



LUDWIG LINK

AUGUST 2016

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Scientific retreat
hosted by Ludwig
San Diego

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Unboxed: Sangeeta
Bhatia, Ludwig MIT
investigator

LUDWIG
CANCER
RESEARCH

LIFE-CHANGING SCIENCE

LETTER



I like to think of each issue of the *Link* as a sort of milestone measuring the progress Ludwig Cancer Research is making in pursuit of its mission. Judging from the research featured in these page, that progress proceeds apace.

Ludwig scientists have lately published studies advancing the development of liquid biopsies, identified drugs that might be repurposed to enhance cancer therapy and parsed how metastasizing breast cancer cells are guided out of a tumor. They've launched a trial to evaluate the combination of checkpoint blockade, chemotherapy and an experimental immunotherapy for the treatment of ovarian cancer. And all this is just a small sampling (of a sampling) of Ludwig's recent contributions to cancer research.

We aren't the only people noticing: Our scientists continue to win accolades and awards. And it seems they stay busy outside the lab as well. One just topped off a portfolio of stellar scientific publications with a children's book. I won't say who, but here's a hint: The colorfully illustrated book is all about stem cells.

We also have in here an interview with Ludwig MIT scientist Sangeeta Bhatia—engineer, scientist, inventor and mentor extraordinaire. Take a look to find out how she keeps the flame of innovation alive in her laboratory.

Happy reading!

Sincerely,
Rachel Steinhardt
Vice President for Communications

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On the cover: Andy Shiau, Karen Oegema and Arshad Desai of Ludwig San Diego (left to right)

CHANGING LANES

Sir David Lane stepped down as our Scientific Director at the end of June to focus more on his own research. Under his leadership, Ludwig Cancer Research took some solid steps in building for the future in line with its new operating model. As Ludwig President and CEO Ed McDermott pointed out, David's signature achievement was his role in the establishment of a new core Branch of the Ludwig Institute in Lausanne, Switzerland. The Branch will focus almost exclusively on tumor biology and cancer immunotherapy. Ludwig's search committee is currently working closely with an executive search firm to recruit another world-class scientist to lead Ludwig's roster of stellar scientists. The Ludwig community wishes David the best in his more sciencey and less administrative future.



Sir David Lane
Ludwig Institute

STEADY HAND

After 13 years, Fred Berger is stepping down from the board of the Ludwig Institute and the Ludwig Fund. During his tenure, Fred has had the pleasure of watching ideas championed by Ludwig and its board—most notably in immunotherapy—mature and bear fruit. They have generated new treatments that are now being commercially developed and therapeutic strategies that are already transforming cancer care. His financial acumen and wise counsel helped us weather the financial crisis of 2008 and the severe recession that ensued.

“From his very first board meeting, Fred demonstrated a keen interest in the work of Ludwig researchers, an eagerness to better understand the complexities of cancer and an unwavering commitment to the health of the Institute,” said Ed McDermott, Ludwig's president and CEO. “We will miss his reassuring presence and steady hand on the board.”

Fred's career took a rather circuitous route—from pharmaceuticals at Hoffman-LaRoche and Pharmavision to finance at Merrill Lynch and Julius Baer to the world of scientific discovery at Ludwig. “In reflecting on my journey, I couldn't have planned it better if I'd tried,” he said.



Fred Berger
Ludwig Board

THE PIONEER'S PIONEER

Ludwig MIT Director Robert Weinberg was honored for his seminal contributions to cancer research and cancer biology with the 13th annual American Association for Cancer Research (AACR) Award for Lifetime Achievement in Cancer Research at the AACR Annual Meeting in New Orleans in April. Bob revolutionized the field of oncology with his discovery of the first human cancer-causing gene, the *Ras* oncogene, and the isolation of the first known tumor suppressor gene, *Rb*. These discoveries laid the foundations of modern cancer biology and precision medicine for the treatment of malignancies.

BREAK-DOWN RESISTANCE

Ludwig Lausanne scientist Ping-Chih Ho has won a Young Investigator Award from the Society for Immunotherapy of Cancer–Melanoma Research Alliance. He will use the funding to explore how the unique metabolic processes of tumor cells contribute to their ability to evade anticancer immune responses. The ultimate goal of his research is to develop new therapies to awaken antitumor immune responses put to sleep by such “immunometabolic editing.” Ping will conduct his studies under the mentorship of Ludwig Lausanne Director George Coukos.



