LUDWIG LINK

NOVEMBER 2019

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

LUDWIG LINK

ludwigcancerresearch.org NOVEMBER 2019

LETTER

If it's been a bit of a whirlwind year for you, we think you'll find this issue of Ludwig Link captures that spirit. It has certainly been all that and more for Ludwig Oxford's Peter Ratcliffe, who shared the 2019 Nobel Prize for Physiology or Medicine in October with William Kaelin of the Dana-Farber Cancer Institute and Gregg Semenza of Johns Hopkins University. Peter and his co-recipients were recognized for their discovery of how mammalian cells sense and respond to the availability of oxygen. You can read a little more about it in the Awards and distinctions section (and in our profile of Peter in the 2019 Ludwig Highlights report).

Our Q&A this time around (page 15) is with Web Cavenee, a scientist's scientist and three-decade member of the Institute who has made more than a few landmark discoveries in cancer biology—and isn't even close to stopping, even if he is soon retiring from the Institute.

Our research briefs in this issue illustrate, as always, the fine work being done across Ludwig's Centers and Branches. You'll read about the preclinical development of a nanotech urine test for colon tumors that furnishes results—via color change—within the hour; the discovery of a new "don't-eat-me signal" exploited by cancer cells to ward off macrophage attack; and a potential breakthrough in culturing blood-forming stem cells that could transform bone marrow transplantation for the treatment of cancer and a number of other diseases.

In our Ask a Scientist section, we asked some Ludwig people whether decentralizing science leads to more reliable results. Find out what they said on page 21.

Happy holidays!

Rachel Reinhardt
Vice President for Communications

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On the cover: Peter Ratcliffe of Ludwig Oxford

Awards and distinctions

Our Nobel laureate

Ludwig Oxford's Sir Peter Ratcliffe received the 2019 Nobel Prize for Physiology or Medicine in October. He was recognized by the Nobel Committee for his landmark discoveries on the mechanisms by which mammalian cells sense and respond to the availability of oxygen. Peter shared the prize with U.S. researchers William Kaelin of the Dana-Farber Cancer Institute and Gregg Semenza of Johns Hopkins University. Their discoveries, which were made independently through the 1990s and early 2000s, have had a profound influence on our understanding of biological processes and disorders ranging from heart disease to wound-healing to cancer. Peter and his two co-winners built sequentially on discoveries made in each of their labs to identify a cellular oxygen sensor. The gene expression driven by oxygen starvation was reported by Gregg Semenza's lab to be governed by proteins known as hypoxia-inducible factors (HIFs), though how they were controlled remained a mystery. Peter and his team discovered how that control occurs and described the elegant mechanism by which a set of enzymes directly link the availability of molecular oxygen to HIF activity. Those findings were simultaneously made by William Kaelin and his colleagues. Some variation of the oxygen-sensing system Peter discovered has since been found in all animals, and he has over the years fleshed out the molecular biology and genetic regulation of hypoxic signaling in a variety of biological processes, most notably cancer: oxygen starvation at the core of solid tumors is known to contribute significantly to drug resistance and metastasis. Just this summer, he and his colleagues reported in *Science* their discovery of an entirely novel cellular oxygen sensor—one so ancient in its evolutionary origins that it is shared by plants (see page 12). For more on Peter Ratcliffe and his research career, see this profile in the Ludwig 2019 Research Highlights report. Congratulations, Peter!

FOR PIONEERING RESEARCH

Ludwig Harvard Co-director Joan Brugge received ASCO's 2019 Science of Oncology Award and Lecture in June. Joan made her mark in cancer research isolating and characterizing the first product of a viral oncogene (Src) and its mammalian counterpart when she was a post-doctoral researcher. Her work contributed significantly to the current understanding of how dysregulation of intracellular signaling proteins drives the emergence of cancer. Her more recent studies have focused on using 3-D cultures to explore the cell biology and dynamics of breast cancer initiation and progression, the cellular heterogeneity of tumors and mechanisms of drug resistance in cancer. Joan's award lecture covered the history of research that led to her work on Src, the roles of antioxidants in cancer and some of the mechanisms by which cancer cells overcome intrinsic barriers to malignant transformation, such as programmed death.

◀ **Joan Brugge**
Ludwig Harvard

Bert Vogelstein ▶
Ludwig Johns Hopkins

Irv Weissman ▶
Ludwig Stanford

FOR TRANSFORMATIVE DISCOVERY

Ludwig Johns Hopkins Co-director Bert Vogelstein and Ludwig Stanford Director Irv Weissman received the prestigious Albany Prize. A pioneer in cancer genetics, Bert transformed cancer research through his work on colorectal tumors. His early research on colon cancer, in which he described how the sequential mutation of proto-oncogenes and tumor suppressor genes drives malignancy, is a paradigm of cancer research and led to the development of the first at-home kit for colon cancer detection. His subsequent work mapping cancer genomes spawned a revolution in diagnostics, with companies now racing to develop liquid biopsies for cancer, including one Bert established in partnership with his Ludwig Johns Hopkins colleagues. Irv, a pioneer in the field of stem cell biology, isolated the first blood-forming stem cells in mice and humans and described how mutations in those cells drive leukemia. His more recent discovery of "don't-eat-me" signals transmitted by cancer cells to the immune system—he has now discovered three in all (see page 11)—has also led to the ongoing clinical evaluation of an exciting new cancer therapy by a company he co-founded. The $500,000 Albany Prize is given to those who "have transformed our understanding of cancer and contributed to the development of new methodologies for detection and treatment of cancer and for regenerative medicine." Both Irv and Bert clearly fit that bill.

