focused on treating cancer than preventing it. The government has responsibility in this area, but there is much more progress to be made. In 2015, we launched a cancer prevention initiative in partnership with the Hilton Foundation. It has expanded to include a number of Ludwig scientists and we're now starting to get some new players involved like the City of Hope, Cancer Research UK, the Wellcome Trust and the Medical Research Council of the UK.

What excites you about the future of Ludwig?
Having Chi aboard as the new scientific director is absolutely critical to taking Ludwig to the next level. The transition over the past 6 to 7 years has set us up to move in a more efficient manner. The amount of overhead in rent and administrative assistance in nine different locations was substantial and the structures were too rigid. We're now down to three locations and the percentage of funds available as a consequence of the moves we've made is giving the new people coming in the opportunity to go where the excitement is and to pursue what they want to do. I think the new teams will have a lot more flexibility and cash to move forward in different directions. It's up to them to decide where. They're the scientists. The doctors. That's why I am really very optimistic about the future of Ludwig especially now—I am going to repeat myself here—

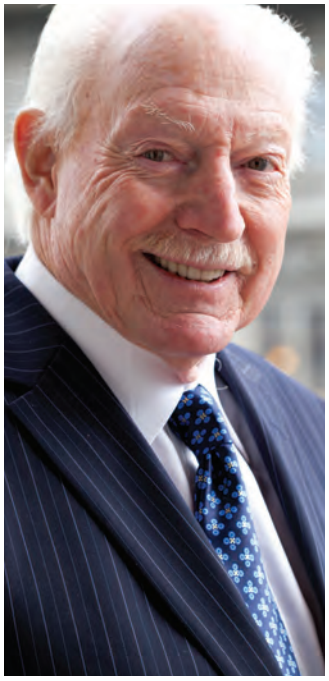
“Prevention isn't being funded by pharma because the pharmaceutical companies are more focused on treating cancer than preventing it. The government has responsibility in this area, but there is much more progress to be made.”

but it's very important that we have somebody like Chi on board now. With him, our team now is as good as it's ever been.

Looking back at your career now, what is the most surprising decision you made?
I think it's probably when I left Mr. Ahmanson to go to work for Mr. Ludwig. I was a rising star in the Ahmanson organization and president of a bank and I took a substantial pay cut to work for someone I didn't even know.

What achievements are you most proud of in your career so far?
Without a doubt, the Ludwig Institute has to be at the top of the list along with the Hilton Foundation, where I am a member of the board of directors and chair of the finance and audit committee. Another would be creating and building Westlake Village. Not many people can say they've built a city. Today it's recognized as one of the most successful master-planned communities in the US.

What are your favorite hobbies or interests?
I love studying languages and right now I'm working on my Spanish. I speak pretty good French and am fluent in German. Wine is another interest of mine. I like reading about it, tasting it and drinking it. Exercise is also very important to me – I've exercised all my life and rarely does a day go by that I haven't spent an hour or two exercising.



"I am really very optimistic about the future of Ludwig especially now ... our team is as good as it's ever been."

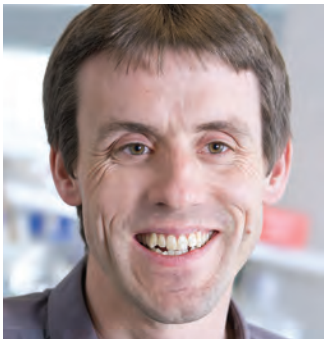
Are pre-prints the future of biology?

The popularity of pre-prints underscores the need for additional safeguards by labs to ensure that all submitted data are accurate, reproducible and meaningful. A key concern is that the rapid dissemination of non-peer-reviewed data by the media may circumvent essential checks that help ensure the quality and significance of new scientific findings.

SAMEER CHOPRA
Ludwig Harvard

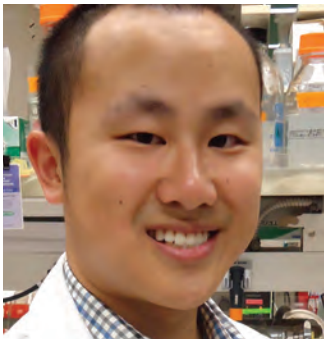
Preprinting has been gaining traction in the scientific community as an expeditious way of disseminating new findings. The Technology Development team fully supports accelerating the pace of science from the bench to the bedside. For this reason, we encourage Ludwig scientists to keep our team informed of their research early on, so that promising opportunities can be identified and patented ahead of any public disclosures.

ECE AUFFARTH
Ludwig New York



Roughly six months go by between submission and publication. So preprints are a great way to accelerate knowledge dissemination. The downside is, of course, that we risk a flood of low quality preprints. But remember, bad preprints can quite damage one's reputation, so scientists are careful before putting their work on bioRxiv, and a lower quality in preprints compared to peer-reviewed articles has not been observed in other fields where preprints are extensively used.

DAVID GFELLER
Ludwig Lausanne



Preprints are a fantastic way to expedite exciting results into the hands of the scientific community. Caution is warranted, however, to ensure that unrefereed materials are held to the highest of standards. An agreement is needed to determine whether preprints merit citations in grants/papers or establish "first dibs" over scientific discoveries.

PETER LY
Ludwig San Diego

Publishing in biological sciences has always been competitive and there is widespread fear that ideas or data might be stolen. However, preprints give researchers a good platform to showcase their work early on, garner constructive feedback and potentially facilitate unusual collaborations. They also mitigate the current time-consuming peer review process, including "journal hopping" to lesser impact journals.

NATASHA SAHGAL
Ludwig Oxford

Ludwig Chicago

Oncotarget 2017 September
Progesterone receptor isoforms, agonists and antagonists differentially reprogram estrogen signaling.

