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MAY 2016

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

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ludwigcancerresearch.org MAY 2016

LETTER

We love putting this newsletter together. This is not just because we learn something—or a whole lot—new every time. It is also because we hope that by keeping you abreast of what your colleagues have been doing, we might occasionally expose opportunities for new collaborations.

You will notice there's an abundance of such opportunity. Over the past few months, Ludwig scientists have, among other things, settled a controversy over the identity of a blood-forming stem cell, exposed a molecular mechanism that drives the pediatric brain cancer neuroblastoma and devised a new type of CRISPR-Cas9 genome editing.

You'll see that nine of our scientists were among the most highly cited scientific researchers in the world in their fields. And we hope you enjoy the interview we've included with Ludwig Harvard Center Co-Director Joan Brugge.

If any of these stories inspires you to find out more about your colleagues, comment on their papers or get in touch, you will soon have a tool to help you do all that and more. We've just started rolling out Ludwig's new intranet. Some of you already have access to it; those who do not will soon enough. We hope it will help us all forge a closer Ludwig community.

Happy reading!

Sincerely,
Rachel Steinhardt
Vice President of Communications

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On the cover: Glenda Eger of Ludwig Uppsala

VERSATILE ENGINEER

Ludwig MIT scientist Sangeeta Bhatia has been named a 2015 Fellow of the National Academy of Inventors (NAI) for her work adapting and applying the tools of semiconductor manufacturing to solve biomedical problems. A prolific and creative researcher, Sangeeta has, among other things, harnessed chip-making technology to engineer miniaturized liver constructs that model disease, infection, and drug toxicity, demonstrated a prototype cancer detection technology that relies on nanoparticles and a urine test, and recently engineered probiotic bacteria to similarly help detect liver metastases.

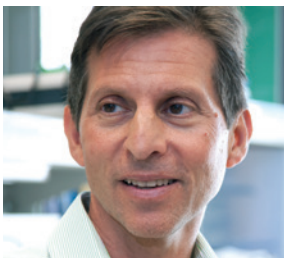
The NAI was founded in 2010 to recognize researchers at universities and non-profit institutes who translate their research findings into inventions with the potential to benefit society. The 168 Fellows were inducted April 15 during the Fifth Annual Conference of the National Academy of Inventors in Alexandria, Virginia.

Sangeeta Bhatia
Ludwig MIT

BRAINY BUSINESS

Ludwig San Diego's Paul Mischel has been elected Fellow of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society and publisher of the influential journal *Science*. The honor recognizes his distinguished contributions to science and its applications to cancer research, in particular the biology and treatment of glioblastoma multiforme (GBM), one of the deadliest and most aggressive types of brain cancer.

Paul's work has significantly advanced our understanding of GBM's biology and furnished invaluable clues to developing therapies for the currently incurable cancer. His most recent studies captured how GBM cells alter the reading of their genomes, and described several mechanisms by which they reengineer their metabolism and evade therapy. This year's 346 Fellows were honored at the Fellows Forum held on February 13 during the AAAS Annual Meeting in Washington, D.C.



Paul Mischel
Ludwig San Diego

HOT CROP

Nine Ludwig scientists made Thomson Reuters' list of *The World's Most Influential Scientific Minds*, which is derived from an analysis of more than a decade of research paper citations in 21 scientific fields. Ludwig Harvard scientists Bradley Bernstein , George Demetri, Jeffrey Engelman, Rakesh Jain and Arlene Sharpe, Ludwig MSK scientist Alexander Rudensky, Ludwig MIT scientist Bob Weinberg and Ludwig San Diego scientists Bing Ren and Don Cleveland were named to the list. Reuters, a multinational mass media and information firm, compiles its annual list from scientists who rank among the top one percent by citations received in their respective fields.