Beata Mierzwa
Ludwig San Diego

FOR MODELING POSSIBILITY

Ludwig San Diego's Beata Mierzwa is one of 125 women in science, technology, engineering and mathematics (STEM) selected as an AAAS IF/THEN Ambassador. In this capacity, Beata, a postdoctoral researcher in Karen Oegema's lab (and a gifted scientific illustrator and designer), will connect with students in person and through various media platforms, including YouTube and network television shows, and serve as a role model for middle-school girls. IF/THEN, a national initiative of Lyda Hill Philanthropies, aspires to shift the way the world thinks about women in STEM, which requires improving their visibility. In October, the Ambassadors will participate in a summit in Dallas.

Alexandra Johnson
Ludwig Institute

NEW LUDWIG BOARD MEMBER

Alexandra Johnson was appointed in September to the Board of Directors of the Ludwig Institute for Cancer Research. She is a partner at the Swiss law firm Bär & Karrer and has 17 years of experience in international arbitration law. Based in Geneva, Alexandra serves on the Board of Directors of ArbitralWomen and is a member of the Swiss Chambers' Arbitration Institution Court of Arbitration. She has served as counsel in arbitration proceedings on matters ranging from international joint venture agreements to mergers and acquisitions and even sports-related disputes. She also frequently sits as an arbitrator and regularly speaks and writes on matters related to international arbitration. Alexandra earned her law degree from the University of Neuchâtel, Switzerland, and an LLM degree from Harvard Law School, which she attended as a Fulbright Scholar.

Paul Mischel
Ludwig San Diego

MEMBRANE MATTERS

While driven by genetic mutations, cancer cells are also forced to reprogram their uptake, production and use of nutrients and metabolites to fuel their constant proliferation. This induces in them dependencies that may be exploited for cancer therapy. In a September paper in *Cell Metabolism*, researchers led by Ludwig San Diego's Paul Mischel described how an enzyme involved in building cell membranes, LPCAT1, links hallmark changes in the cancer cell's membrane structure to its metabolic and growth-promoting genetic alterations. Paul and his colleagues discovered that LPCAT1 subtly tweaks the chemical composition of the external cell membrane in a way that boosts the transmission of proliferative signals in cancer cells driven by dysregulated growth factor signaling. Cancers of this sort are notably dependent on the enzyme. When LPCAT1 was genetically depleted in mouse models of multiple types of cancer, including the aggressive brain cancer glioblastoma and lung cancer, tumors shrank dramatically and survival times improved.

Ralph Weichselbaum
Ludwig Chicago

BORROWED RESISTANCE

Radiation damages tumors in part by activating an immune response against them. But it has long been thought to also kill T cells, which are essential to that response. This supposition has long been a limiting factor in the use of radiotherapy in trials examining its combination with immunotherapy for the treatment of cancer. A team led by Ludwig Chicago's Ralph Weichselbaum reported in a September paper in *Nature Communications* that T cells within tumors might be more resilient than was believed. Ralph and his colleagues found that a large proportion of T cells with some characteristics of tissue resident T cells in irradiated tumors not only survive radiotherapy, but are more activated than T cells from unirradiated tumors and can attack tumors without support from a new infusion of infiltrating T cells. Their analysis indicated that T cells are genetically reprogrammed by the tumor microenvironment to resist radiation, a capability they found to be regulated in part by the factor TGFβ, which is generally thought to be immunosuppressive. The findings suggest that focal irradiation of multiple tumors could improve overall results in combination trials of radio- and immunotherapy.

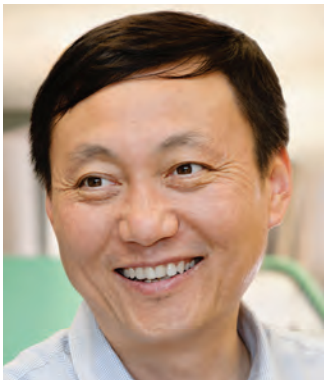
FAT TARGET

A study led by Ludwig Scientific Director Chi Van Dang and his colleagues at Stanford University uncovered a novel vulnerability in tumors that are driven by a common cancer gene known as MYC. Such cancers, the researchers reported in a September paper in *Cell Metabolism*, are highly dependent on the cell's machinery for making fats and other lipids, and this dependency might be exploited for therapy. MYC, they found, controls the gene expression required for almost every stage of lipid synthesis, from the generation of precursor molecules to the construction of complex lipids. It does so by boosting the expression and then ramping up the activity of SREBP1—a regulator of gene expression that controls lipid production. The researchers also identified a lipid signature associated with MYC-driven cancers and, using mouse models of MYC-induced tumors, showed that cancers of the blood, lungs, kidneys and liver are highly dependent on fatty acid synthesis. Inhibiting an early step of that process led to tumor regression. MYC is the third most amplified gene in human cancers and Chi and his colleagues at Stanford University show that even tumors driven by other oncogenes are susceptible to the inhibition of fatty acid production if they indirectly activate MYC.

