LUDWIG LINK

JANUARY 2016

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

LUDWIG LINK
ludwigcancerresearch.org JANUARY 2016

LETTER

Ludwig may be many things—global organization, employer, philanthropy—but it is above all an entity dedicated to science and technology for the prevention, diagnosis and treatment of cancer.

As you'll notice while browsing through this issue of Ludwig Link, our researchers have been rather busy on both the science and technology fronts. They've probed the darkest recesses of the cancer cell and tumor biology, shed new light on the immune system's cellular foot soldiers and taken big steps toward the creation of a new kind of cancer diagnostics. They have made waves even in the buttoned down business of clinical trials: Our researchers are among the architects of a far more flexible approach to testing experimental therapies for glioblastoma multiforme, the deadliest type of brain tumor in adults.

You will also see that Ludwig's numerous contributions to cancer research and care have, happily, not gone unnoticed. Our scientists have continued to rack up honors, awards and accolades, and we mention some of them here. We also have an interview with Ludwig San Diego's new director, Richard Kolodner, in which he talks about his extremely well trained border collie, Levi, his research career, and the opportunities and challenges posed by the profusion of new technologies for biomedical inquiry. This got us wondering what our postdocs think about the pace of technological change in the sciences, so we asked. Check out what a select few had to say in our "Ask a scientist" section.

Happy reading!

Sincerely,
Rachel Steinhardt
Vice President of Communications

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On the cover: Geoffrey Greene of Ludwig Chicago

CARRYING COLEY'S TORCH

Ludwig MSK scientist Alexander "Sasha" Rudensky received the Cancer Research Institute's (CRI) 2015 William B. Coley Award for Distinguished Research in Basic Immunology for his pioneering work on regulatory T (Treg) cells. These are the immune system's peacekeepers. They calm down the immune response after a battle has been won—preventing collateral damage to healthy tissues—and play a critical role in preventing autoimmunity. But the cells are also recruited by tumors to shield them from immune clearance, making them choice targets for novel immunotherapies. Sasha's lab, along with others, discovered that the transcription factor Foxp3 is essential for differentiation of Treg cells and for their ability to suppress potentially deadly, runaway inflammation. The award was established in 1975 in honor of William B. Coley, who pioneered cancer immunotherapy. Sasha delivered the William B. Coley Lecture at the CRI-CIMT-EATI-AACR Inaugural International Cancer Immunotherapy Conference on September 17 upon receiving the award.

Alexander "Sasha" Rudensky
Ludwig MSK

A HAT TRICK IN SAN DIEGO

Ludwig San Diego's Bing Ren was named a principal investigator in two components of the National Institute of Health's recently launched 4D Nucleome Program. This ambitious, multi-institutional project will map the three-dimensional structure of chromosomes, link those structures to the chemical—or epigenetic—tags on DNA and its protein packaging that control gene expression, and chart out how both the tagging and the expression change over time in different types of tissue. Bing is to be a principal investigator in a $20.2 million organizational hub that will integrate the efforts of all six of the program's interrelated initiatives. He is also the contact principal investigator for the $8.6 million Nuclear Organization and Function Interdisciplinary Consortium, which will develop the next generation of high-throughput technologies to produce dynamic, three-dimensional maps of mammalian genomes. The program will furnish data of lasting relevance to multiple fields of human biology, not least cancer research.

But wait, there's more. Bing also just received a three-year, $2.3 million grant to create computational models to pin down the DNA variants in noncoding regions of the genome that contribute to age-related macular degeneration, the most common cause of age-related blindness. Some 90% of sequence variations reside in such stretches of the genome, and many of them affect whether and to what extent genes are expressed.

Bing Ren
Ludwig San Diego

THE INDUCTED

Ludwig Johns Hopkins co-director Kenneth Kinzler and Alexander "Sasha" Rudensky, director of Ludwig MSK, were elected to the National Academy of Medicine. They join a select group of 80 other inductees from around the world who received the honor this year. The academy provides independent, objective analysis and advice on national issues related to medicine and health, and helps shape public policy.

Ken was recognized for his role in identifying genetic mutations responsible for colorectal cancers, and his distinguished work in cancer genomics, including the sequencing of the first cancer genomes. Sasha was recognized for his groundbreaking contributions to immunology, most notably to our understanding of regulatory T cells, which tamp down immune responses. Therapies that activate or switch off these cells are now being explored for the treatment of autoimmune diseases and cancers.