Ping-Chih Ho
Ludwig Lausanne

ATOP THE SANDBOX

Ludwig MSK's Jedd Wolchok and Ludwig Stanford's investigator Crystal Mackall have been tapped as center directors of the San Francisco–based Parker Institute for Cancer Immunotherapy at their respective home institutions. Established with a \$250 million grant by tech entrepreneur Sean Parker of Napster and Facebook, the new institute seeks to accelerate progress in the already sizzling field of cancer immunotherapy. Parker wants to create what he calls a virtual “sandbox” for scientific innovation, in which affiliated researchers can work together without compromising or complicating their claims to intellectual property. The institute includes six university-based centers, as well as partnerships with nonprofit health organizations and biotechnology and pharmaceutical companies.

If this has you thinking that Jedd and Crystal would make any team a Dream Team, you aren't alone. The Stand Up to Cancer–affiliated scientists have each received a \$200,000 Phillip A. Sharp Innovation in Collaboration Award for research proposals they separately submitted in partnership with junior researchers. Jedd and his partner will focus on developing models to predict the efficacy of immunotherapy, while Crystal and hers have proposed a trial treating highly mutated childhood tumors with anti-PD-1 checkpoint blockade therapy.



Jedd Wolchok
Ludwig MSK



Crystal Mackall
Ludwig Stanford

HIGH ACHIEVERS

Ludwig Johns Hopkins Co-director Kenneth Kinzler and Ludwig Harvard investigator Myles Brown have been elected to the National Academy of Sciences (NAS) in recognition of their “distinguished and continuing achievements in original research.” Ken has played a pivotal role in defining the genetic alterations responsible for the formation of human tumors, and developed novel methods for sequencing and analyzing cancer genomes. Myles is widely recognized for his work on steroid receptors and their role in human malignancies, such as breast and prostate cancers. The two were among 84 new members and 21 new foreign associates from 14 countries elected to the NAS. Membership is one of the most prestigious honors given to academic researchers.



Kenneth Kinzler
Ludwig Johns Hopkins



Myles Brown
Ludwig Harvard

GENE GENIES

Ludwig Johns Hopkins scientist Luis Diaz and his colleague Victor Velculescu, cofounders of Personal Genome Diagnostics (PGDx), have received the 2016 Ernst & Young EY Entrepreneur of the Year award in the Maryland region in the innovative technology category. The researchers launched PGDx to harness the current wealth of genomics data and mine it to address age-related diseases such as cancer. The company provides advanced cancer genome analysis and testing services to characterize genomic alterations in tumors using tissue and liquid biopsies from cancer patients. The company’s growing menu of state-of-the art, high-quality cancer DNA testing services supports the development and dispensation of personalized cancer therapy. This year marks the 30th anniversary of the EY awards program, which recognizes outstanding entrepreneurs who “demonstrate excellence and extraordinary success in such areas as innovation and personal commitment to their businesses and communities.”



Luis Diaz
Ludwig Johns Hopkins

A TRANSATLANTIC TAP

Ludwig Uppsala Director Calle Heldin and Karen Vousden, a scientific advisor to Ludwig, were elected members of the American Academy of Arts and Sciences. Calle is a molecular biologist by day, and chairman of the board of the Nobel Foundation and the Science for Life Laboratory by night. Karen, a former Ludwig assistant member and head of the human papillomavirus group at the St. Mary's Branch, has been the director of the Cancer Research UK Beatson Institute in Glasgow, Scotland, and has recently taken up the post of chief scientist for Cancer Research UK. She is an expert on p53, the so-called guardian of the genome, which is mutated in about half of all cancers. The 213 new members of the academy include some of the world's most accomplished scholars, scientists, writers and artists, as well as civic, business and philanthropic leaders. Calle and Karen will be formally inducted at a ceremony on October 8 in Cambridge, Massachusetts.



Calle Heldin
Ludwig Uppsala



Karen Vousden
Ludwig Scientific Advisory
Committee

AIMING FOR THE MOON

Ludwig MIT investigator Tyler Jacks was named one of three co-chairs for a panel advising US Vice President Joe Biden's National Cancer Moonshot initiative. The US National Cancer Institute, part of the National Institutes of Health (NIH), convened the panel from a pool of cancer researchers, industry leaders and patient advocates. It will help guide the Moonshot initiative and develop recommendations for the NIH on everything from cancer vaccines to early detection to data sharing. Members of the research community and the public can engage in the initiative by subscribing to updates on the Moonshot's [main website](#) or by emailing the panel at cancerresearch@nih.gov.



Tyler Jacks
Ludwig MIT

COME TOGETHER!