Chi Van Dang
Ludwig Institute

CRE-ATING MAPS

The genome is littered with small stretches of DNA sequences that play a critically important role in biology by controlling the expression of genes near and far. While researchers have identified hundreds of thousands of these Cis-regulatory elements (CREs) across the human genome, which gene, or genes, each of them regulates has remained relatively hazy. A team led by Ludwig San Diego's Bing Ren sought to clarify that picture by mapping the long-range interactions of chromatin—the term for DNA in its protein packaging—involving 18,943 gene promoters in 27 human cell/tissue types. (Promoters are DNA sequences that mark where the reading of a gene should begin.) Bing and his colleagues used this information to infer the target genes of 70,329 candidate regulatory elements and identified 27,325 variant CRE sequences associated with 2,117 physiological traits and diseases. An analysis of these maps revealed the influence of CREs on many common molecular pathways underlying distinct groups of human traits and diseases. The work was published in September in *Nature Genetics*.



Bing Ren
Ludwig San Diego

Sangeeta Bhatia
Ludwig MIT

SMALL IS GOLD

Ludwig MIT's Sangeeta Bhatia and her colleagues have developed a prototype diagnostic test for cancer and possibly other diseases that can be easily and inexpensively used and makes its report in under an hour through a color change in urine. She and her colleagues built their technology around gold nanoclusters (a.k.a. AuNCs) that are small enough to accumulate in tumors, slip through the kidneys' filtration systems and be cleared via urine. They then linked these AuNCs to a large carrier protein using another strip of protein that is specifically snipped by an enzyme known as MMP9. Colon tumors express high levels of MMP9, so when the nanoparticles made their way into such tumors in mice, they were freed of their protein burden, set adrift in the blood, filtered out through the kidneys and expunged in urine. Subjected to the right chemicals, the AuNCs turn blue, enabling the detection of colon tumors with a simple urine test. Trials in mice with and without colon tumors showed the detectors to be accurate, quick to give results and nontoxic. The researchers hope to use modified versions of the nanosensors to detect other diseases as well. A report of the study appeared in a September paper in N*ature Nanotechnology*.

Xin Lu
Ludwig Oxford

BEING SELECTIVE

The tumor suppressor protein p53 is a master regulator of gene expression that is involved in myriad cellular processes, from growth arrest to suicide to metabolism. It is also the most frequently mutated protein in human cancers. Modulation of which genes are controlled by p53 in a specific context underpins the cellular life-or-death balance, yet it is incompletely understood. In an August paper in the *Proceedings of the National Academy of Sciences*, Ludwig Oxford Director Xin Lu and her team reported a mechanism by which iASPP, an inhibitor of p53, influences p53's selection of target genes. Using next generation sequencing, the researchers characterized the signature DNA sequences of genes that are jointly regulated by iASPP and p53. They also examined a crystal structure of the partnered proteins and found that iASPP disrupts a p53 domain that interacts with the signature sequences of iASPP co-regulated genes, providing an explanation for p53 target selection. iASPP's interaction mode differs from previously characterized cellular p53 partners—though, intriguingly, overlaps with the interaction site of an oncoprotein from the cancer-causing pathogen HPV—and could open new opportunities for designing anticancer agents targeting p53.

AN INHERENT VULNERABILITY

Overexpression of the EGF receptor (EGFR), a cell surface protein that transmits growth-promoting signals, contributes to the proliferation and survival of many types of cancer cells. A number of targeted cancer drugs seek to disable the receptor. A team led by Ludwig San Diego's Frank Furnari reported in an August paper in *Molecular Cancer Research* two novel enhancers of gene expression located within the first intron—a noncoding stretch of DNA within a gene—of the EGFR gene in models of the brain cancer glioblastoma and head and neck squamous cell carcinoma. Frank and graduate student Nathan Jameson characterized these novel enhancers, finding that their effects are mediated by the AP-1 family of transcription factors (which control gene expression) and BET bromodomain proteins. Genetic or pharmacologic disruption of interactions between AP1 or BET with the enhancers suppress EGF receptor expression, providing a rationale for targeting these interactions to treat EGFR-positive tumors, which can be highly dependent on the receptor's signaling. AP1 and BET bromodomain proteins can be targeted by either existing or experimental drugs.

Frank Furnari
Ludwig San Diego

DON'T EAT ME, PRETTY PLEASE?