Ken Kinzler
Ludwig Johns Hopkins

Alexander "Sasha" Rudensky
Ludwig MSK

SHARPER IMAGE

Ludwig Stockholm scientist Rickard Sandberg received a 2015 Vallee Foundation Young Investigator Award, which recognizes originality, innovation and promise in early career researchers and gives winners a $250,000 grant to support their basic biomedical research. An international leader in single-cell genomics and bioinformatics, Rickard studies genomic expression and regulation, using single-cell RNA-sequencing technologies to capture the subtlest of differences between individual cells. In this project he will use single-cell RNA sequencing to study variations in the expression of alleles—a term used to describe a single copy of each gene of an inherited pair—across tissues and cell types. Alleles can differ slightly from each other, so such studies will enrich our understanding of how variations in gene expression give rise to diverse traits and diseases.

Rickard Sandberg
Ludwig Stockholm

SCIENCE GUIDE

Ludwig's Web Cavenee has been appointed chair of the National Foundation for Cancer Research (NFCR) Scientific Advisory Board. NFCR supports cancer research and public education for the prevention, early diagnosis and treatment of cancer. Web will work with other board members to provide scientific, strategic and clinical guidance for NFCR's basic science and translational research programs. Over the past three decades, Web has built an enviable portfolio of scientific discovery, most notably in his work elucidating the initiation, progression and resistance mechanisms of glioblastoma multiforme, the most common and deadliest type of brain tumor in adults. He is also well known for having found, early in his career, the first genetic evidence for the existence of tumor suppressor genes in humans.

Web Cavenee
Ludwig Strategic Alliances in CNS Cancers

EXPERIENCE ON THE ROSTER

Christophe Quéva has been appointed chief scientific officer of Ludwig spin-off iTeos Therapeutics. Christophe received his PhD from the University of Lille, completed his postdoctoral studies at the Fred Hutchinson Cancer Center and spent more than 15 years in oncology R&D at AstraZeneca, Amgen and Gilead Sciences. He has received several patents in the fields of cancer biology, immune therapy and drug discovery. His experience will be invaluable to iTeos, which hopes to develop a battery of mechanistically novel immunotherapies.

Christophe Quéva
iTeos Therapeutics

Peter Kim was inducted as the Virginia and D.K. Ludwig Professor of Biochemistry at a ceremony held on September 15 at Stanford University School of Medicine.

HEALERS & PEACEKEEPERS

Regulatory T cells (Treg cells), grown-ups of the T cell crowd, rush in to calm things down after a heated battle against invading viral forces or seditious cancer cells. Now it turns out they aren't just peacemakers. In a study published August 27 in *Cell*, Ludwig MSK researchers led by Alexander "Sasha" Rudensky report that Treg cells also moonlight as healers. They show that a selective deficiency in the production of amphiregulin, a growth factor, by Treg cells can lead to severe lung damage during influenza infection. Treg cell production of amphiregulin appears dependent on immune cell signaling molecules known as interleukins, specifically IL-18/IL-33. Sasha and his team also show that this healing activity occurs independently of the Treg cells' suppression of inflammatory immune responses, a capability that depends on T-cell receptor activation. Treg cells' role in healing, by contrast, does not. These findings indicate that Treg cells have a major role in tissue repair and maintenance—one that is quite distinct from their role in suppressing immune responses and inflammation.

SHED EVIDENCE

More than 550,000 cases of head and neck cancer are thought to occur annually worldwide. Ludwig Johns Hopkins researchers Nishant Agrawal, Ken Kinzler and Bert Vogelstein report in a June 24 study in *Science Translational Medicine* that tumor DNA can be detected with high accuracy in the blood and saliva of patients with such cancers. Though their results will have to be confirmed in larger studies, the finding could lead to the development of reliable screening tests and improved monitoring of patients diagnosed with head and neck cancers.