As amazing as 21st century communications technology can be, nothing beats meeting colleagues face to face. A scientific retreat recently hosted by Ludwig's San Diego Branch proved to be an ideal forum for students and postdocs to share their research in presentations and posters. "It was great experience for all of our scientists, especially those at early-stage career development, and provided the New York leadership team an opportunity to engage in informal discussions spanning many areas, ranging from current advances in cancer research to future career opportunities," said Bob Strausberg, executive vice president for research. "The retreat provided a wonderful venue for interactions with everyone in the Ludwig community."

Here are a two snapshots from the event. Many thanks to Ludwig San Diego postdoc Binzhong Li for serving as photographer extraordinaire for the day!



THREE-FER TO ZAP A TUMOR

Pancreatic cancer is hard to diagnose and even harder to treat. Even immunotherapy, the hottest therapy on the block, has come up short. This is probably because few activated T cells infiltrate these tumors. A team of Ludwig researchers led by Ralph Weichselbaum investigated whether they could undo this malignant recalcitrance with a strategy of sequential interventions. They report in the June 13 [issue](#) of *Oncotarget* that when they treated tumor-bearing mice with a cancer vaccine and radiation followed by checkpoint blockade immunotherapy, activated killer T cells flooded into the tumor. The treatment also slowed the cancer's growth in tumor-bearing mice and extended their survival. The researchers propose that radiotherapy activated the immune response, drawing vaccine-primed T cells into the tumors. That response was then boosted by the immunotherapy—a PD-L1 antibody—which disabled a key mechanism of immune suppression employed by cancer cells.



Ralph Weichselbaum
Ludwig Chicago

COUNTERING A DEADLY TRANSFORMATION

Transforming growth factor- β (TGF- β) is a protein that can suppress tumors. But when it is chronically active, or when the biochemical pathways by which it signals are dysfunctional, it can just as surely contribute to the progression of tumors. An important way it does so is by inducing epithelial-to-mesenchymal transition (EMT), a dramatic internal transformation that makes cells mobile and promotes cancer cell metastasis. It can also turn epithelial cells—which line body cavities—into agents that drive the buildup of fibrous tissue in organs and tumors. Aristidis Moustakas and Calle Heldin of Ludwig Uppsala led a team of researchers including Andy Shiau and Timothy Gahman of the Ludwig Small Molecule Discovery Program in San Diego to screen for chemicals that might reverse these pathological effects but leave the other, tumor-suppressing effects of the factor intact. The researchers [report](#) the discovery of such molecules in the July 19 issue of *Scientific Reports*. Significantly, their studies reveal that one such compound, a naturally occurring cholesterol metabolite, activates nuclear receptors known as LXRs. Their paper also shows that the activation of these intracellular receptors appears to

counter the EMT-inducing effects of TGF- β , suggesting LXRs could be useful targets for drugs to treat tissue fibrosis and cancer.



Aristidis Moustakas
Ludwig Uppsala



Calle Heldin
Ludwig Uppsala



Andy Shiau
Ludwig Small Molecule
Discovery Program



Timothy Gahman
Ludwig Small Molecule
Discovery Program

TO PREPARE AN EGG

Ludwig San Diego researchers led by Arshad Desai have discovered a key way in which the roundworm egg sets the biochemical stage for the earliest steps of embryonic development. Their [study](#), published April 7 in *Cell*, shows how certain small RNA molecules help create the perfect balance of proteins in the fertilized egg of the roundworm *Caenorhabditis elegans*. The small RNAs, they show, direct an enzyme called CSR-1 to slice selected messenger RNAs, which are transcripts of genes ready

for translation into proteins. The researchers report that by varying the number of small RNAs bound to the CSR-1 enzyme—which belongs to a family of RNA-silencing proteins known as Argonautes—eggs can precisely tune their internal composition. Their findings are likely to be of relevance to higher organisms, since mice too use an Argonaute protein and small RNAs to achieve the precise balance of proteins required for the first steps of development.

BREADCRUMBS TO AN EXIT

A component of the extracellular matrix that supports the cells of solid tissues, fibronectin has long been known to play a role in cancer metastasis. What that role is, however, has been less clear. A team of researchers led by Ludwig MIT's Frank Gertler has just found an answer. In a [paper](#) published in May in *Cancer Discovery*, the researchers show that invasive breast cancer cells in mice appear to take a path that follows a gradient of fibronectin to the periphery of tumors and the vicinity of blood vessels, from where they can escape. This process is promoted by MENA^{INV}, a protein in cancer cells also known to drive invasive behavior. Frank and his colleagues show that MENA^{INV} boosts the cancer cell's interaction with fibronectin. That event, in turn, drives fibronectin to alter the structure of another extracellular matrix protein, collagen, which forms stiff rails along which the cancer cells can migrate. The researchers report that fibronectin and MENA^{INV} levels are correlated in breast cancer patients, and confirm that high levels of MENA^{INV} correlate with higher breast cancer recurrence and poorer survival.