Immune cells called macrophages can gobble up cancer cells and initiate an anti-cancer immune response. Cancer cells, for their part, often express proteins that tell macrophages not to do so. Ludwig Stanford Director Irv Weissman's lab has previously discovered a couple of such proteins, and an antibody he and his team developed to block one of them, CD47, is today in clinical trials as a cancer therapy. In August, Irv and his colleagues reported in *Nature* their discovery that the protein CD24 transmits yet another "don't eat me" signal to macrophages and that it too appears to be used by certain cancer cells to protect themselves. Macrophages sense the CD24 signal through a receptor called SIGLEC-10. Blocking that interaction prompted macrophages to get back to their cancer cell repast and, in mice implanted with human breast tumors, induced tumor regression and extended the survival of the mice. Tough-to-treat ovarian and triple-negative breast cancers were especially vulnerable to such intervention. Notably, Irv and his team also found that cancers that resist CD47 blockade are susceptible to CD24 blockade—and vice versa—suggesting either or both antibodies might cover treatment of a broad spectrum of cancer types.

Irv Weissman
Ludwig Stanford

Hiro Nakauchi
Ludwig Stanford

POWER IN NUMBERS

Patients undergoing stem cell transplants for blood cancers and other diseases today must endure highly toxic—sometimes lethal—rounds of chemotherapy and radiation to clear their bone marrow of diseased blood-forming stem cells, or hematopoietic stem cells (HSCs). A further problem is that collecting sufficient numbers of donor HSCs for transplantation is challenging because they are very rare cells and difficult to culture. Now a team of scientists at Ludwig Stanford led by Hiro Nakauchi might have found a way around both these issues. In a July *Nature* paper, they and their colleagues in Japan reported a method of culturing mouse HSCs that prompts the stem cells to renew themselves hundreds or even thousands of times within just 28 days. The researchers accomplished this by altering the medium, growth stimulating factors and physical conditions of the culture. They then demonstrated that, with such large numbers of HSCs available for infusion, successful transplantations could be done in mice without first eliminating the recipients' own HSCs. If the method works on human HSCs, it could dramatically expand the number of patients eligible for bone marrow transplantation and help to expand the use of umbilical cord blood HSCs for transplantation. It could also permit the use of a patient's own genetically corrected stem cells in gene therapies to treat genetic diseases like sickle cell anemia.

Peter Ratcliffe
Ludwig Oxford

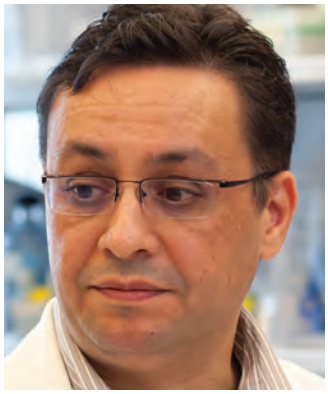
ANCIENT SENSOR

Ludwig Oxford's Peter Ratcliffe is among the researchers who first discovered, about 20 years ago, how cells sense and respond to the availability of oxygen. That system centered on the oxygen-dependent degradation of hypoxia-inducible factors, or HIFs, which govern programs of gene expression that help cells adapt to oxygen starvation, or hypoxia. In July, Peter and his colleagues reported in *Science* that they've discovered a second system for oxygen sensing in animal cells, one so ancient that it is shared by plants. It is mediated by an enzyme, cysteamine (2-aminoethanethiol) dioxygenase, or ADO, which splits molecular oxygen (O2) and attaches each atom of the pair to an amino acid, cysteine, on its protein targets—participants in the newly discovered hypoxia pathway. This alteration allows the cysteines to be recognized by another enzyme that further modifies them, tagging the oxidized proteins for destruction. A similar system mediated by enzymes known as PCOs, which resemble ADO, operates in plant cells. While both the ADO system and the HIF system sense oxygen in similar ways, they work on different timescales. The discovery of a new cellular oxygen sensor could lead to the development of drugs for many disorders, including cancer.

THREE'S A CHARM

Tumors whose infiltrating T cells are exhausted respond poorly to immunotherapies like PD-1 blockade. In a July paper in the *Journal of Clinical Investigation*, researchers led by Ludwig MSK's Jedd Wolchok and Taha Merghoub identified a potentially novel approach to overcome this problem without compounding autoimmune side effects. The strategy focuses on antigen presenting cells (APCs), scouts of the innate immune system that present antigens to T cells to activate them. Jedd, Taha and their colleagues treated a single melanoma tumor in mice bearing multiple tumors with two agents that cooperatively activate APCs—monophosphoryl lipid A and a stimulatory antibody against the protein CD40. They also gave the mice systemic injections of an anti-PD-1 antibody, which reinvigorates exhausted killer T cell responses against tumors. They found that the combination therapy led to a depletion of exhausted T cells in tumors and elicited potent anti-tumor T cell responses that induced regressions of untreated tumors as well. The mice did not respond to anti-PD-1 therapy alone. The combination treatment also spared non-malignant tissues. Notably, gene expression patterns in the treated mice resembled those seen in patients who respond well to anti-PD-1 therapy. The team is now planning clinical trials of the regimen.