A NOTABLE APPOINTMENT

Ludwig Stockholm Director Thomas Perlmann was appointed Secretary-General of the Nobel Assembly and Nobel Committee in February. This means he will now serve as director of the Nobel Office and the Medical Nobel Institute, and spokesperson for the Nobel Assembly, the Nobel Committee, and the Nobel Prize in Physiology or Medicine. The Secretary-General is selected from among the members of the Nobel Assembly, where Thomas has been a member since 2006. He has also served as a member of the Nobel Committee for the past four years.

Thomas Perlmann
Ludwig Stockholm

THREE'S A CHARM

Ludwig Oxford's Peter Ratcliffe has been named Clinical Research Director of The Francis Crick Institute, a biomedical research institute headquartered in London. It is an initiative of six British scientific and academic organizations: the Medical Research Council (MRC), Cancer Research UK (CRUK), the Wellcome Trust, University College London, Imperial College London and King's College London.

Peter's research has transformed our understanding of how cells sense and respond to changes in oxygen levels, an important component of many diseases, including cancer. He will assume the new role in May and divide his time between the Francis Crick Institute and Oxford, where he will run his Ludwig lab and serve as Director of the Target Discovery Institute.

Peter Ratcliffe
Ludwig Oxford

CATCHING CANCER'S BADDEST BOY

Pancreatic cancer is among the deadliest of malignancies. It is tough to diagnose, rarely caught at an early stage and so almost always fatal. One challenge to diagnosis is that it is often hard to differentiate between run-of-the-mill pancreatic cysts and precancerous ones. In a November *Gastroenterology* study, a team of researchers led by Ludwig Johns Hopkins' Anne Marie Lennon describes a new diagnostic approach to distinguishing one from the other.

Using gene tests, a mathematical model and a fixed set of clinical criteria, the researchers analyzed data from 130 patients with benign or precancerous cysts and identified molecular markers and clinical features that classified cyst type with 90-100% sensitivity and 92-98% specificity. Their panel of molecular markers correctly identified 67 of the 74 patients who did not require surgery. Current methods for making such determinations are only about 63% accurate. The authors calculate that their test, if validated in larger trials, could help reduce the number of unnecessary pancreatic surgeries in cases of suspected cancer by as much as 91%.

Anne Marie Lennon
Ludwig Johns Hopkins

CRISPR ON DEMAND

CRISPR/Cas9, a gene editing technology that allows scientists to target and modify DNA with extraordinary ease and accuracy, is one of the hottest things going in cancer research and, for that matter, every other nook of the biomedical field. It consists of a DNA cutting enzyme, Cas9, attached to a short RNA molecule that guides said protein to a precise location in the genome. In a study published December 22 in the *Proceedings of the National Academy of Sciences*, Ludwig San Diego scientists Don Cleveland and Moira McMahon, in collaboration with Ionis Pharmaceuticals researchers, report how they gussied up the already elegant system. Their innovation replaces the guide-RNA with an RNA drug that permits them to turn the CRISPR-Cas9 system on and off at will. The researchers also made a version in which the Cas9 enzyme can additionally be switched off on demand by an associated RNA drug. Their approach is more efficient and accurate than the predominant CRISPR/Cas9 technology, which means it may be better suited to therapeutic applications.

Don Cleveland
Ludwig San Diego

SAFETY BRAKE

Mutations to the thrombopoietin receptor are known to contribute to a class of ailments known as myeloproliferative disorders. An international team of researchers led by Ludwig Brussels scientist Stefan Constantinescu and colleagues at Stony Brook University in New York published a study in the *Journal of Biological Chemistry* showing how the thrombopoietin receptor (TpoR or Mpl) is protected from aberrant activation. A single amino acid at the beginning of the part of the receptor that crosses the cell membrane has, it appears, been evolutionarily selected to counteract the effect of mutations that if acquired can lead, in other species, to aberrant activation and cancer. In healthy humans, the receptor is critical for platelet formation and hematopoietic stem cell (HSC) renewal. Platelets help the blood clot and HSCs are responsible for the constant renewal of blood.