Frank Gertler
Ludwig MIT

EARLY DIVERGENCE

Mouse embryos are routinely used as models for human embryonic development. But mice are not men, or women, for that matter. So how do they differ in these earliest stages of life? In a [study](#) published May 5 in *Cell*, Ludwig Stockholm scientist Rickard Sandberg and his colleague Fredrik Lanner of the Karolinska Institutet serve up the first installment of an answer. By analyzing global gene expression in 1,529 individual cells from 88 early human embryos, the researchers show that mouse and human embryos differ significantly in their developmental course and gene expression patterns over the first seven days of development. They report that three distinct precursor cell types that emerge at this stage form later and mature more simultaneously in human embryos than they do in mice. They further report that genes on the human X chromosome are regulated very differently from those on other chromosomes at this early stage. The gene expression data generated from this study will be of value to developmental biology, stem cell research and regenerative medicine.



Rickard Sandberg
Ludwig Stockholm

NEW PURPOSE

Drug repurposing, in which new uses are found for existing drugs, has gained traction as a practical means to bypass the time-consuming and costly process of developing new ones from scratch. A team of University of Chicago researchers led by Ludwig Chicago Co-director Ralph Weichselbaum set out to find available agents that might enhance the effects of radiation. After conducting a large-scale screen of existing investigational molecules, drugs and natural products, the team identified 19 agents that appeared to be safe and possibly effective, and evaluated them in a mouse model of radioresistant melanoma. This process identified the antibiotic cephalexin, one of the most commonly prescribed generic drugs in the United States, as a promising radiosensitizer. The [findings](#), published online April 25 in *Oncotarget*, show that combined treatment with cephalexin and radiation significantly slows tumor growth in mice without increasing toxicity to healthy tissue. The antibiotic (and others like it) seem to boost oxidative damage to tumor cell DNA.



Ralph Weichselbaum
Ludwig Chicago

PANNET PROBE

Pancreatic neuroendocrine tumors (PanNETs) are clinically challenging. In an April 19 *Proceedings of the National Academy of Sciences* [study](#), a team of Stanford researchers led by Ludwig scientists Irv Weissman and Geoffrey Krampitz characterized the biology of these tumors, showing that they are driven by signaling via the hepatocyte growth factor receptor and activation of the *MET* proto-oncogene. The researchers identified a very aggressive population of PanNET cells in which an enzyme named aldehyde dehydrogenase A1 is highly active, and which express high levels of the cell surface protein CD90 as well as CD47. The latter is a receptor that transmits a ‘don’t eat me’ signal to macrophages, which are important frontline soldiers of the immune system. Hitting the tumors with an anti-CD47 antibody in a mouse model inhibited tumor growth, promoted engulfment by macrophages, blocked metastasis and extended survival.



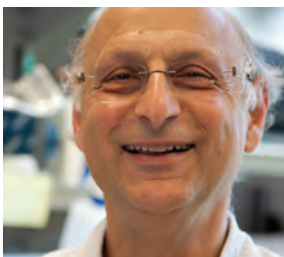
Irv Weissman
Ludwig Stanford



Geoffrey Krampitz
Ludwig Stanford

IN SERVICE TO STABILITY

An unstable genome can cause any number of problems, not least cancer. So cells have evolved a passel of genes that in one way or another prevent rearrangement of chromosomes and other large-scale genetic errors. Not all such genome instability-suppressing (GIS) genes have been identified, however. Now a team of researchers led by Ludwig San Diego's Richard Kolodner and Christopher Putnam has developed an approach that combines methods from bioinformatics and yeast genetics to find such genes. The researchers [reported](#) April 13 in *Nature Communications* how they used their method to first identify 182 genetic modifiers of gross chromosomal rearrangements (GCRs) in yeast—98 of which hadn't been described before—and 438 “cooperating GIS genes” that, though not GIS genes themselves, play some role in suppressing instability. They then used this information to search the Cancer Genome Atlas for mutations to GIS genes that are associated with cancer. They found that 93% of ovarian and 66% of colorectal cancers have one or more defects in their GIS genes, whereas acute myeloid leukemia, a cancer with little genome instability, has none.



