



LUDWIG LINK

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\$10 million program

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LUDWIG
CANCER
RESEARCH

LIFE-CHANGING SCIENCE

LETTER



We asked. You answered.
A big thank you to everyone who completed the communications survey in December. We learned that our efforts have helped you connect and engage with the Ludwig community and have kept you up to date on its major

research achievements. Your comments provided a useful snapshot of what we're doing right and how we might better serve our community.

Many ranked the eLudwigNews, our semi-weekly news clips featuring Ludwig and general cancer news, as a favorite, though some of you would prefer less frequent but fuller emails. We've taken that suggestion. You also suggested that the entire Ludwig community receive these updates. We're working on making that happen. And if the survey accurately captures how folks feel, this digest seems to be a hot favorite as well.

This issue of Ludwig Link recaps some of the most exciting research to date. You'll read about how our scientists have made a big leap forward in personalized medicine, discovered how DNA damage caused by radiotherapy triggers an immune response, and shown why 80% of bowel cancers may be susceptible to an entirely new class of drugs.

We also have an interview with Ludwig San Diego's Karen Oegema. She told us about the discovery that has excited her the most, how she balances work and family, and her advice for young scientists.

Happy reading!

Sincerely,
Rachel Steinhardt
Vice President of Communications

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On the cover: Michael Clarke and Diane Heiser,
Ludwig Stanford

FOR MAGNIFICENT MENTORING

Mentors pay it forward and, in doing so, help shape the quality and focus of scientific discovery. Masterful mentors Don Cleveland and Andrew Scott were both recently recognized for their guidance of early-career researchers.

Don Cleveland of Ludwig San Diego won the Chancellor's Award for Excellence in Postdoctoral Scholar Mentoring. The award, for which he was nominated by postdoc Jie Jiang, honors faculty who "serve as effective advisors, advocates, role models and colleagues for their postdoctoral scholars and who promote high standards of professionalism and research integrity." Don has an amazing training record: 48 of 55 total postdoctoral fellows from his lab have obtained independent academic positions at the end of their postdoctoral training. Don has made landmark contributions to our understanding of mechanisms of chromosome inheritance and the influence of aneuploidy - the leading genetic cause of miscarriage and congenital birth defects - in tumorigenesis as well as in ALS and Huntington's disease. We have little doubt his trainees are forging inspired careers of their own.

Ditto for those trained by Ludwig Melbourne's Andrew Scott, who was awarded the Austin Medical Research Foundation Distinguished Scientist Award. The honor recognizes Andrew's contributions to the research community at Austin Health and his commitment to training the next generation of researchers. A clinician

and a scientist, Andrew is a noted expert on colorectal cancer. He also played a key role in a global Ludwig collaboration that led to the development of monoclonal antibody 806, an unusually specific antibody against a mutated receptor that fuels many glioblastoma tumors. The antibody was adapted by AbbVie to make ABT-414, a highly specific drug in early clinical trials that is already making waves in brain cancer circles.



Don Cleveland
Ludwig San Diego



Andrew Scott
Ludwig Melbourne

FOR LINKING XYZ & DNA

Rockefeller University presented Lucy Shapiro, a member of the Ludwig Scientific Advisory Committee and Virginia and D.K. Ludwig Professor at Stanford University, with the 2014 Pearl Meister Greengard Prize. The annual award, established by Nobel laureate Paul Greengard in memory of his mother, celebrates the achievements of outstanding women in science. Lucy's pioneering work revealed that the bacterial cell cycle is controlled by an integrated genetic circuitry functioning in time and space. This engineering paradigm underlies asymmetric cell differentiation and the generation of diversity.



Lucy Shapiro
Ludwig Scientific Advisory Committee

FOR FOUNDATIONAL DISCOVERY

Ludwig Stanford Director Irv Weissman was honored in Zurich with the Charles Rodolphe Brupbacher Prize for Cancer Research, which recognizes internationally acknowledged achievements in fundamental cancer research. Irv was recognized for his contributions to our understanding of cancer stem cells and how the immune system might be trained against them. His research has far-reaching clinical implications. Irv will also receive the McEwen Award for Innovation from the McEwen Centre for Regenerative Medicine at the International Society of Stem Cell Research meeting in Stockholm this June. The award, which he shares with Hans Clevers of the Hubrecht Institute, recognizes their groundbreaking work on the identification, purification and characterization of adult stem cells from a variety of human tissues.