Stefan Constantinescu
Ludwig Brussels

A LETHAL ABSENCE

A team of scientists led by Ludwig Stanford Deputy Director Michael Clarke found that colon cancer patients with a particular gene expression pattern might benefit from chemotherapy after surgery. In a retrospective study published January 21 in the *New England Journal of Medicine*, the researchers categorized colon cancer patients based on the presence or absence of a protein called CDX2, which is found in mature colon cells. They report that 4% of colon cancer patients have tumors that don't express CDX2. Examining data on 466 patients with any stage of colon cancer, the team discovered that 41% of CDX2-negative patients lived disease-free for five years compared to 74% of CD2X-positive patients. Interestingly, a closer look at the data revealed that 91% of CDX2-negative patients with stage-2 disease who were treated with chemotherapy after surgery lived disease-free for five years, versus 56% of those who did not receive chemotherapy. The findings, which are of immediate clinical relevance, will have to be confirmed in larger trials.

Michael Clarke
Ludwig Stanford

THE PROPHETIC GUT

Cancer immunotherapy has its risks. One particularly troubling side effect is the acute onset of immune-mediated colitis, a potentially dangerous inflammation of the colon's inner lining. Given how extensively our menagerie of intestinal microorganisms regulates the immune system, a team of researchers led by Ludwig MSK's Jedd Wolchok investigated whether this "microbiome" holds any clues to the risk of colitis following treatment with anti-CTLA-4 antibodies. To find out, they examined stool samples from 34 patients with metastatic melanoma before and after they were given such treatment. They report that one-third of the patients developed colitis within weeks of treatment. Those who did had relatively low levels of gut bacteria belonging to the phylum *Bacteroidetes* prior to immunotherapy. Their microbiomes also appeared to be less able to produce Vitamin B12 and transport polyamines, a class of biochemicals essential to colonic health. The study opens the door to identifying and treating patients at risk for colitis following immunotherapy.

Jedd Wolchok
Ludwig MSK

MUCOSAL MILITIA

Using single-cell RNA sequencing, a team led by Ludwig Stockholm scientist Rickard Sandberg and Jenny Mjösberg of the Karolinska Institutet discovered new subgroups of innate lymphoid cells (ILC). These immune cells, which were identified relatively recently, maintain the barrier function of mucosal tissue—the soft lining of inner body cavities that serves as a first line of defense against pathogens. In an April study in *Nature Immunology*, the researchers report their analysis of global gene expression in individual tonsil cells. They found three previously unknown subgroups of ILCs that exhibit different gene expression patterns and differ in how they react to signaling molecules and in their ability to secrete proteins. They also uncovered the expression of numerous genes of previously unknown function in ILCs, indicating that the cells have some currently unknown functions. Delving into the complexities of ILC biology and understanding the contributions these sub-populations make to inflammatory immune responses might prove beneficial in the development of new drugs for a variety of ailments.

Rickard Sandberg
Ludwig Stockholm

STRUCTURES OF RESISTANCE

Patients with estrogen receptor–positive metastatic breast cancer might initially respond to endocrine treatments, such as tamoxifen, but they inevitably become resistant. Two estrogen receptor (ER) mutations that help the cancer circumvent the drugs' effects, D538G and Y537S, are frequently the culprits that instigate such resistance. In a February 2 *eLife* study, a team of University of Chicago researchers led by Ludwig Chicago Co-Director Geoffrey Greene, describes how these mutations confer drug resistance by altering the structure of the receptor in a manner that keeps it in a constantly activated state. The researchers also report that the mutations reduce the receptor's affinity to both its activating hormone—estradiol—and the antiestrogen drugs that switch it off. The study could prove useful to the design of new drugs for resistant ER-positive breast cancers.