Saliva samples were taken from 93 patients newly diagnosed with head and neck cancer or with recurrent cancer, and 47 of these patients also gave blood samples. The researchers found tumor DNA in the saliva of 71 patients and in the blood of 41 patients. In 45 of the 47 who gave both blood and saliva, investigators identified tumor DNA in at least one of the fluids. Saliva tests were better at identifying cancers in the mouth (all 46 oral cavity cancers were identified), whereas blood tests detected more cancers in the pharynx and larynx. The researchers plan to validate the findings in larger studies.

Nishant Agrawal
Ludwig Johns Hopkins

Ken Kinzler
Ludwig Johns Hopkins

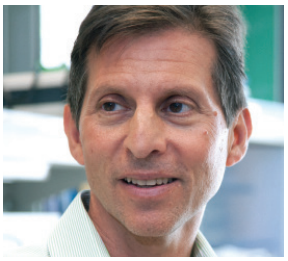
Bert Vogelstein
Ludwig Johns Hopkins

SWEET & SOUR SUSTENANCE

Tumors have long been known to take up copious quantities of glucose and acetate, and there appear to be many reasons why. In a July 28 study in *Proceedings of the National Academy of Sciences*, Ludwig San Diego researchers Paul Mischel and Web Cavenee and their colleagues add to the growing list. Glioblastoma multiforme (GBM) cells, they report, harness these nutrients to evade targeted therapies against mutant forms of the epidermal growth factor receptor (EGFR), which are found in more than half of these deadly brain tumors.

The researchers discovered that the protein complex mTORC2, which is switched on by EGFR and plays a key role in regulating a cell's metabolism, increases the utilization of glucose and acetate in cancer cells. Glucose and acetate then return the favor by switching on mTORC2. Further, in the presence of one of these two nutrients, mutant EGFR-targeting drugs erlotinib and gefitinib fail to switch off mTORC2 signaling—something they do just fine otherwise. The researchers show that glucose and acetate activate mTORC2 through a chemical produced when they are metabolized named acetyl coenzyme A. The study further suggests that drugs used to manage brain swelling in GBM patients, which tend to increase blood glucose, might inadvertently be spurring tumor growth. Targeting mTORC2 and regulating how nutrients are used to maintain the activity of oncogenic signaling pathways may provide paths to beating back GBM, and possibly other types of tumors.

Web Cavenee
Ludwig Strategic Alliances in CNS Cancers



Paul Mischel
Ludwig San Diego

CHINK IN THE LINKS

Nearly 60% of all glioblastoma multiforme (GBM) tumors are fueled by amplified and mutated forms of the epidermal growth factor receptor (EGFR). A particular mutant form of the protein called EGFRvIII is found on tumor cells in up to a third of patients, potently promoting tumor growth. In a study published October 15 in *Molecular Cell*, a team of Ludwig San Diego researchers, including Paul Mischel, Bing Ren and Andy Shiau, show how EGFRvIII drives critical processes that alter the reading of the genome, how each process is linked to the other, and how their interconnections could potentially be exploited to treat GBM using a class of experimental cancer drugs known as BET bromodomain inhibitors.

ENVIRONMENTAL PROTECTION

A team of Melbourne scientists led by Joan Heath published a study August 1 in *Disease Models & Mechanisms* on the function of the colon cancer marker glycoprotein A33 (GPA33) and its role in maintaining the intestinal barrier, which bars entry to toxins and pathogens. Damage to this barrier can promote hypersensitivity to foods, inflammatory bowel disease and colitis-associated cancer. Joan and her colleagues deleted the gene encoding Gpa33 in mice and exposed them to either a potent carcinogen alone or that agent in combination with another that can trigger colitis, a severe inflammation of the colon. The mice exposed to both agents exhibited damage to the intestinal barrier, heightened immune activity in the colon, a hypersensitivity to food typically associated with inflammatory bowel disease, and a striking increase in colitis-associated tumors. Those treated with the carcinogen alone showed no increase in sporadic tumor formation, showing how dependent colitis-associated cancer is on inflammatory stimuli. The Gpa33(–/–) mice provide a valuable model for studying the mechanisms linking intestinal barrier integrity to colonic diseases and cancer.