Irv Weissman
Ludwig Stanford

FOR YOUTHFUL ACCOMPLISHMENT

The European Molecular Biology Organization (EMBO) has selected Mads Gyrd-Hansen of Ludwig Oxford for its Young Investigator Program. He is one of 27 young researchers selected for the honor by EMBO, which promotes excellence in the life sciences. The program includes an award of €15,000 and the opportunity to apply for additional funds. It seeks to advance the careers of Europe's elite researchers aged 40 or younger by supporting their networking and collaborative efforts. Recipients also receive access to European Molecular Biology Laboratory core facilities and funding for themselves and their group members to attend conferences. Mads' research focuses on the molecular

switches that protect the body from pathogens but can also contribute to chronic inflammation and cancer progression.



Mads Gyrd-Hansen
Ludwig Oxford

FOR EVEN MORE YOUTHFUL ACCOMPLISHMENT

Ludwig Harvard's Cigall Kadoch made Forbes magazine's "30 Under 30" list of rising stars in science and health. She studies the role of nuclear protein complexes called BAF complexes, which remodel chromatin to regulate gene expression in human cancer. She and her team have found that BAF components are mutated in about a fifth of all cancers. By studying the biochemical mechanisms by which well-defined lesions to BAF complexes cause a mesenchymal cancer, synovial sarcoma, she and her team want to understand how changes in BAF components cause malignancies. They hope to use this knowledge to discover new cancer therapies.



Cigall Kadoch
Ludwig Harvard

FOR GLOWING SERVICE

Ralph Weichselbaum, co-director of Ludwig Chicago and chairman of the departments of radiation and cellular oncology at the University of Chicago, has been named the Daniel K. Ludwig Distinguished Service Professor. Ralph has devoted his career to translational research in cancer. He is a nationally recognized authority on DNA repair, cancer metastasis and the application of that knowledge to improve radiotherapy for cancer. More recently, he has extended his expertise to encompass the immune system's response to radiotherapy and the exploitation of this response to develop novel immunotherapies.



Ralph Weichselbaum
Ludwig Chicago

A CRISPR PROOF

Time was when a researcher eager to study how a mutation affects a mouse had to engineer the genomes of mouse embryonic stem cells, cross her fingers and wait—and then wait and wait some more for the mouse to grow up—assuming the embryo survived the engineering. No longer. In a [study](#) published October 16 in *Nature*, a team of Boston-based researchers led by Ludwig MIT scientist Tyler Jacks showed how the powerful genome editing tool CRISPR can be used to model gene mutations linked to lung cancer in adult mice. By targeting the genomes of adult mice that had been engineered to express a mutated cancer gene named

Kras only in the lung, the researchers reconfirmed the driving role of two mutations known to interact with *Kras* to generate lung cancer. They also discovered that another mutation, to a tumor suppressor named APC, fuels lung cancer in the presence of *Kras*. Tyler's study establishes proof of concept that CRISPR, as elegant and precise as it is powerful, can be used to quickly examine how any number of complex interactions between mutated genes influence the progression of cancer.



Tyler Jacks
Ludwig MIT

A BOOST FOR CANCER PREVENTION

Ludwig Cancer Research and the Conrad N. Hilton Foundation announced the launch of a \$10 million research program to advance dietary interventions and technologies for the prevention of colon cancer. The new program, to which each organization will contribute \$5 million over five years, expands an existing partnership between the two organizations to develop DNA tests to detect the recurrence of colon cancer in patients.

The program has three overarching goals. One is to investigate and experimentally validate nutritional interventions for the prevention of colon cancers, and to ready them for clinical evaluation. Another is to develop reliable, noninvasive DNA tests for the routine detection of precancerous growths and incipient cancers of the colon. The third, longer-term objective is to engage public health experts, epidemiologists, educators, patients and opinion leaders in introducing new cancer prevention strategies to the general public and policymakers.