Geoffrey Greene
Ludwig Chicago

ERROR AT THE SOURCE

Neuroblastoma is the most common cancer in infants, the fourth most common in all children, and accounts for 15% of all pediatric cancer deaths. In a January 25 paper in *Developmental Cell*, Ludwig Stockholm researchers led by Susanne Schlisio offer new clues to its origins. They report that KIF1Bβ, a gene often lost in those afflicted with this cancer, allows neural crest cells to evade death at the appropriate time during sympathetic nervous system development. Their previous studies have shown that KIF1Bβ, located on chromosome 1p36, might be the neuroblastoma tumor suppressor gene long thought to reside in that part of the chromosome. Susanne and her colleagues report that KIF1Bβ plays a critical role in controlling the activity of an enzyme named calcineurin, which signals in response to the influx of calcium into cells. They show that a critical signal triggered by calcineurin and required to induce cell death by fragmenting the mitochondria—the "batteries" of the cell—is compromised by the loss of KIF1Bβ. The loss of this gene is also associated with poor prognosis. The work opens up an avenue to new neuroblastoma therapies.

Susanne Schlisio
Ludwig Stockholm

THE ROOTS OF THOUGHT

An international group of researchers, led in part by Ludwig Stockholm scientist Rickard Sandberg, developed and applied a novel method called Patch-Seq to profile individual neural cells of the neocortex. Though this region of the brain is critical to cognition, relatively little is known about the distinguishing traits of its constituent cells. The researchers applied patch-clamp recording, which is used to measure the activation and connections between neurons, with single-cell RNA sequencing. This permitted the researchers to link the morphological and functional properties of single neurons directly to their gene expression profiles. The technique might help identify the specific brain cell dysfunctions that underlie psychiatric illnesses and, perhaps, facilitate the development of new interventions. The team found, for example, that four genes associated with autism and schizophrenia are expressed by neurons of a particular cell type. The findings were published in February in *Nature Biotechnology*.

Rickard Sandberg
Ludwig Stockholm

TELL-TALE MARKER

Researchers have long been stymied in their efforts to distinguish long-term hematopoietic stem cells (HSCs) — the ones that can regenerate indefinitely—from the less long-lived versions of such cells. Long-term HSCs are not only rare but also tough to find. A team led by Ludwig Stanford Director Irv Weissman screened more than 100 genes and identified a single one, Hoxb5, that is expressed in bone marrow and limited to long-term HSCs in mice. This unique marker allowed the researchers to isolate the most fundamental form of the cell that can replicate indefinitely and is critical to the lifelong production of blood and immune cells. The researchers also showed that more than 90% of these long-term HSCs reside in the venous sinusoids, a particular type of blood vessel that is primarily found in the bone marrow. The findings were reported February 11 in *Nature*. The discovery goes a long way toward settling an age-old dispute over the identity of long-term HSCs and lays the groundwork for researchers to grow them in the lab and study their biology in their natural environment within the mouse.

Irv Weissman
Ludwig Stanford

TARGET: MALIGNANT MOTILITY

Periostin is a secreted protein that is expressed at high levels in breast and head and neck cancers, and its over-expression is associated with highly invasive disease. The protein interacts with integrins, which in turn contribute to cancer's metastatic cascade. In a paper published April 15 in the *International Journal of Cancer*, a team of researchers led in part by Ludwig alum Parmjit Jat, Jacques Van Snick of Ludwig Brussels and Ludwig scientists in Oxford and New York, developed six monoclonal antibodies that recognize both human and mouse periostin. The antibodies inhibit binding to the integrin αvβ3 and curtail cell migration in lab assays. Periostin expression was found to be an indicator of prognosis in breast tumor cells. The highly specific anti-periostin antibodies uncovered the functional importance of the fascilin 1-1 domain of the protein and its likely importance in metastasis.