Joan Heath
Ludwig Melbourne

CIN AND ITS CONSEQUENCES

A team of Ludwig Uppsala researchers led by Calle Heldin and Maréne Landström report in the July 20 issue of *Journal of Cell Biology* that CIN85, a protein that regulates cell signaling and is overexpressed in invasive cancers, boosts TGFβ signaling by ramping up the recycling of its receptor (TGFβRI) to the cell surface. Aberrant TGFβRI signaling is known to drive cancer cell invasion and metastasis. When the expression of CIN85 was blocked with small interfering RNA, TGFβRI accumulated in intracellular compartments. When it was amped up, TGFβR1 accumulated on the cell surface—a phenomenon that could be reversed by inhibiting the movement of vesicles bearing proteins to the cell's surface. The researchers also report that the level of CIN85 expression corresponds to the aggressiveness of prostate cancer, an important bit of information on a cancer whose malignancy varies drastically from patient to patient.

Calle Heldin
Ludwig Uppsala

Maréne Landström
Ludwig Uppsala

CRAZY GLUE

Cohesin is a protein complex that associates with chromosomes and is crucial for cell division and DNA repair. In a paper published October 22 in *Cell Stem Cell*, a team of researchers led by Ludwig Stanford's Ravi Majeti explores how mutations in cohesin components drive cancers, especially those of the blood and bone marrow. Although several different cancer types can harbor such mutations, they're relatively more common in leukemias. The researchers inserted mutant cohesin into normal blood stem cells to see how they might contribute to cancer. They found that the more specialized progeny of the stem cells expressing mutant cohesion components retained certain stem cell qualities that they should have lost. The mutant cohesin, it turns out, alters the structure of chromosomes in such a manner as to change the spectrum of genes that are expressed when stem cells divide to produce more specialized progeny. These regions encode genes that are thought to contribute to stem-like traits—genes that should be silenced as cells become more specialized. When they're active, the progeny retain capabilities associated with stem cells, such as constant division and a lack of appropriate differentiation, which are hallmarks of cancer cells. Many researchers suspect that stem-like cancer cells sustain tumors, seed cancer recurrence after therapy, and drive metastasis and drug resistance.

Ravi Majeti
Ludwig Stanford

HI-DEF BRAIN TUMORS

Cancer cells are greedy for the raw materials that they need to multiply. They sate their appetites in part by overexpressing a protein called pyruvate kinase M2 (PKM2). This protein functions like a master switch for cell metabolism and plays a critical role in generating some of the molecular building blocks of cells. In a paper featured on the cover of the October 21 issue of *Science Translational Medicine*, researchers led by Ludwig Professor at Stanford University Sam Gambhir report the development of a molecular tracer that exposes PKM2 activity and so helps pinpoint cancer cell metabolism in the brain. The new tracer, called [^{11}C] DASA-23, specifically binds to PKM2 dimers—complexes of two PKM2 molecules that are more abundant in cancer cells and that promote the production of the amino acids the cell requires to make proteins. The researchers labeled DASA-23 with a radioactive carbon molecule and showed that when the mice had PET scans, the tracer exposed cancer cells against a background of normal ones. The researchers expect that if it is approved for use in humans, the system could quickly and reliably inform oncologists about whether their treatment of choice is leading to early metabolic changes in brain tumor cells, predicting drug efficacy.

Sam Gambhir
Ludwig Stanford

THRIFT AS LIABILITY

Find recycling confusing? Turns out some cancer cells do too, particularly when they're recycling DNA bases from yesterday's dinner or from the body's dying cells. In a paper published August 6 in *Nature*, Ludwig Oxford researcher Skirmantas Kriaucionis and his colleagues report that cancer cells that overexpress an enzyme named cytidine deaminase tend to muck up their sorting of chemical variants of the nucleoside deoxycytidine (containing the 'C' of DNA's bases)—and that this confusion might be exploited to develop new cancer drugs. Cytosines in DNA are occasionally tagged with chemical modifiers as markers to turn genes on and off. So if those tags hang around during the recycling and get incorporated in random sites along the new DNA strand of a cell, they can cause lethal confusion.

Skirmantas and his team were looking at how certain known modifications of cytosine are handled by cells. They found, first, that the modified deoxycytidines they were looking at are rejected from the feedstock of recycled DNA bases. But they also noticed that some cancer cells aren't quite as picky as healthy ones, and that this sloppiness ultimately leads to the incorporation of a toxic base in their DNA. The researchers report that cancer cells prone to this behavior tend to over-express cytidine deaminase. They also show that certain modified deoxycytidines might be useful as a specific anticancer agent against such cells. The researchers note that their finding might open a new door to the treatment of pancreatic cancer, which is highly resistant to therapy but also over-expresses cytidine deaminase.