Ludwig researchers at Johns Hopkins University in Baltimore, Maryland, and Memorial Sloan Kettering Cancer Center in New York will participate in the effort. They bring expertise in a range of disciplines critical to the program. “This partnership allows us to lay the foundation for practical interventions that will benefit everyone,” said Bob Strausberg, executive director of Ludwig’s collaborative sciences. “There’s a real and urgent need to build the evidence base for dietary cancer prevention, which has the potential to contribute to curtailing the growth of colon cancer worldwide.”



Bob Strausberg
Ludwig Collaborative Sciences

BY HIERARCHY BOUND

In a [study](#) published November 24 in *Developmental Cell*, Ludwig San Diego’s Kevin Corbett, in collaboration with Abby Dernburg at UC Berkeley, examine how HORMA domain proteins, which can be overexpressed in cancer, assemble along chromosomes during meiosis in *Caenorhabditis elegans*. The researchers found that HORMA domain proteins link up in a specific, hierarchical pattern. A better understanding of this process will shed light on both meiotic chromosome structure and genetic recombination, the mixing and matching of

corresponding DNA segments on chromosomes that helps generate genetic diversity.



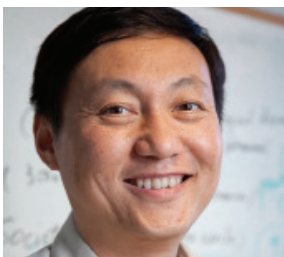
Kevin Corbett
Ludwig San Diego

TAGGING BIAS

The February 19 issue of *Nature* marked the official end of the US National Institutes of Health's Roadmap Epigenome Project with an eight-paper bonanza that captured the most important discoveries made on the road to the map. Taken as a whole, the map describes the chemical modifications made to DNA and its protein packaging to control gene expression. These "epigenetic" tags account in large measure for how such a dizzying array of cell types and tissues are generated from a single genetic instruction manual. Two of the eight *Nature* papers were led by Ludwig San Diego's Bing Ren.

The [first](#) looks at how gene expression differs between matching genes, or alleles, on matching chromosomes—one of which comes from Mom, the other from Dad. Bing's team found that for 30% of all human genes, each allele is expressed at a different level depending on which parental chromosome it resides on.

The [second](#) study integrates data from the first to obtain a more realistic portrait of how gene expression is altered as the epigenetic tags and three-dimensional structures of chromosomes change in different types of tissues and as embryonic stem cells become more specialized. "Every chromosome exists in three dimensions, and its regulation in the living cell is intimately tied to its 3-D structure," says Bing. "We believe that our data will help researchers get a more realistic picture of the gene regulation involved in almost every area of human biology and disease—not just cancer."



Bing Ren
Ludwig San Diego

CANCER'S AIM

About two decades ago, Ludwig Board Member Sam Hellman and Ralph Weichselbaum of Ludwig Chicago identified an intermediate state of metastasis between a treatable localized disease and widespread metastasis. They named it oligometastasis. In the February 28 [issue](#) of *Oncotarget*, Ralph, Sam and their colleagues describe a small cluster of gene-blocking microRNAs expressed only by oligometastatic cells. MicroRNAs play a key role in the regulation of gene expression, and the researchers found that 14 of them are located at the chromosomal address 14q32. Mutations on this genomic block are linked to several developmental disorders.

The researchers found that the genes suppressed by these microRNAs are involved in pathways that allow cells to adhere to other cell types, invade tissues and migrate to distant sites, all of which metastatic cancer cells must do as well. "Tumor cells that express certain microRNAs from 14q32 lack the ability to adhere, invade or migrate—we call it the AIM phenotype," said Ralph. "Instead they give rise to a small number of less aggressive tumors, many of which are curable with local therapy." These microRNAs could be used as personalized biomarkers to help physicians predict how aggressively a tumor might spread and determine an appropriate course of treatment.



Sam Hellman
Ludwig Board Member



Ralph Weichselbaum
Ludwig Chicago

A NEW GLIOBLASTOMA MULTIFORME DEFENSE

Glioblastoma multiforme is the most aggressive and swiftly lethal of adult brain tumors, with a median survival after diagnosis of only 9 to 15 months, even with treatment. Many of these tumors are fueled by mutated forms of the epidermal growth factor receptor (EGFR) and should be prime candidates for a class of drugs known as tyrosine kinase inhibitors (TKIs). But glioblastoma multiforme is a canny quarry, and it quickly becomes resistant to such therapies.