Jacques Van Snick
Ludwig Brussels

TWO ROUTES TO MEMORY LANE

When called into battle, CD8+ T cells rapidly expand and differentiate into memory precursor effector cells (MPECs) that remember the enemy and short-lived effector cells (SLECs) that do the fighting. In a February 9 *Cell Reports* study, a team of Ludwig Lausanne researchers led by Lianjun Zhang and Pedro Romero describes the role of mammalian target of rapamycin complex 2 (mTORC2) in stimulating the production of MPECs. A deficiency of its core component, Rictor, promotes CD8 memory generation without affecting the ability to mount effector responses. The effect is mediated by the transcription factor FoxO1. This suggests mTORC2 may be an important target for immunotherapy interventions, as it is a critical regulator of CD8 T cell differentiation.

In a related January 16 paper in *EBioMedicine*, they reported that another class of T cells—stem cell-like memory T cells—can be generated when the related protein complex mTORC1 is suppressed. These memory T cells behave like stem cells, persisting over the long term and replenishing the pool of immune cells targeting a particular antigen. Both studies are likely to be of great value to the development of adoptive T cell therapies for cancer as well as for therapeutic vaccine design.

Lianjun Zhang
Ludwig Lausanne

Pedro Romero
Ludwig Lausanne

FOLDING UNDONE

In a paper published March 10 in *Blood*, a team of Ludwig Brussels researchers led by Stefan Constantinescu describes the mechanism by which mutations to the chaperone protein calreticulin induce myeloproliferative neoplasms, a collection of chronic blood cancers in which blood cells are overproduced. Calreticulin helps to fold freshly made proteins and it is mutated in a significant proportion of patients with myeloproliferative neoplasms. The researchers show that calreticulin mutants specifically activate the thrombopoietin receptor, which controls the production of blood-clotting platelets. Such uncontrolled activation is known to play a central role in some myeloproliferative neoplasms. The researchers point out that the mechanism they uncovered represents a new paradigm in cell signaling. Stefan and his colleagues also published a companion paper in *Blood* demonstrating that calreticulin mutations can induce thrombocytosis, a disorder in which the body produces too many platelets, in a retroviral mouse model.

Stefan Constantinescu
Ludwig Brussels

TEAMING UP

Ludwig spin-off iTeos announced a new partnership with Adimab, a leader in the discovery of monoclonal and bispecific antibodies. Adimab will identify fully human therapeutic antibodies against targets selected by iTeos. The antibodies will be transferred to iTeos, which will be responsible for further product development, including manufacturing and clinical trials. Drug candidates will be clinically evaluated as both monotherapies and in combination with leading immuno-oncology drugs.

BETTER TARGETING

Ludwig Lausanne and Ludwig spin-off company TCMetrix have teamed up with Medigene, a biotech company that develops personalized T cell-based immunotherapies targeting various types and stages of cancer. The parties have agreed to collaborate on establishing better and faster methods for selecting tumor-specific T cell receptors to arm a patient's own T cells. Such engineered T cells are better able to detect and kill cancer cells. Medigene will have access to NTAmer, a state-of-the-art technology that accurately predicts the function of tumor-specific T cells for different cancer cell types. The technology was developed by TCMetrix, and further refined in collaboration with Ludwig Lausanne scientists.

GOING VIRAL

We don't normally think of viruses as the good guys. But oncolytic viruses are just that, from our perspective, at least, if not the cancer cell's. This is because such viruses have a yen for malignant cells, which they infect and selectively kill, sometimes even stimulating an anti-tumor immune response. Researchers have been trying for decades to get such viruses to work as cancer therapies. They're finally making some headway with the rise of checkpoint immunotherapy, which is a natural partner to the approach. Now Ludwig and the Cancer Research Institute (CRI) have agreed to evaluate ONCOS-102, an adenovirus developed by Targovax, an Oslo-based biotechnology company, in early stage clinical trials. The oncolytic virus, which also encodes a factor that stimulates the immune system (GM-CSF), will be evaluated in combination with other immunotherapies, such as checkpoint inhibitors, through the Ludwig-CRI CVC Clinical Trials Network.