Skirmantas Kriaucionis
Ludwig Oxford

SURVIVAL DECODED

A team of researchers led by Ash Alizadeh of Ludwig Stanford has compiled a database named—SciFi fans will like this—PRECOG (for prediction of cancer outcomes from genomic profiles). The powerful database integrates gene expression patterns of 39 types of cancer from nearly 18,000 patients with information on how long each patient survived. The researchers reported online on July 20 in *Nature Medicine* that high expression of *FOXM1*, a gene involved in cell growth, was associated with a poor prognosis across many types of cancer, while the expression of the *KLRB1* gene, which regulates the body's immune response to cancer, seemed as broadly to have a protective effect. The team also used Cibersort, a method for analyzing the spectrum of individual cell types in sample tissues also developed in Ash's lab, to analyze the types of immune cells that had infiltrated patient tumors. They discerned complex associations between patient survival and the presence of some 22 distinct types of immune cells in tumors. Their findings in some cases held true across a variety of cancer types. The combined use of these two resources will guide new drug development and improve the treatment of patients using existing therapies, which is something the researchers are already investigating.
The team has made the database and associated analytical tools available at http://precog.stanford.edu.

Ash Alizadeh
Ludwig Stanford

ATYPICAL TRIAL

A global team of researchers has announced the launch of GBM AGILE (for Adaptive, Global, Innovative Learning Environment) to find desperately needed new treatments for glioblastoma multiforme (GBM), the deadliest of adult brain cancers. A new kind of clinical trial, GBM AGILE will involve more than 130 clinical and laboratory researchers from the US, China, Australia and Europe, and permit researchers not only to tailor treatments to the molecular profiles of GBM tumors but also to drop failed treatment strategies in midstream and apply new ones as new information comes to light. This applies to the trial itself as well as to individual patients. GBM AGILE, which is expected to begin enrolling patients by mid-2016, will apply Bayesian statistics to interpret data. It will be led by Anna Barker of Arizona State University, Al Yung of MD Anderson Cancer Center and Ludwig San Diego's Web Cavenee. Its primary aims are to test more individualized combination therapies for GBM and to begin validating novel biomarkers to guide treatment—an effort that will be led by Ludwig San Diego's Paul Mischel. One of the organizations behind this trial, Cure Brain Cancer, explains GBM AGILE in a brief video: http://bit.ly/1SiyYRg. A more detailed interview with GBM AGILE leaders (including Web) can be found here: http://bit.ly/1Xc84sk.

Web Cavenee
Ludwig Strategic Alliances in CNS Cancers

Vice President Joe Biden and Ludwig's Robert Strausberg

PEDAL TO THE METAL

Ludwig and the New York-based Cancer Research Institute are currently running a pair of clinical trials. The first, a phase 2 trial, is evaluating an immunotherapy for the treatment of the brain cancer glioblastoma multiforme. This is the most common and aggressive form of adult brain cancer; median life expectancy for patients hovers around 15 months, even with treatment. The trial is testing the effects of durvalumab, a human monoclonal antibody that targets the PD-L1 protein, which is co-opted by cancer cells to help tumors thwart immune attack. Additionally, the trial is testing the effects of durvalumab in combination with anti-angiogenesis drug bevacizumab, an antibody that targets VEGF, which is typically used in the treatment of this patient population.

The other trial is a phase 1, nonrandomized, multicenter trial evaluating the combination of durvalumab with tremelimumab, an immune checkpoint inhibitor that targets the CTLA-4 molecule on T cells. Combining the two can have an effect on the immune response akin to lifting the brakes while stepping on the accelerator. The combo is being tested against a variety of advanced solid tumors, including those of ovarian cancer, colorectal cancer, cervical cancer and kidney cancer. Ludwig is the regulatory sponsor, and the Clinical Trials Management team is responsible for the implementation and conduct of the trials at MSK, DFCI and other clinical sites within the CVC Clinical Trials Network in collaboration with MedImmune, the research and development arm of AstraZeneca.