Jedd Wolchok
Ludwig MSK



Taha Merghoub
Ludwig MSK

Bert Vogelstein
Ludwig Johns Hopkins

A CYST ASSESSMENT

More than 99% of pancreatic cysts detected by doctors do not progress into pancreatic tumors. But distinguishing between low- and high-risk cysts is very difficult. A research team led by Johns Hopkins Co-director Bert Vogelstein has now harnessed machine learning to create a test for this purpose that coordinately assesses selected clinical features, imaging, and genetic and biochemical markers in cyst fluid to produce an answer. CompCyst was trained on data from 436 patients to identify people who needed surgery, those who should be monitored and those who needed no further surveillance. It was then evaluated in an international, multicenter study of another 426 patients. The researchers compared CompCyst's predictions against the gold standard diagnostic: post-surgical histopathological evaluation of the cysts. CompCyst correctly predicted 60% of patients who should have been sent home, as opposed to the 19% detected using standard preoperative criteria. If CompCyst had been used to decide care for these patients, 60% to 74% of them might have avoided unnecessary surgery. CompCyst detected 49% of people who should simply have been monitored, compared to 34% using current methods, and 91% who needed surgery, compared to 89% using existing methods. The findings were published in July in *Science Translational Medicine*.

A NECESSARY CIRI

Favored by nerdy bettors, "in-game win probability" uses a continuous stream of various data to predict, in near real time, the likely outcomes of contests. Maximillian Diehn and Ash Alizadeh and their Stanford colleagues Mohammad Shahrokh Esfahani and David Kurtz used a version of the method to create a computer algorithm called Continuous Individualized Risk Index (CIRI) to assess how well a cancer patient is doing at a given point during treatment. The method, which incorporates information on such things as treatment responses and circulating tumor DNA, could help identify patients in need of more aggressive therapy. The researchers trained their algorithm to detect patterns associated with whether a patient lived for at least 24 months after treatment without a relapse using data on more than 2,500 people treated for diffuse large B-cell lymphoma (DLBCL), a common blood cancer. They also included data on 132 patients whose circulating tumor DNA had been monitored. If the value of 1 constitutes a perfect predictive score, CIRI's dynamic risk profiling yielded a score of 0.8 vs. 0.6 for existing methods. Their paper, published in July in *Cell*, also showed how CIRI might be used to identify new biomarkers for risk profiling.

◀ **Maximilian Diehn**
Ludwig Stanford

◀ **Ash Alizadeh**
Ludwig Stanford

George Coukos ▶
Ludwig Lausanne

CROSSING GUARDS

Chemokines, signaling proteins that mediate the traffic of immune cells, help T-cells home in on tumors and can affect tumor immunity and the outcome of immunotherapy. In a June paper in *Cancer Cell*, Ludwig Lausanne Director George Coukos and his colleagues showed that two key chemokines, CCL5 and CXCL9, are consistently implicated in T cell infiltration into solid tumors. CCL5 is expressed by cancer cells, while CXCL9 is produced by macrophages and dendritic cells, immune cells that are usually present in solid tumors. George and his team report that when T cells drawn by CCL5 reach the tumor and are activated, they release a signaling protein called interferon-γ. This causes macrophages and dendritic cells in the tumor to secrete CXCL9, which dramatically boosts the infiltration of circulating T cells. The researchers show that when cancer cells suppress production of CCL5, CXCL9 expression drops, resulting in the progressive depletion of killer T cells in tumors. This loss of CCL5 expression correlates with a chemical modification to DNA known as epigenetic silencing that suppresses the expression of targeted genes. CCL5 and CXCL9 could be useful biomarkers for immunotherapy and help identify patients more likely to be responsive to immunotherapies. The findings will also inform new strategies for cancer immunotherapy.

WEB CAVENEE

LUDWIG INSTITUTE
DIRECTOR OF STRATEGIC ALLIANCES
IN CENTRAL NERVOUS SYSTEM CANCERS

If someone wrote your biography, what would the title be?
Prepared for Serendipity

You influenced how scientists now think about the onset of cancer and its progression when you demonstrated proof of tumor suppressor genes in humans. Was this a totally unexpected finding?
Actually, we had what we thought was a reasonable expectation based on epidemiological analyses by Al Knudson at Fox Chase, cytogenetic findings by Bob Sparkes at UCLA and a unique family that was reported by Louise Strong at MD Anderson. Putting all of that together and

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There are several collaborative initiatives directed at GBM now, with the idea being that conjoint efforts by investigators with varying approaches and viewpoints are more likely to accelerate progress in understanding and treating the disease.

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testing the hypothesis using the new tools that Ray White and I were developing was compelling to us, although not so much for most in the cancer genetics community. Thankfully, the three years of hard work it took to actually be able to do the experiment validated our expectations.