DID YOU KNOW…

The secret to success is a good night's sleep. No joke. The Dalai Lama sleeps soundly (and probably very profoundly) for eight or more hours a day. So does the slightly less relaxed Amazon founder Jeff Bezos, as well as Facebook COO Sheryl Sandberg, Microsoft's Bill Gates, Oscar-winning actor Matthew McConaughey and media mogul Arianna Huffington, whose new bestseller is aptly titled **The Sleep Revolution**. Albert Einstein, it is said, logged a whopping 10 hours every night—and snuck in a couple of daytime naps to boot. Maybe that's when he did his thought experiments.

Sadly, most of us are not Einstein. Nor do we get enough zzz's. This makes us forgetful, not to mention cranky. But if you think counting sheep is way too yesterday, or if it only reminds you of lamb chops—which sends you to the fridge for a midnight snack—Ludwig Link has a solution for you. A suitably high tech, totally vegetarian, today kind of solution. IBM and Apple, we hear, have joined forces to bring us all the SleepHealth iPhone app and a patient-driven SleepHealth Mobile Study. Although it is almost certainly a part of their Secret Plan to Rule the World, they say it will also help you connect the dots between your sleep habits and your health.

So, can't sleep? Well, then, **click here** to download a free app that will monitor your sleep habits and show you how to improve them. Or, for all our sleepy sakes, visit **Sleeptember.org** to participate in the SleepHealth study.

The cell doctor: Joan Brugge, Co-Director of the Ludwig Harvard Center

If you could solve one big problem in cancer research, what would it be?
Prevent cancer's recurrence. Despite all the advances we've made in cancer therapeutics, too many patients must deal with the news that their cancer is back because of resistance to therapies. Drug resistance is complicated by tumor heterogeneity—this includes heterogeneity between tumors from different individuals, but even more significantly, within an individual tumor and between tumors at different sites in the same patient. Tumors are challenging to control and we need to better understand why drugs that are effective at treating tumors initially, still leave patients vulnerable to relapse.

How is the Ludwig Center at Harvard addressing this challenge?
We brought together the best brains from across the Harvard community to work together to accelerate progress in identifying cancer cells' vulnerabilities that we can target therapeutically and develop new strategies to overcome therapy resistance. We're all committed to providing a deeper understanding of the causes of therapy resistance as well as ways to intervene and monitor it. This unique collaborative research model encompasses a diverse cross-section of experts in cancer research and cancer biology as well as oncologists, pathologists and immunologists. Every Monday morning we spend two hours sharing ideas and presenting data and then brainstorming about what the data means and where to take it next. Right now, our efforts are focused on melanoma, small cell lung cancer, acute myeloid leukemia and triple negative breast cancer— cancers where current therapies work well initially, but in which the tumors inevitably recur.

You spent several years in industry. What motivated you to make the move?
I was very excited about the overall objectives and approaches that the start-up company was aiming for—using

structure-based drug design to develop inhibitors of protein-protein interactions, which is an ongoing challenge in designing drugs. I felt that it would be very satisfying to do discovery research in an environment where it could be translated into something meaningful for patients. For me it was an opportunity to take my research to the next level and use my different talents and skills in developing drugs designed to inhibit the proteins we had identified and discover pathways crucial for disease processes. And, it would all happen under one roof.

What advice do you have for someone contemplating a move from academia to industry?