In a [paper](#) published January 15 in *Cancer Research*, Ludwig San Diego researchers Frank Furnari, Paul Mischel, Web Cavenee and their colleagues identify a new mechanism of resistance to TKIs and suggest some strategies to restore TKI sensitivity. Using a model of acquired resistance to TKIs, the researchers show how an enzyme known as urokinase plasminogen activator (uPA) helps glioblastoma multiforme cells circumvent the blockade of EGFR's signaling circuit. The researchers also show how the alternative signaling circuit turned on by uPA can be overcome—but so far just in the laboratory. “We are hopeful that this analysis will open the possibility of developing new drugs to improve outcomes for glioblastoma multiforme,” said Frank.

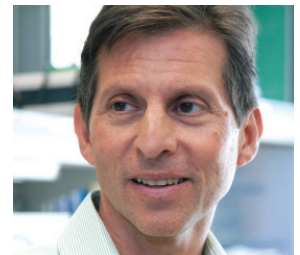
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We are hopeful that this analysis will open the possibility of developing new drugs to improve outcomes for glioblastoma multiforme

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Frank Furnari
Ludwig San Diego



Paul Mischel
Ludwig San Diego



Web Cavenee
Ludwig San Diego

A SIGNATURE STUDY

A landmark [study](#) in the *New England Journal of Medicine* published December 4 identified how a response to immune-based drugs may be written into a tumor's DNA. Ludwig New York researcher Jedd Wolchok and Timothy Chan from Memorial Sloan Kettering Cancer Center have surprising insights into why some tumors respond to immunotherapy and others don't. Timothy, Jedd and their colleagues ran a sophisticated computational analysis of the full complement of genes expressed (the "exome") by tumor cells isolated from 25 patients treated with the checkpoint blockade antibody ipilimumab.

Tumors in patients who respond well to ipilimumab, they found, tend to have a relatively large number of passenger mutations—that is, mutations in genes that do not themselves drive cancer—and express one or more of a set of peptide sequences, each four amino acids long (tetrapeptides). Intriguingly, the mutations in some tetrapeptides make them resemble peptide sequences found in viruses and bacteria that are known to infect humans and cause disease. To test the prognostic power of these signatures, the researchers sequenced the exomes of tumors from another 39 similarly treated melanoma patients. Responders all had one or several of the signature sequences. Those who failed to respond did not. "We are confident that our findings will, if developed further, help guide the selection of patients likely to respond to checkpoint blockade," said Jedd.



Jedd Wolchok
Ludwig New York

SWITCH FOR MOBILITY

In a [study](#) published November 16 in *Nature Cell Biology*, Ludwig Oxford researchers led by Xin Lu report that the tumor suppressor protein ASPP2 functions as a molecular switch that controls epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET) in epithelial cells, which line inner cavities of the body. EMT is a suite of changes in a cell that make it more mobile, whereas MET describes the reverse process, by which cells settle down. Xin Lu and her team show in mouse models that ASPP2 contributes to MET and that its deficiency significantly boosts breast and liver cancer metastasis.

The study shows that ASPP2 stabilizes two proteins that build the junction between epithelial cells: E-cadherin and β -catenin. It turns out that ASPP2 anchors β -catenin to the junction. This prevents β -catenin from darting down to the nucleus, where it can fuel the expression of genes that drive EMT—and metastasis. Finally, Xin and her team show that reduced ASPP2 expression in tumors taken from patients is associated with poor survival in liver and breast cancers.



Xin Lu
Ludwig Oxford

JUMPING JAK AS THERAPY

An international team of scientists led by Ludwig Melbourne's Toby Phesse, Michael Buchert, and Matthias Ernst, who are now all at the newly formed Olivia Newton-John Cancer Research Institute, has shown that more than 80% of bowel cancers could potentially be treated with existing drugs. In a [study](#) published September 30 in *Science Signaling*, the researchers report that inhibiting a signaling protein known as Janus kinase (JAK) slows tumor growth in those preclinical models of bowel cancer and in human bowel cancer cells, which carry mutations in the tumor suppressor gene *APC*. These are the most common mutations in human bowel cancer and result in aberrant activation of the Wnt signaling cascade that is otherwise required for continuous replacement of the intestinal mucosa.