INKT DEAL

Ludwig and Isis Innovation, the University of Oxford's technology commercialization company, have recently spun out a new company, iOx Therapeutics. iOx will develop a novel cancer immunotherapy discovered through a collaboration between Ludwig and professor Vincenzo Cerundolo, director of the MRC human immunology unit at the Weatherall Institute of Molecular Medicine. Supported in part by Ludwig for the past 12 years, Vincenzo and his team have developed multiple synthetic lipid compounds that activate invariant natural killer T (iNKT) cells, which have emerged as important regulators of the immune response. When activated, iNKT cells can either kill tumor cells themselves or direct another set of immune cells—dendritic cells—to switch on the killer T cell response that helps eliminate cancer cells. iOx's compounds impact the growth of tumors in animal models, and will be tested in combination with other immunotherapies in human clinical trials.

TARGET: TUMORS

Boston-based Mersana Therapeutics and Recepta Biopharma signed an exclusive license agreement in which Mersana will use its proprietary Fleximer technology to develop and commercialize an antibody-drug conjugate (ADC) using an antibody that was discovered by Ludwig. ADCs are designed to selectively kill cancer cells while reducing the effects of chemotherapy on healthy cells. The antibody targets a molecule found on cancer cells and delivers the conjugated molecule only to the tumor.

DID YOU KNOW…

Ludwig has cycling superheroes?

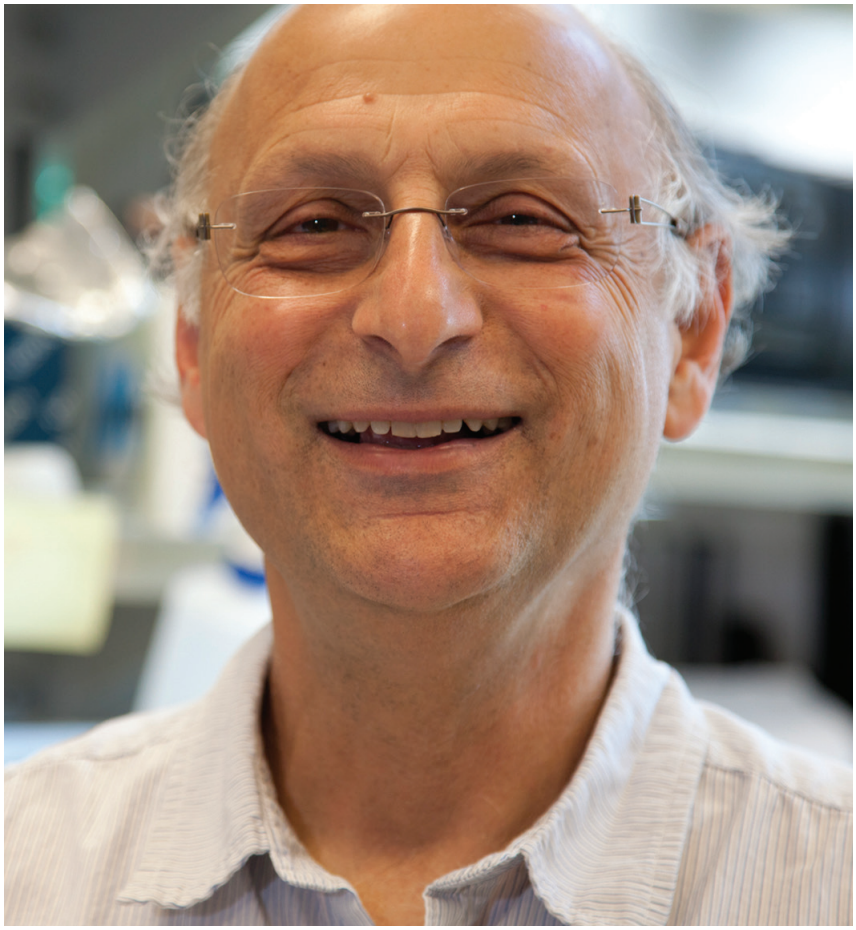
Scientists from Ludwig Oxford donned Lycra suits—capes, apparently, were optional—and cycled 150 km from Oxford to Cambridge. For those who think in miles, that's our CEO Ed McDermott's daily round trip commute from his home in Connecticut to New York City. He'll confirm it's quite a haul.