There are many exciting and challenging jobs in industry that would be very attractive to research-oriented scientists. Before you make the leap, weigh the pros and cons of the potential move. You may love research but you may be leery about running an academic lab because of the many demands on your time. Industry scientists generally have a better work-life balance and can stay focused on their research without the added commitments of teaching, advising students, publishing and applying for grants that come with an academic job. At the same time, industry research is geared towards a product rather than knowledge itself and a product-driven mission means that research freedom can be limited. A company has to prioritize their efforts and activity, which means they're focused on the information that they "need to know versus the things that would be nice to know." Academic investigators have the flexibility to investigate a promising lead and pursue those odd findings that don't fit the norm. That being said, many companies allow investigators to carry out independent research for a small percentage of their time, allowing them to engage in more risky research. Bottom line, industry environments vary considerably and you need to assess your own strengths and weaknesses and decide the best fit where you'll continue to excel in what you love to do and enjoy most.

How can we reach out and draw more young, bright minds into science?

Schools are so focused on teaching to the test and preparing students to score well, that there's no time to work on projects that would awaken them to the thrill of discovery research. Real learning is achieved through the investigative process and kids

> "Real learning is achieved through the investigative process and kids have to be encouraged to search for the answers themselves."

have to be encouraged to search for the answers themselves. Science classes should be geared toward understanding a topic and less about memorizing facts. If we teach students to think like scientists - let them test an idea, evaluate evidence, ask a question about how the world works and perhaps discover how difficult it can be to find an answer, I think we could get more kids hooked early on.

How do you unwind outside the lab?
Tennis and scuba diving. Weekly tennis games are the perfect outlet to take my mind off work and allow me to enjoy friendships outside of work. Scuba diving is just a phenomenal, awe-inspiring experience. There is something about neutral buoyancy that is very spiritual and allows you to experience this incredibly beautiful world around you. Nothing rivals the experience of being suspended weightlessly in water while floating effortlessly along a coral reef. And there's nothing quite as exhilarating as swimming next to whale sharks, which we did in Raja Ampat—it's one of life's ultimate bucket-list experiences.

Do you think more attention should be paid in training scientists to communicate effectively?
Absolutely. Communication is part of a scientist's everyday life—giving talks, writing papers and grants, and communicating with different audiences. But for a lot of our trainees, English is their second language, which can be challenging, especially when writing a scientific paper or presenting research orally. Communicating complex ideas in a clear, transparent way is an essential tool and we need to find more opportunities for postdocs to practice and hone their skills. I have my lab members 'practice' their writing skills by drafting reviews of manuscripts being considered for publication; this is a very effective way to encapsulate their thoughts and distill the research down to just a few paragraphs and to use their critical thinking skills.

What's on the cancer horizon?
Right now we're looking at a very complex scenario for cancer treatment—especially in terms of precision medicine. There is an enormous diversity within a tumor—different regions have different mutations—and we need to identify predictive markers for the cancer state rather than for every genetic alteration within a tumor. We need to develop therapies targeting a cancer's state as opposed to trying to sort out the

> "Communicating complex ideas in a clear, transparent way is an essential tool and we need to find more opportunities for post docs to practice and hone their skills."

optimal therapy for every genetic alteration or combination of genetic alterations. Immunotherapies are going to play more and more of a role in cancer therapy and we need to have a critical understanding of how immunotherapies should be integrated with targeted therapy and how we can optimally design immunotherapies in order to avoid more generalized immunostimulation.

How do you inspire creativity in your lab members?

Breakthrough research requires the confidence to try things out, take risks and make mistakes. When my lab members are working on a project, I give them a great deal of independence in allowing them to be the first to interpret the data and propose the next steps. If there's another direction I think they should consider, I ask rather than tell. Asking the right questions encourages them to shift gears and dig deeper, with the goal of finding a new or alternate way of approaching and solving a problem.

How do you achieve career-life balance?

Juggling the demands of a career and a personal life is an ongoing challenge for me, and I have to admit I'm not very good at it. The overwhelming demands on my time are a constant struggle. I feel that it

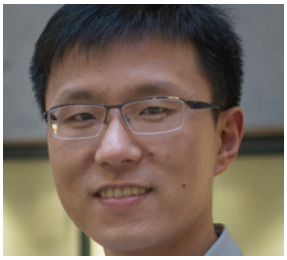
is important to engage in recreational activities in order to get a break from work; however, one has to prioritize because it isn't feasible to participate in all of the things in which you are interested. At work, consider all the demands that compete for your time, and decide which ones to keep and what to discard. Take on only those commitments that you know you have time for and that you truly care about.