What is glioblastoma (GBM), and why is it so hard to treat?
GBM is the most common intracranial tumor and, unfortunately, one of the most lethal, with an average survival from diagnosis of about 14 months. This is because of some intrinsic features of GBM, including inherent radio-resistance, inherent and acquired chemo-resistance, the migratory nature of the cells that limits complete surgical resection, and the heterogeneity and genetic plasticity of the tumors.

What new treatments are being investigated for glioblastoma?
Most new treatments are targeted at specific mutations in GBM cells, although immunotherapies, radio-sensitization and viral or nanoparticle delivery are all being tested.

Does the heterogeneity of glioma cells limit the efficacy of immunotherapy?
GBM heterogeneity has been the major impediment to therapeutic progress with any modality. Another major issue is that the tumor resides behind the blood-brain barrier, which limits the distribution of therapeutic agents.

Tell us about the Defeat GBM Research Collaborative and your role in it.
There are several collaborative initiatives directed at GBM now, with the idea being that conjoint efforts by investigators with varying approaches and viewpoints are more likely to accelerate progress in understanding and treating the disease. The Defeat group, under the auspices of the National Brain Tumor Society (NBTS), was one of the first such efforts. I had the pleasure of being one of the instigators (Bob Strausberg was as well) of that multi-institutional initiative and one of its first investigators and leaders. In its first four years, the Defeat group has developed new agents and approaches that are now entering clinical trials. The NBTS has also announced that it will support Defeat #2, with some of the original investigators as

well as some new ones. I fully believe that this has and will continue to accelerate progress.

What is GBM AGILE?

GBM AGILE arose from conversations I had nearly five years ago with Ann Barker, the former Deputy Director of the National Cancer Institute, who is now at Arizona State University and Al Yung, the Ludwig scientific advisor who was then chair of neuro-oncology at MD Anderson, in which we decried the lack of success in extending the survival of patients with GBM. We posited that a more unified approach might be an answer and held a series of brainstorming meetings over the following couple of years, soliciting and focusing the views of more than 150 international neurosurgeons, neuro-oncologists, neuroradiologists, researchers, mathematicians, bioinformaticians, pharma representatives, and FDA personnel and patients. A major issue identified through these meetings was the need to address the way that clinical trials are conducted. They were hamstrung with way too many restrictions. That included their serial nature; the requirement that half the enrolled patients be assigned to the control arm; the limited number of patients that could be enrolled at any one institution, which in turn limited the numbers of drugs that could be tested and which necessitated a very limited stratification of patients; and limited clinical or scientific follow-up.

What makes it different from other clinical trials?

GBM AGILE was developed as a new construct to address the shortcomings I've mentioned. It's truly unique in its flexibility and adaptability, qualities that took three years to design. It encompasses several distinctive features: Bayesian algorithm-driven patient randomization and arm assignment that incorporates the use of biomarkers; a master protocol, which allows arms to enter or exit the trial without having to revise it and have it reapproved; an international agent

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GBM AGILE was designed to allow candidate treatments to “fail fast” and “correct even faster.” That comes with many advantages to the patients as well.

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selection group; multiple arms, so as to minimize the number of patients needed for the control arm; a common data analytic and tissue repository; and an FDA-approved design that allows seamless transition of succeeding drugs or combinations of drugs through randomized Phase 2 to registration quality Phase 3 trials. It is sponsored by a new 501(c)3 organization named the Global Consortium for Adaptive Research (GCAR), and I serve on its Board of Directors and as interim Chief Scientific Officer. Some 40 sites in the US are currently being evaluated and discussions are active with regulatory agencies in Canada, China, Australia, Europe and Israel. This extended network will provide a sufficient number of patients to rapidly test many agents singly and in combination.

The Henry Ford Cancer Institute just enrolled its first patient in a GBM AGILE trial this past August. Tell us how being a part of AGILE makes a difference for this patient?

GBM AGILE was designed to allow candidate treatments to “fail fast” and “correct even faster.” That comes with many advantages to the patients as well. Just two: the testing of several drugs in separate arms of the trial permits the use of a common control arm, minimizing the numbers of patients who will not receive an experimental drug; and the longitudinal design of the trial means that the response of patients to a drug is followed carefully and in a highly prescribed manner, so that a patient who is not responding can be quickly moved to another arm, offering them a second chance at a potentially successful therapy.

How did joining Ludwig advance or change your career?

It is hard to believe, since Ludwig is now such a dominant force in cancer research, but when Hugh Butt and Donald Park first approached me in the early 1980s, it was still a small and relatively unknown entity. I was a young grant-funded faculty member, and, when we finally connected, they offered access to a newly developing Ludwig network that included some of the most renowned researchers in the world. Moreover, the Institute was international, interactive and well-supported. I clearly remember asking Hugh what the catch was, and he told me to look in the mirror and understand that my success or failure depended on me alone. No excuses. I relished this challenge and it turned out to be exactly right as, over the years, Ludwig has afforded me the opportunity to do science at the highest level, to develop and exercise abilities in constructing teams for scientific inquiry and to participate on the international stage. I am very grateful for the 33 years of support that Ludwig has provided to me and proud of the two outstanding and widely recognized Branches that I assembled in Montreal and San Diego. It has been a wonderful run!