The "Tour de Coeur" was a huge success: our cycling scientists worked off some pounds, got their hearts pounding and raised over £800 for the British Heart Foundation. (Apologies for this shameless peddling of puns. HR policy gives us one of these a year.)

Congratulations to Derek Leske, Mattia Zucca, Richard Owen, Giovanni Stracquadanio, Felix Zhou, Neele Drobnitzky, Jens Rittscher, Carlos Ruiz Puig, Emma Fenech and Martin Cusack.

Ludwig San Diego's new leader

What did it feel like when you realized that you had tracked down the gene responsible for the most common form of inherited colon cancer?
Fundamentally, it was a new approach to looking at the development of cancer but I didn't appreciate how important it was until after the fact. The realization that there was a gene in which defects cause an inherited cancer susceptibility syndrome was exciting. The fun was in doing the work, a lot of which I did myself. The most rewarding aspect of doing the work itself was in learning new ways of doing science and new ways of doing experiments—that's what scientists live for. One of the most memorable moments was when we heard that some of our early genetic data were used to identify an asymptomatic patient with a genetic defect who on re-examination was found to have a previously undetected cancer, possibly saving a life.



Our understanding of cancer and the current approaches for studying it are completely different now than they were three or four decades ago. What has it been like to be a part of this conceptual evolution?
My scientific career has spanned a transformative period in cancer research. It's bridged the formative years of molecular biology and now it's my extraordinary luck to be working in a revolutionary period in genetics. So it's been amazing to be a part of the progress that has directly impacted our understanding and treatment of human diseases. But, to me, what's even more interesting is that we're starting to study mammalian cells in ways that we used to only be able to study microorganisms. Now we can apply insights from these studies to understand the genetics of human cancer susceptibility.

You wear many hats: director of Ludwig's San Diego Branch, member and head of the Laboratory of Cancer Genetics in the San Diego Branch, Distinguished Professor in the Department of Cellular and Molecular Medicine at University of California, San Diego, and Scientific Review Council Head for the Cancer Prevention Research Institute of Texas. What is your secret to juggling all these roles?

No sleep. Seriously, I guess my secret is to break things down to discrete tasks so that I can complete them and cross them off my list. It's important for me to organize my work so I'm not being pulled in multiple directions all at once, which is easier said than done. Managing the flow of email is particularly challenging. As the new branch director, I'm very fortunate because during Web's tenure a lot of very talented, self-sufficient lab heads and staff were brought in. We also have a great administration in place and, maybe most important, we all get along. That coupled with the support we receive from Ludwig makes it a very comfortable environment in which to work and allows the branch to run smoothly on a day-to-day basis.

Many students and postdocs struggle with the decision to choose a career path in research, industry or academia. Do you think there are certain characteristics that make a person well suited for a position in one environment versus another?

A career is often an intersection of talent, personal choices and, to some extent, luck. I look for people who are passionate about conducting experiments and solving interesting problems. And no matter what path a member of my lab takes, it's my responsibility to ensure that they have a solid foundation in conducting experiments and writing papers. I try to learn what it is that excites and energizes them, what their specific talents are and how to best utilize them, and where they see themselves going. But ultimately, I counsel them that what makes them valuable to any organization is the fact that they are accomplished scientists. So whether it's pursuing a career in research, academia or industry, all require a platform of significant, high-quality scientific training and accomplishments. Those are the elements that will offer the most options and choices.

You obviously enjoyed science right from the beginning, but you must have met challenges along the way. Do you have any advice for junior scientists facing challenges?

Once upon a time, people thought the earth was flat and if you went out to the edge you'd fall off. To me, the best scientists are the ones who—when confronted—want to go out to the edge and jump off. When you're out there in the unknown you can't predict everything. You'll do experiments that don't work, but failed experiments are simply a part of lab life. You'll try things that are risky because great opportunities often come from risk taking. You'll be faced with obstacles and setbacks so you'll need a lot of patience, persistence and perseverance to succeed.

> "To me, the best scientists are the ones who—when confronted—want to go out to the edge and jump off."