Richard Kolodner
Ludwig San Diego



Christopher Putnam
Ludwig San Diego

INFLAMMATORY LANGUAGE

Nothing lasts forever, and proteins are no exception. When it's time to go, proteins that have outlived their usefulness are often tagged in a particular way with another protein named ubiquitin, which marks them for disposal and degradation. But ubiquitin isn't just a molecular kiss of death. As its name implies, the protein appears to play a critical role in pretty much every major cellular process, from signaling to cell division. Scientists are currently in a heated race to figure out the language of ubiquitination in those other processes—how various permutations of ubiquitin and its chains are used within the cell, and the effects of each. Ludwig Oxford scientist Mads Gyrd-Hansen and his team are among them. In a March 29 [paper](#) in *Cell Reports*, they describe how a series of proteins and protein complexes that either add or remove ubiquitin molecules regulate the transmission of inflammatory signals by an innate immune receptor. This receptor, NOD2, detects bacteria, and its signals are transmitted to the nucleus through a factor named NF- κ B. This factor is, notably, a key molecular link between chronic inflammation and cancer.



Mads Gyrd-Hansen
Ludwig Oxford

VIRTUES OF SENSITIVITY

Ludwig Stanford scientists Maximilian Diehn and Ash Alizadeh have taken a giant step toward a reliable “liquid biopsy” with a remarkably sensitive and accurate new technique for detecting and profiling DNA shed by tumors into the blood. Researchers and biotechnology companies are rushing to devise such diagnostic tests, which are far less invasive and therefore free of the discomforts and complications that can accompany surgical biopsies. Because they can be more frequently used, liquid biopsies would also greatly improve the ability of physicians to diagnose, routinely monitor and personalize the treatment of cancers. The new technique—dubbed integrated digital error suppression (iDES) and described in the May [issue](#) of *Nature Biotechnology*—detects and computationally removes errors that occur when circulating tumor DNA is captured and prepared for sequencing. The researchers found that iDES could detect as few as one tumor DNA sequence among as many as 400,000 nontumor DNA fragments in the blood of non-small-cell lung cancer patients.



Maximilian Diehn
Ludwig Stanford



Ash Alizadeh
Ludwig Stanford

SEQUENCES AND CONSEQUENCES

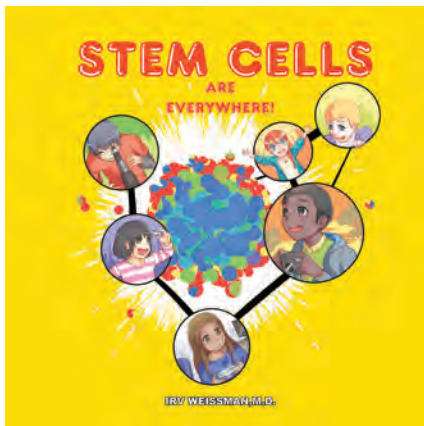
Cancer researchers have long known that spontaneous gene mutations that influence the biochemical pathways involving p53—a protein dubbed the guardian of the genome—play a bigger role than those of any other pathway in a wide variety of cancers. Now an international team of researchers led by Ludwig Oxford’s Gareth Bond has mined a vast trove of genomic data and demonstrated that the same holds true for inherited variations in DNA sequence known as single nucleotide polymorphisms (SNPs) that occur along this pathway. What’s more, the inherited SNPs in the p53 pathway that are associated with cancers appear to have genetic characteristics similar to those of acquired mutations known to promote cancers, which could have important implications in cancer surveillance and treatment strategies. The [findings](#) were published April in *Nature Reviews Cancer*.



Gareth Bond
Ludwig Oxford

STEM CELLS, ANYBODY?

Need a present for the kids? *Ludwig Link* has a suggestion. (Feel free to call it a plug. We support our researchers.) Ludwig Stanford Director Irv Weissman has just published a book for kids on his bailiwick and, we suspect, favorite subject: stem cells. Titled *Stem Cells are Everywhere* and written for seven- to nine-year-olds, the book is written in plain English and flush with bright, cartoony illustrations—including three of Irv himself. It'll also give science-shy grownups a primer on a subject likely to be of medical relevance to many of them someday—and, until then, add a few notches to their biological IQs. The 46-page book explains everything from how the body heals itself and plants grow taller to how some animals can regrow limbs. So whether you're hoping to stanch your six-year-old's ceaseless flow of whys, get a gift for your third-grader or collect grist for cocktail-party banter (it takes all sorts, *Link* says), you'll find what you're looking for in Irv's book.