What scientific finding of yours has been most surprising to you?

The most surprising and gratifying finding arose from work we were doing tracking the origins of recessive mutations in families. This gave us the idea in the

early 1980s that we could use parents, siblings and/or their tumors to predict if a child in the family would develop disease—before it was even diagnosed—simply by following genotypes with the DNA markers I had developed and identifying those associated with affected members. We were elated when we were able to say very accurately that a child would not develop the tumor. In fact, even being able to identify kids who were very likely to develop the disease was also useful because they could be examined even earlier knowing that the risks of anesthesia were justified by the possibility of earlier radiotherapy or surgery. Our (my friends Magnus Nordenskjold at the Clinical Genetics Department at the Karolinska Institute in Stockholm, Brenda Gallie at the Hospital for Sick Children in Toronto and Linn Murphree at the Children's Hospital of Los Angeles) report of this hit like a bombshell because it showed for the first time that it was becoming increasingly possible to identify extremely high-risk individuals and offer them curative therapies in many cases.

Parenthetically, Magnus and I and our families were staying at his summer house in the Stockholm archipelago writing this paper in the evenings and building a tree house for the kids during the day. There were only a couple of phones on the small island but, even so, I was receiving mysterious phone calls from a Dr. Butt who seemed to be all over the world and saying that he understood "I was interested in his job." I had no clue what that was about and so simply ignored it until I returned to the U.S. (where Hugh called me at 6 am the morning after I landed). The rest is history!

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> Ludwig has afforded me the opportunity to do science at the highest level, to develop and exercise abilities in constructing teams for scientific inquiry and to participate on the international stage. I am very grateful for the 33 years of support that Ludwig has provided.
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Do you see a role for nutrition and microbiome research in GBM?
Sure. This is an exciting and promising area for cancer in general. It can be extended to intracellular metabolism, where several Ludwig investigators have made advances showing that cancer cell metabolism can be influenced by oncogenic mutations and thereby affect the growth of those cells or even the normal cells surrounding them.

What do you see in your post-Ludwig career? Will you remain in GBM research or pursue new opportunities, or both?

Definitely both. I want to be sure that the several reviewers who called me "unfocused" continue to be right! Fortunately, there are several other international organizations, including the Global Coalition for Adaptive Research and institutes, universities and companies that value my views. Consulting for them will continue to keep me busy.

What are you most proud of in your career?

My greatest accomplishment is contributing to the training, scientific maturation and ongoing success of the more than 120 students and fellows who have been members of my group, as well as the many hundreds of trainees who have been resident in the other laboratories in the Ludwig Montreal and San Diego Branches. I am proud of every one of them!

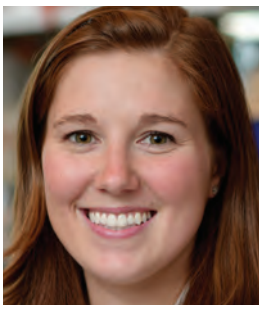
What advice would you give to young investigators today?

Read everything you can, work hard and trust your intuition, but with an open mind.

Who in your life influenced you the most?

There have been so many. Those who immediately come to mind are my father, Jim Cavenee, a career Air Force officer, and my uncle Max Ryan, who was a rodeo rider, dirt-track car racer and interstate truck driver. Both of them actively instilled in me the belief that being honest and standing up for what I believed—regardless of consequence—was how I was expected to lead my life. From a scientific standpoint, another uncle, Web Sawyer, who was head of chemistry for Shell Oil and taught at the University of California, Berkeley, piqued my imagination about the power of science when I was very young. Also, my postdoctoral mentor and friend, Ray White, who demonstrated every day that strength of conviction coupled with healthy skepticism about what are "true facts"; and Lloyd Old, who taught me that anything is possible when dreaming big and then actualizing those dreams. I am, and will be, eternally grateful to them all.

Will decentralizing science lead to more reliable results?



Decentralizing science should enable more reproducible results as independent investigators validate findings with varying protocols, reagents and analysis. However, collaborative efforts that propagate discovery and progress should not be abandoned, but rather strengthened across groups and institutions, with data validated at each level to ensure accurate and reliable results.

SARA SCHAD
Ludwig MSK

Decentralizing is a double-edged sword: multiple independent teams with consistent results suggest the conclusions are reliable and reproducible, but it is also inefficient, as building on previous knowledge deepens our understanding of the world. It may lead to more reliable results, but slower advancement than the scientific world is accustomed to now.

CHRISTINA CHAN
Ludwig Chicago

Decentralization of science might help ensure that results are reproducible and that the science is of top quality. It may however be challenging for independent labs to continuously seek new partnerships. The optimal solution is to be part of a large international constellation of scientifically independent teams, just like Ludwig Cancer Research.

THOMAS BALLIGAND
Ludwig Institute

Required reading

Ludwig Chicago

Nature Communications
2019 September 2

Tumor-reprogrammed resident T cells resist radiation to control tumors.