“We didn’t see any side effects in our preclinical models, as Wnt signaling was otherwise unimpeded in the normal cells of the intestine,” said Toby. “JAK inhibitors only block cell growth in cells with very high Wnt signaling, such as those found in the tumors. This makes it a very attractive therapy for bowel cancer.” The good news: several JAK inhibitors are already approved or far along in clinical trials for other disorders, so they can be quickly repurposed and evaluated against bowel cancers.

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JAK inhibitors only block cell growth in cells with very high Wnt signaling, such as those found in the tumors. This makes it a very attractive therapy for bowel cancer.

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Matthias Ernst
Ludwig Melbourne

MAP OF A MALIGNANCY

Web Cavenee and Paul Mischel of Ludwig San Diego were part of a team of scientists from the US and China who charted the mutational landscape of gastric cancer, describing the characteristics of both aggressive and relatively less aggressive forms of this highly variable malignancy. The [findings](#) were published January 27 in *Proceedings of the National Academy of Sciences USA*. They describe the mutations that most commonly drive gastric cancers and the four pathways that are most frequently affected by those mutations. The researchers note that 10% of the tumors they studied could potentially be targeted by an existing drug. The *BRCA2* gene was mutated in 8% of cases and associated with longer patient survival. “We are very excited about these results, which could ultimately help doctors better assess clinical prognosis and select the most effective therapies for each patient,” said Web. Gastric cancer is the fourth most common cancer and the third leading cause of cancer-related death in the world.



Web Cavenee
Ludwig San Diego



Paul Mischel
Ludwig San Diego

A HELPFUL STING

In a [study](#) published November 20 in *Immunity*, researchers led by Ludwig Chicago’s Yang-Xin Fu and Ralph Weichselbaum report how the body’s frontline defenses—the dendritic cells of the innate immune response—are activated following radiotherapy. “It is now clear that the immune system plays a very important role in the response to radiotherapy,” said Ralph. “Our study shows how radiation, DNA damage and the immune response that follows are linked.”

The researchers report that as dendritic cells encounter the remains of an irradiated tumor, a detector of DNA fragments and viral infection inside them named cGAS activates another protein named STING. This, in turn, amps up the dendritic cell’s production of the immune factor interferon- β , which boosts their ability to activate killer T cells that target cancer cells. Tumors implanted in mice that lack a functional gene for STING are relatively resistant to radiation; dendritic cells from mice whose cGAS genes were shut down or knocked out also failed to activate antitumor T cells. These findings suggest that drugs that activate STING signaling could help enhance the effects of tumor irradiation as well as chemotherapy, which also causes considerable DNA damage.



Ralph Weichselbaum
Ludwig Chicago

OF MICE AND MEDICINE

The house mouse, *Mus musculus*, has long been a mainstay of biological research models and a gold mine for biologists: mice multiply quickly and have been studied from nearly every conceivable angle. But the go-to research model has its limitations as a disease model. New [findings](#) reported by the Mouse ENCODE Consortium and published November 20 in *Nature* by an international team led in part by Ludwig San Diego researcher Bing Ren reiterate that what's true for mice often isn't so for humans. More important, the team has identified cases in which mouse studies might accurately capture processes in the human body, and cases in which they probably will not. "There are a substantial number of mouse genes that are regulated in ways different from similar genes in humans," said Bing. "And the differences aren't random. They're clustered along certain pathways, such as in genes regulating the immune system." The data will help researchers determine how best to use the mouse as a model for human biology and disease.