THREE HITS

Ludwig and the Cancer Research Institute (CRI) have successfully dosed the initial cohort of patients in an international, multicenter phase 1/2 clinical trial of combination immunotherapy for advanced ovarian cancer. The study is assessing the combination of durvalumab, a checkpoint blockade antibody against PD-L1, and motolimod, a TLR8 agonist, with the chemotherapeutic agent PEGylated liposomal doxorubicin. TLR8 is found in a variety of immune cells and is an initiator of the innate immune response. Researchers expect that motolimod's activation of TLR8 will enhance the effects of durvalumab. Further, when given with chemotherapy, motolimod could boost immune responses against cancer cells that are not engaged by durvalumab by helping the immune system 'see' cancer antigens. The trial is being conducted through the CVC Trials Network, which is jointly managed by Ludwig and CRI. The manufacturers of the investigational therapies—MedImmune, a subsidiary of AstraZeneca, and the biotech firm VentiRx Pharmaceuticals—are also collaborating on the study. Ludwig Lausanne Director George Coukos and Brad Monk, director of gynecologic oncology at St. Joseph's Hospital and Medical Center in Arizona, are leading the trial.



George Coukos
Ludwig Lausanne

LASTING EFFECTS

An international team of scientists including Stephen Hodi, a researcher at Ludwig Harvard, reported at the American Society of Clinical Oncology meeting in Chicago in May that 40% of 655 patients with advanced melanoma who were treated with the PD-1 inhibitor pembrolizumab (Keytruda) in a phase 1b trial were still alive three years later. Just as impressively, of the 15% of patients in that trial who experienced complete remission, 89% have remained in remission. Just five years ago, the median survival of people diagnosed with advanced melanoma rarely exceeded a year. Cancer cells engage the PD-1 receptor to suppress T cell attack. Pembrolizumab blocks that receptor and so can lift the brakes imposed on the antitumor immune response. In 2014, the Food and Drug Administration gave pembrolizumab accelerated approval for melanoma and the drug was used recently, and most famously, to treat former US President Jimmy Carter. The antibody has also received breakthrough therapy designation for Hodgkin's lymphoma and certain subtypes of colon cancer, and accelerated approval for lung cancer.



Stephen Hodi
Ludwig Harvard

SILENCING A SUPPRESSOR

The pharmaceutical company AbbVie has entered into a development partnership with argenx, a clinical-stage biotech firm that develops therapeutic antibodies to treat cancers. The two companies will collaborate to develop and commercialize ARGX-115, a preclinical-stage antibody that targets the protein GARP. GARP is found on the membrane of T regulatory cells, which are often co-opted by tumors to suppress immune responses. Binding of the antibody to GARP blocks the production of active TGF- β 1 by T regulatory cells, counteracting their modulation of antitumor immunity. The initial research stems from a Ludwig collaboration with the de Duve Institute of the Université catholique de Louvain in Belgium.

TWINNED TARGETING

iOx Therapeutics, a Ludwig and Oxford University immunotherapy spinout, received a €8.3 million Horizon 2020 grant from the European Union to develop new cancer immunotherapies. The company is part of an international consortium that includes another Ludwig spinout, iTeos Therapeutics. The grant will support the development of a new product that combines iOx's iNKT agonist with Ludwig's NY-ESO-1 tumor vaccine. iOx anticipates that the resulting IMM65 nanoparticle will fight tumors better than either of its components can separately. The grant will fund the manufacture of IMM65 and its preclinical and clinical evaluation as a therapy for bladder, ovarian, lung and other solid cancers.

Did you know...

DID YOU KNOW...

Are you a compulsive Candy Crusher? Brazenly Bejeweled? Terminally Tetrised? Are too many minutes of your finite life lost in a blur of luminous screens and tapping thumbs? Well, *Ludwig Link* has some excellent news: You can now redeem yourself. Maybe even turn your obsession into a virtue. Gaming can be useful. Lifesaving, in fact. Such are the wonders of the digital age.

Scientists have been teaming up with programmers for several years now to create a rapidly proliferating lineup of video games to address nettlesome challenges in data analysis. Their games get players to team up and, merely by playing, help tackle some of the biggest scientific problems of our day—from climate change to the links between genetics and disease.

There's certainly a need. Thanks to advances in genome sequencing, imaging and sensors and the general automation of many research and data-collection processes, scientists in a variety of fields find themselves lost in a tsunami of data. Sorting through terabytes of the stuff may seem like the perfect job for a supercomputer, but too often, it is not. Many complex tasks involve pattern recognition or creativity. The human eye and brain are better at these things than the world's finest

computer.

In 2011, gamers playing Fold.it solved a retroviral protein structure in three weeks that had stumped scientists and their computers for 15 years. A year later, a pair of American gamers playing Planet Hunters discovered a strange solar system of four stars holding a Neptune-like exoplanet in their orbit. The planet was named PH1 in the game's honor.