What would our readers be surprised to know about you?
I have a pet border collie named Levi who I train to compete in agility trials, which consist of running through timed obstacle courses. They're tough because he has to weave through poles, clear jumps, sprint into tunnels, run over elevated walkways and run up and down a teeter-totter—all without making a mistake. And it might surprise people to know that he's better at it than I am. So far he's earned seven different agility titles, and because of the great weather in Southern California, he competes about a dozen times a year.

What new directions are you headed in now?
Right now we're trying to identify and develop therapeutic targets whose inhibition might selectively kill cancer cells. We're also continuing our work on studying the pathways that prevent genome instability and the inherited defects in human recombination and repair genes to better understand how such defects cause cancer susceptibility.

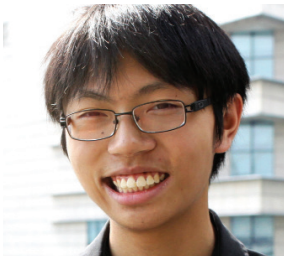
In a 1994 interview you're quoted as saying, "I like to do experiments. That's what I like most." Is that still true today?
I do love to do experiments. They give me great joy. Unfortunately I don't really have the time for the hands-on aspects of doing experiments. There are a few that I would like to do but, right now, I'm only involved in designing and critiquing experiments and interpreting the data.

What has been the most satisfying part of your research?
The long-term success of the people who have been students and postdocs in my lab. That's the legacy you leave to the world. Over time even the most important scientific discoveries are relegated to the textbooks and become part of our baseline knowledge to the extent that they seem like trivial facts. I'm not saying it's easy to make those discoveries, but when I go to a meeting in my field and find that many of the invited speakers are people who trained in my lab, I'm reminded once again that their success is my most important contribution to science.

What's missing from a technical perspective that would help move your field forward?
We're not suffering from many technical limitations. One of the biggest challenges in science today is how best to use all the technology that's available right now. The question becomes, how can we exploit all these new insights and technologies, how do we gain access to them, and how do we learn to use them? And, maybe most important, can we afford them, and afford to use them properly? As the technology has become more complex and more costly, we often want or need to work with scientists in other labs who can offer resources or technical expertise that complements what's available in my lab in order to move the work forward. But as you increase the number of labs working on a specific project, it's not only tougher to manage the collaborations but it's tougher to manage the quality of the work.

"The long-term success of the people who have been students and postdocs in my lab. That's the legacy you leave to the world."

Is technology moving too fast for scientists to keep up?

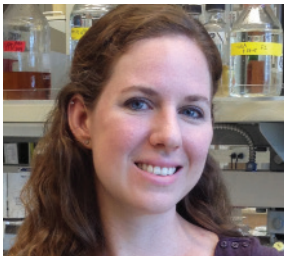


Technology is not moving too fast for researchers to keep up. After all, researchers are responsible for the pace of technological development. Coordinated deployment of avant-garde diagnostics and therapies in the clinic is the next hurdle—to seamlessly link noninvasive cancer screening with immunotherapies and oncogene-specific chemical inhibitors.

KYLE LOH
Ludwig Stanford

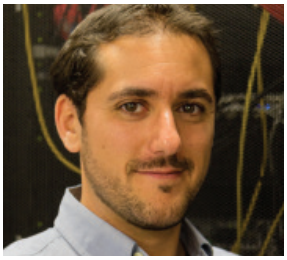
The great advances in technology present a challenge, but primarily allow us to study biology and address questions in a way that previously was not possible. However, a deeper understanding of the method used is needed in order to appreciate the benefits and drawbacks and therefore be able to draw proper conclusions.

PER JOHNSSON
Ludwig Stockholm



Scientists have always been quite quick to embrace new and changing technology. This willingness to work with cutting-edge techniques has allowed science to keep moving forward. In fact, the need for better tools to investigate difficult scientific questions often drives the development of technology.

EVA M. GOELLNER
Ludwig San Diego



High-throughput technologies are generating massive data sets at unprecedented speeds. However, the current challenge is to interpret this data at nearly the same pace, in order to generate novel biological and clinical insights. Both deep-learning algorithms and large-scale mining techniques can help scientists to keep up with the analyses of these large “omics” data sets.

GIOVANNI STRACQUADANIO
Ludwig Oxford

Required reading

Ludwig Chicago

Molecular Cancer Research 2015 November 4 [Epub ahead of print]
Linking cancer metabolism to DNA repair and accelerated senescence

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