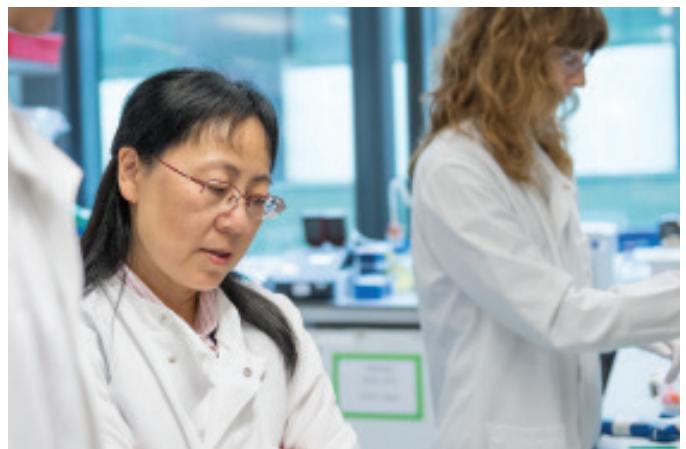


Bing Ren
Ludwig San Diego

OF iASPPS & BROKEN HEARTS

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic, progressive heart condition in which heart muscle cells are replaced by fatty and scar tissue. It can result in heart failure and sudden death. In a [study](#) published March 3 in *Proceedings of the National Academy of Sciences USA*, a team of researchers led by Xin Lu of Ludwig Oxford showed that iASPP, an inhibitor of tumor suppressor p53, also regulates the integrity and functioning of desmosomes, which link each heart cell to its neighbor. Genetic defects in desmosome components account for about half of human ARVC cases; in the other half the causes remain unknown.

Xin and her colleagues find that iASPP-deficient mice die of sudden death and that heart muscle cells from human ARVC patients exhibit reduced levels of iASPP at the cell junctions, suggesting that iASPP may play a critical role in the condition. "This study suggests that iASPP may be a potential new target when screening patients with heart abnormalities," said Xin.



Xin Lu
Ludwig Oxford

FRUIT OF COLLABORATION

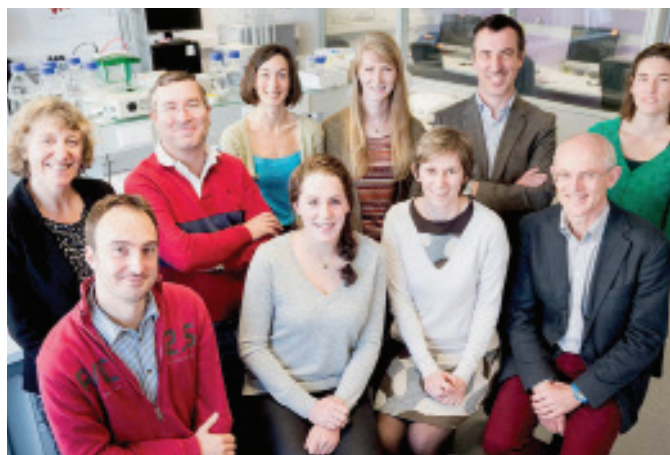
At the 19th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology, held November 13–16 in Miami, AbbVie presented encouraging results from a phase 1 clinical study of its antibody-drug conjugate ABT-414 in patients with glioblastoma multiforme, an aggressive brain cancer that is highly resistant to treatment. Ludwig had a hand in this happy outcome, as we played a critical role in developing the new drug. The antibody part of the conjugate, known as ch806, was discovered and taken through early clinical evaluation by a global Ludwig collaboration.

After a small and but successful safety trial conducted by Ludwig in Australia, the antibody was licensed to Life Science Pharmaceuticals. It was then sublicensed to the company now known as AbbVie. The company linked the antibody to a toxin and tested it in clinical trials for glioblastoma multiforme. The antibody is generating rare excitement among researchers and clinicians alike. Ludwig Melbourne principal investigators Hui Gan and Andrew Scott participated in the recent study, which evaluated ABT-414 as a monotherapy, in combination with chemotherapy, and in combination with radiation and chemotherapy. Four of the 12 patients achieved an objective response, which is a measurable response to cancer treatment. Two achieved complete responses. Last August AbbVie received orphan drug status from both the European Medicines Agency and the US Food and Drug Administration for the treatment of glioblastoma multiforme.

T CELL TWEAKER

iTeos Therapeutics, a biotechnology company spun out from a partnership between Ludwig Cancer Research and the de Duve Institute at the Université Catholique de Louvain, has established a strategic collaboration with Pfizer. Under the agreement, Pfizer gains commercialization rights to iTeos' preclinical IDO1 and TDO2 inhibitor programs. These enzymes are expressed at high levels by a variety of tumors. Pioneering research by Ludwig Brussels' Benoît Van den Eynde, scientific founder of iTeos, revealed that the enzymes suppress immune responses against cancer cells in part by degrading tryptophan, an amino acid essential for the activation of antitumor T cell responses.