Our main point here is that whether you're a gaming nerd or a newbie, you can channel your inner geek to do some real-life science today. Want to help chart the wiring of the brain? Well, Eyewire's your game. Or you could play Phylo to contribute to DNA analysis for a variety of fields—including cancer research. If the far reaches of our awesome cosmos excite you, you can help classify deep space images at Poppin' Galaxy; if it's animals you like, work on images from the vast African savanna at Computer Vision: Serengeti. You'll find a free, crowdsourced game or volunteer opportunity for almost any interest at Zooniverse.

Check it out. Lab coat optional.

Unboxed: Sangeeta Bhatia, Ludwig MIT investigator

What inspired you to adapt technologies developed in the computer industry for medical innovation?

As the daughter of Indian immigrants, I like to joke that the three career paths open to me were doctor, engineer or entrepreneur. When I was in high school my dad thought I'd be a great engineer. I was strong in math and science and liked tinkering, but had no conception of what engineering was. He took me to visit a family friend in mechanical engineering at MIT who was trying to use focused ultrasound to heat tumors for cancer therapy, and the idea that engineers could use instruments to impact human health grabbed hold of me and has never let go.

Why are tiny technologies important?

Billions of dollars have been invested in miniaturization. Think about how computers transformed our lives when they became small enough for us to carry around in our pockets. The decades of work by engineers that have gone into creating instruments to make our computer chips faster have created a set of technologies that now allow us to address human health challenges like cancer and infectious diseases. So we've borrowed these tools to tackle complex problems like drug toxicity, tissue regeneration and cancer therapeutics. In my lab we're using them to model human disease, monitor the body and make artificial organs.



How are micro-livers used in research?

We developed artificial human micro-livers by using techniques for semiconductor microfabrication to 'print' colonies of human liver cells amidst supportive neighboring cells. We can use them to test new drugs that are potentially harmful to the liver and also study the pathogens that uniquely infect the liver. Our platform is being commercialized through a spin-off company called Ascendance, which manufactures the micro-livers at scale and distributes them to pharmaceutical companies to test drug safety and metabolism in liver cells before doing clinical trials. Today, over 40 companies around the world use them. We've also

used these micro-livers to study infectious diseases that affect the liver such as hepatitis C, hepatitis B and malaria.

What project really energizes you right now?

That's like trying to pick a favorite child. One that I'm very involved with at the moment is our cancer detection project. We developed a technology that relies on nanoparticles that interact with tumor-associated enzymes called proteases, each of which can release hundreds of biomarkers that are detectable in a patient's urine. We are working on ultrasensitive detection of a panel of proteases involved with the spread of colon cancer to the liver (a process known as metastasis). So far, the test is more sensitive than existing blood biomarkers or imaging methods for this tumor type (in mice). We now need to figure out how to bring this technology to patients. This raises many questions that sit at the nexus of our science, oncology, regulatory and commercial landscapes.

How successful has Keys to Empowering Youth been in encouraging young girls to pursue science and engineering as a career?

We don't have comprehensive data—just 23 years of experience and lots of anecdotes from girls who have come through the program and have been inspired to pursue careers in science and engineering. Several have gone on to the Women's Technology Program, which is an undergraduate summer residential program here at MIT. One



student came to us because her grandmother reached out to say how influenced her granddaughter had been by her early exposure at MIT. We invited her to spend a summer doing research with us while she was at Carnegie Mellon and she's now pursuing graduate studies in biomedical engineering. Stories like this are one of the main motivators for making myself visible. While it can be more comfortable to stay in the lab and not talk to the press, I believe you can't be a role model if people can't see you. Once these girls have been to one of our Saturday workshops and see women training to be scientists and engineers and get hands-on experience in a lab filled with the coolest technology, we hope they begin to understand and appreciate how much engineering impacts all of our lives. And how they can play a part in it. Whether it's

“

While it can be more comfortable to stay in the lab and not talk to the press, I believe you can't be a role model if people can't see you.

”

inside their smartphones or whatever new gadget they're playing with, engineering is behind it.

How close are you to engineering a liver from scratch?

Engineering complex tissues, like the liver, to be available on demand for patients in need is a grand challenge. It is in the category of 'truly lifetime difficult' and clinical trials remain years away, so it's doubtful I'll be done in the next decade. One of the biggest challenges is the problem of scale: we need a liver with billions of cells to support a patient. One approach we're taking is to pair engineering scale-up methods (like 3D printing) with biology scale-up methods (like triggering regeneration). Together with Chris Chen's lab at Boston University, we've recently shown this combination approach can help grow an organ in situ by about 50-fold.