Singhal H, Greene ME, Zarnke AL, Laine M, Al Abosy R, Chang Y-F, Dembo AG, Schoenfelt K, Vadhi R, Qiu X, Rao P, Santhamma B, Nair HB, Nickisch KJ, Long HW, Becker L, Brown M, Greene GL.

Ludwig Harvard

Science 2017 October 12 [Epub ahead of print]
Metabolic recycling of ammonia via glutamate dehydrogenase supports breast cancer biomass.

Spinelli JB, Yoon H, Ringel AE, Jeanfavre S, Clish CB, Haigis MC.

Science 2017 July 7
Origins of lymphatic and distant metastases in human colorectal cancer.

Naxerova K, Reiter JG, Brachtel E, Lennerz JK, van de Wetering M, Rowan A, Cai T, Clevers H, Swanton C, Nowak MA, Elledge SJ, Jain RK.

Ludwig Johns Hopkins

Proceedings of the National Academy of Sciences USA 2017 September 19
Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers.

Cohen JD, Javed AA, Thoburn C, Wong F, Tie J, Gibbs P, Schmidt CM, Yip-Schneider MT, Allen PJ, Schattner M, Brand RE, Singhi AD, Petersen GM, Hong SM, Kim SC, Falconi M, Doglioni C, Weiss MJ, Ahuja N, He J, Makary MA, Maitra A, Hanash SM, Dal Molin M, Wang Y, Li L, Ptak J, Dobbyn L, Schaefer J, Silliman N, Popoli M , Goggins MG, Hruban RH, Wolfgang CL, Klein AP, Tomasetti C, Papadopoulos N, Kinzler KW, Vogelstein B, Lennon AM.

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Chronic cigarette smoke-induced epigenomic changes precede sensitization of bronchial epithelial cells to single-step transformation by KRAS mutations.

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Ludwig Lausanne

Nature Communications 2017 September 19
Tumour-derived PGD2 and NKp30-B7H6 engagement drives an immunosuppressive ILC2-MDSC axis.

Trabanelli S, Chevalier MF, Martinez-Usatorre A, Gomez-Cadena A, Salomé B, Lecciso M4, Salvestrini V, Verdeil G, Racle J, Papayannidis C, Morita H, Pizzitola I, Grandclément C, Bohner P, Bruni E, Girotra M, Pallavi R, Falvo P, Leibundgut EO, Baerlocher GM, Carlo-Stella C, Taurino D, Santoro A, Spinelli O, Rambaldi A, Giarin E, Basso G, Tresoldi C, Ciceri F, Gfeller D, Akdis CA, Mazzarella L, Minucci S, Pelicci PG, Marcenaro E, McKenzie ANJ, Vanhecke D, Coukos G, Mavilio D, Curti A, Derré L, Jandus C.

Nature Immunology 2017 September 18
α-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming.

Liu PS, Wang H, Li X Chao T, Teav T, Christen S, Di Conza G, Cheng WC, Chou CH, Vavakova M, Muret C, Debackere K, Mazzone M, Huang HD, Fendt SM, Ivanisevic J, Ho PC.

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Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF.

Quail DF, Olson OC, Bhardwaj P, Walsh LA, Akkari L, Quick ML, Chen IC, Wendel N, Ben-Chetrit N, Walker J, Holt PR, Dannenberg AJ, Joyce JA.

Ludwig MIT

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Coordinated splicing of regulatory detained introns within oncogenic transcripts creates an exploitable vulnerability in malignant glioma.

Braun CJ, Stanciu M, Boutz PL, Patterson JC, Calligaris D, Higuchi F, Neupane R, Fenoglio S, Cahill DP, Wakimoto H, Agar NYR, Yaffe MB, Sharp PA, Hemann MT, Lees JA.

Ludwig MSK

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Overall survival with combined nivolumab and ipilimumab in advanced melanoma.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS1, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbé C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J.

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Blockade of surface-bound TGF-β on regulatory T cells abrogates suppression of effector T cell function in the tumor microenvironment.

Budhu S, Schaer DA, Li Y, Toledo-Crow R, Panageas K, Yang X, Zhong H, Houghton AN, Silverstein SC, Merghoub T, Wolchok JD.

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Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient.

Jiménez-Sánchez A, Memon D, Pourpe S, Veeraraghavan H, Li Y, Vargas HA, Gill MB, Park KJ, Zivanovic O, Konner J, Ricca J, Zamarin D, Walther T, Aghajanian C, Wolchok JD, Sala E, Merghoub T, Snyder A, Miller ML.

Ludwig San Diego

EMBO Journal 2017 August 15
The AAA+ ATPase TRIP13 remodels HORMA domains through N-terminal engagement and unfolding.

Ye Q, Kim DH, Dereli I, Rosenberg SC, Hagemann G, Herzog F, Tóth A, Cleveland DW, Corbett KD.

Genes & Development 2017 July 19 [Epub ahead of print]
Glioblastoma cellular cross-talk converges on NF-κB to attenuate EGFR inhibitor sensitivity.

Zanca C, Villa GR, Benitez JA, Thorne AH, Koga T, D'Antonio M, Ikegami S, Ma J, Boyer AD, Banisadr A, Jameson NM, Parisian AD, Eliseeva OV, Barnabe GF, Liu F, Wu S, Yang H, Wykosky J, Frazer KA, Verkhusha VV, Isaguliants MG, Weiss WA, Gahman TC, Shiau AK, Chen CC, Mischel PS, Cavenee WK, Furnari FB.

Ludwig Stanford

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Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma.

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