This way you will get satisfaction from these commitments, people will respect you for the job that you get done and they will understand when you say no to other requests. It's a discipline that doesn't come naturally to most of us, especially me.

Have we unleashed an indomitable beast in the CRISPR/Cas9 tool?

Not at all! CRISPR/Cas9 has already demonstrated tremendous value in biomedical research allowing many to test hypotheses not possible a few years ago. It is likely to aid in the development of new drugs and holds the real promise of a viable therapeutic against genetic diseases currently with limited treatment options.

MOIRA A. MCMAHON
Ludwig San Diego



This genome-editing tool is being broadly implemented in the field of functional genomics. It allows us to, comprehensively, experimentally model candidate cancer driver mutations identified through bioinformatics. It has already uncovered novel biology in the lab, but also holds great promise to accurately and efficiently rewrite the human genome for cancer therapy.

PING ZHANG
Ludwig Oxford

The astoundingly rapid spread of CRISPR/Cas9 technology has reinvigorated fundamental ethical questions surrounding genome editing. CRISPR/Cas9 promises to yield an immeasurable wealth of knowledge as a research tool and may create novel therapeutic opportunities. These enormous potential gains offset the risk that this technology may be misapplied, yet underscore the importance of collectively defining ethical boundaries for its use.

KRISTEN E. MENGWASSER
Ludwig Harvard

Required reading

Ludwig Brussels

Blood 2015 March 10
Calreticulin mutants in mice induce an MPL-dependent thrombocytosis with frequent progression to myelofibrosis.

Marty C, Pecquet C, Nivarthi H, Elkhoury M, Chachoua I, Tulliez M, Villeval JL, Raslova H, Kralovics R, Constantinescu SN, Plo I, Vainchenker W.

Blood 2016 March 10
Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants.

Chachoua I, Pecquet C, El-Khoury M, Nivarthi H, Albu RI, Marty C, Gryshkova V, Defour JP, Vertenoeil G, Ngo A, Koay A, Raslova H, Courtoy PJ, Choong ML, Plo I, Vainchenker W, Kralovics R, Constantinescu SN.

Journal of Biological Chemistry 2016 February 5
His499 regulates dimerization and prevents oncogenic activation by asparagine mutations of the human thrombopoietin receptor.

Leroy E, Defour JP, Sato T, Dass S, Gryshkova V, Shwe MM, Staerk J, Constantinescu SN, Smith SO.

Ludwig Chicago

Elife 2016 Feb 2
Estrogen receptor alpha somatic mutations Y537S and D538G confer breast cancer endocrine resistance by stabilizing the activating function-2 binding conformation.

Fanning SW, Mayne CG, Dharmarajan V, Carlson KE, Martin TA, Novick SJ, Toy W, Green B, Panchamukhi S, Katzenellenbogen BS, Tajkhorshid E, Griffin PR, Shen Y, Chandarlapaty S, Katzenellenbogen JA, Greene GL.

Ludwig Johns Hopkins

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A combination of molecular markers and clinical features improve the classification of pancreatic cysts.

Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA Jr, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM.

Ludwig Lausanne

Cell Reports 2016 February 9
Mammalian target of rapamycin complex 2 controls CD8 T cell memory differentiation in a Foxo1-dependent manner.

Zhang L, Tschumi BO, Lopez-Mejia IC, Oberle SG, Meyer M, Samson G, Rüegg MA, Hall MN, Fajas L, Zehn D, Mach JP, Donda A, Romero P.

EBioMedicine 2016 January 16
Modulation of mTOR Signalling triggers the formation of stem cell-like memory T cells.

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