How did it feel to win the Lemelson-MIT Prize?

It was truly incredible. The award is given for both prolific invention and for inspiring the next generation. As a scientist, an engineer, a doctor, an educator, an entrepreneur, a diversity advocate and a daughter of immigrants, I don't fit neatly into any one box. So, being recognized as an inspirational inventor crystallized all these disparate roles into a cohesive one for me. More than anything, I lead a team. Everything we accomplish is the product of creativity and innovation, of everyone sharing ideas and working hard together.

So, the award is really for the whole team, past and present.

Why is it important to encourage a spirit of tinkering in your lab?

We're in a profession that has a high failure rate and the pace of research can seem unreasonably slow. On top of that, Cambridge is a veritable pressure cooker and the elite institutions are full of brilliant people trying to carve a path for themselves. I think there needs to be a way to remember why you're here and why you chose this profession. So in order to keep the invention process fun in my group, I have the students spend 20% of their time outside of their difficult and important projects doing what we call tinkering—just playing. To spark creativity, to stay curious, to be inspired. Not all of these projects turn into wonderfully productive ideas. Some of them never go anywhere, but then again, some of our biggest breakthroughs have happened this way, too.



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In the next 20 years, do you think the way we treat cancer is going to be drastically different from the way we treat it now?

It's hard to predict the future of cancer care. Siddhartha Mukherjee, who wrote *The Emperor of All Maladies*, framed the trajectory of cancer treatment as an accumulation of modalities. In the beginning we did surgery, then chemotherapy, followed by radiation. Now we have molecularly targeted therapies and the development of immunotherapy. There's a parallel story on the detection side. It used to be that that you had to palpate (feel) for a mass, then you could do anatomic imaging and then molecular imaging, then blood tests, and now development of next-generation noninvasive monitoring methods. I think collectively what it will look like in 20 years will be quite a bit different from what it looks like now, even though many of these tools will still be in our armamentarium.

Is cancer therapy on the cusp of changing?

Our understanding of cancer has reached a new milestone over the last 10 years, where we deeply understand its molecular makeup in a way that we didn't before. And what we now know is that cancer is over 200 different diseases, and they're not all going to be vulnerable to the same approach. One thing that has been really promising about immunotherapy is the durable remissions that have emerged in a subset of patients. Broadening immunotherapy's impact is definitely going to come in the next 20 years. I wouldn't



say that it's going to be a panacea but it's absolutely a growth area.

Who was your most influential role model?

I have always loved Marie Curie. She was an amazing scientist, a mother and a Nobel laureate whose older daughter also won the Nobel Prize. But from a scientific perspective, I really didn't have a single living role model. I did have a series of incredible male mentors that I looked up to. Mehmet Toner, who is an engineer on the faculty at Harvard Medical School, with a lab embedded in Mass General Hospital, was my graduate advisor and a fantastic mentor. He was also the most influential. He had the foresight and the belief in me to push me way beyond my comfort zone, and was the first person to tell me I should be a professor just as my dad said I should be an engineer. He believed in me and saw more in me than I saw in myself. I try hard to pay that forward with my own trainees.

Is crowdsourcing hype or here to stay?



Crowdfunding is a great way for scientists to explore new ideas and learn how to communicate the relevance of their research to the public. However, this funding mechanism is unlikely to fully replace traditional funding sources, which are more reliable means of ensuring support for resource-intensive, long-term biomedical studies and for employing research personnel.

LINDA FOIT

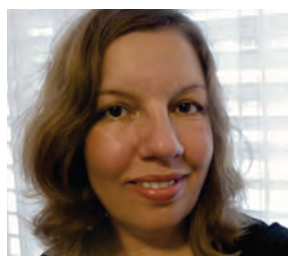
Ludwig New York



Crowdsourcing is here to stay! It allows both for scientists to get extra funding and for a wider public to donate according to their finances and interests. However, in order for crowdfunding to last, scientists must conduct their projects following high ethical standards and provide continuous feedback to their donors to keep their trust.

LAIA CAJA PUIGSUBIRA

Ludwig Uppsala



I think that crowdsourcing is here to stay and is potentially an important resource for less-established researchers to launch creative, high-risk, proof-of-principle projects. There is a 'catch-22' in the traditional system—you need data before you can compete for grants to collect those data, not just great ideas!

MELITA IRVING

Ludwig Lausanne

Required reading

Ludwig Chicago

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Ludwig Lausanne

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Ludwig Stockholm

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