Arina A, Beckett M, Fernandez C, Zheng W, Pitroda S, Chmura SJ, Luke JJ, Forde M, Hou Y, Burnette B, Mauceri H, Lowy I, Sims T, Khodarev N, Fu YX, Weichselbaum RR.

Ludwig Institute

Cell Metabolism
August 22 [Epub ahead of print]

The MYC oncogene cooperates with sterol-regulated element-binding protein to regulate lipogenesis essential for neoplastic growth.

Gouw AM, Margulis K, Liu NS, Raman SJ, Mancuso A, Toal GG, Tong L, Mosley A, Hsieh AL, Sullivan DK, Stine ZE, Altman BJ, Schulze A, Dang CV, Zare RN, Felsher DW.

Ludwig Johns Hopkins

Science Translational Medicine
2019 July 17

A multimodality test to guide the management of patients with a pancreatic cyst.

Springer S, Masica DL, Dal Molin M, Douville C, Thoburn CJ, Afsari B, Li L, Cohen JD, Thompson E, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Simpson RE, Fernandez-Del Castillo C, Mino-Kenudson M, Brugge W, Brand RE, Singhi AD, Scarpa A, Lawlor R, Salvia R, Zamboni G, Hong SM, Hwang DW, Jang JY, Kwon W, Swan N, Geoghegan J, Falconi M, Crippa S, Doglioni C, Paulino J, Schulick RD, Edil BH, Park W, Yachida S, Hijioka S, van Hooft J, He J, Weiss MJ, Burkhart R, Makary M, Canto MI, Goggins MG, Ptak J, Dobbyn L, Schaefer J, Sillman N, Popoli M, Klein AP, Tomasetti C, Karchin R , Papadopoulos N, Kinzler KW, Vogelstein B, Wolfgang CL, Hruban RH , Lennon AM.

Ludwig Lausanne

Cancer Cell
2019 June 10

Cooperation between constitutive and inducible chemokines enables T cell engraftment and immune attack in solid tumors.

Dangaj D, Bruand M, Grimm AJ, Ronet C, Barras D, Duttagupta PA, Lanitis E, Duraiswamy J, Tanyi JL, Benencia F, Conejo-Garcia J, Ramay HR, Montone KT, Powell DJ Jr, Gimotty PA, Facciabene A, Jackson DG, Weber JS, Rodig SJ, Hodi SF, Kandalaft LE, Irving M, Zhang L, Foukas P, Rusakiewicz S, Delorenzi M, Coukos G.

Ludwig MIT

Nature Nanotechnology
2019 September 2
[Epub ahead of print]

Renal clearable catalytic gold nanoclusters for in vivo disease monitoring.

Loynachan CN, Soleimany AP, Dudani JS, Lin Y, Najer A, Bekdemir A, Chen Q, Bhatia SN, Stevens MM.

Ludwig MSK

Journal of Clinical Investigation
2019 July 22

In situ vaccination with defined factors overcomes T cell exhaustion in distant tumors.

Khalil DN, Suek N, Campesato LF, Budhu S, Redmond D, Samstein RM, Krishna C, Panageas K, Capanu M, Houghton S, Hirschhorn D, Zappasodi R, Giese R, Gasmi B, Schneider M, Gupta A, Harding JJ, Moral JA, Balachandran VP, Wolchok JD, Merghoub T.

Ludwig Oxford

Proceedings of the National Academy of Sciences USA
August 8 [Epub ahead of print]

iASPP mediates p53 selectivity through a modular mechanism fine-tuning DNA recognition.

Chen S, Wu J, Zhong S, Li Y, Zhang P, Ma J, Ren J, Tan Y, Wang Y, Au KF, Siebold C, Bond GL, Chen Z, Lu M, Jones EY, Lu X.

Science
2019 July 5

Conserved N-terminal cysteine dioxygenases transduce responses to hypoxia in animals and plants.

Masson N, Keeley TP, Giuntoli B, White MD, Puerta ML, Perata P, Hopkinson RJ, Flashman E, Licausi F, Ratcliffe PJ.

Ludwig San Diego

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2019 August 23
[Epub ahead of print]

Intron 1-mediated regulation of EGFR expression In EGFR-dependent malignancies is mediated by AP-1 and BET proteins.

Jameson NM, Ma J, Benitez J, Izurieta A, Han JY, Mendez R, Parisian A, Furnari F.

Cell Metabolism
epub July 11
[Epub ahead of print]

Oncogene amplification in growth factor signaling pathways renders cancers dependent on membrane lipid remodeling.

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Ludwig Stanford

Nature
2019 July 31
[Epub ahead of print]

CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy.

Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, Krishnan V, Hatakeyama J, Dorigo O, Barkal LJ, Weissman IL.

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Cell
July 4 [Epub ahead of print]

Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction.

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2019 May 29
[Epub ahead of print]

Long-term ex vivo haematopoietic-stem-cell expansion allows nonconditioned transplantation.

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