The two companies have also partnered to discover new targets for immunotherapies against cancer. "This strategic collaboration is a transformative opportunity and a successful milestone for iTeos," said Michel Detheux, chief executive officer of iTeos. "Pfizer's expertise will accelerate and expand the IDO1 and TDO2 programs. The successful integration of Ludwig Cancer Research science into iTeos' preclinical discovery platform made this collaboration possible."



iTeos Therapeutics

IMMUNOTHERAPEUTIC TRIFECTA?

Agenus, a development-stage biotechnology company specializing in immune system–related therapies, has been a pioneer in the development of cancer vaccines. It recently acquired the company 4-Antibody, with which Ludwig was collaborating to discover and develop a handful of immunotherapeutic antibodies. In December, Ludwig granted Agenus an exclusive license to further develop and commercialize the antibodies resulting from the collaboration. These are antibodies for three molecules—GITR, OX40 and TIM3—that play distinct and important roles in immune cell regulation and are highly promising targets for activating immune responses against tumors.

“Agenus is committed to advancing these therapies and bringing them to patients as quickly as possible,” said Jonathan Skipper, Ludwig’s executive director of

technology development. “Preclinical studies suggest that these antibodies have the potential to be highly effective treatments either as monotherapies or in combination with the now approved immune checkpoint antibodies targeting CTLA-4 and PD1.” Ludwig receives a license fee, development and commercial milestone fees, and royalties from future net sales of the antibodies.



Jonathan Skipper
Ludwig Technology Development

DID YOU KNOW...

Cancer’s an odd name for a disease.

The origin of the word goes back to around 400 BC, when the Greek physician Hippocrates named the disease *karkinos*, the Greek word for crab. Why he chose the cute crustacean and gave it such a bad rap has been lost to history, but theories abound.

Some say it was because the tumors he examined were rock hard, like the protective shell of a crab. Others hypothesized that the pain of a malignant tumor felt like the sharp pinching of a crab’s claw. Another idea was that the tenacity with which a crab bites and refuses to let go resembled the resistance of a tumor to any

type of treatment. The Roman medical writer Celsus (c. 25 BC – c. 50 AD) translated it to *cancer*, the Latin word for crab.

So why isn’t a cancer doctor called a cancerologist?

Another Greek physician, Galen (c. 130–200 AD), described tumors with the word *oncos*, which is Greek for swelling. And even though the crab analogies still ring true today in terms of cancer’s tenacious nature and patients’ determination in battling the disease, Galen’s term won out as the name for cancer specialists—oncologists.

Role Model

How did you become interested in molecular cell biology?

I went to Caltech, where I majored in chemical engineering, but I had a crisis of conscience in my senior year when I saw the kind of research my friends were doing—watching bubbles rise through glycerol or collecting emissions from the top of fast food restaurants. It made me think back to working in my dad's lab when I was in high school—he is a proteoglycan biochemist who specializes in orthopedic surgery research—and I realized that I wanted to do basic research in a field related to biology.

So, I decided to go to graduate school at University of California, San Francisco (UCSF). During my first year at UCSF, I was influenced by the amazing group of cell biologists that were working on the cell cycle and the cytoskeleton there at that time, particularly Tim Mitchison, Bruce Alberts, Mark Kirschner, Ron Vale, Andrew Murray and David Morgan. This was the time when people were just beginning to develop methods to visualize the cytoskeleton and membrane trafficking in living cells, and the breathtaking beauty of cell structure got me hooked. I joined Bruce's lab because of the emphasis of his group on biochemistry and the attraction of being able to develop parallel means to study processes in vitro and in vivo. After Bruce left

to become president of the National Academy of Sciences, I worked with Tim Mitchison, who became a major mentor and scientific role model for me.

Can you give a layperson's description of your research?

We focus on how cells structurally remodel themselves as they divide and how similar kinds of shape changes are involved in the formation of tissues during development. One of our main projects is aimed at understanding how the microtubule-based machine that segregates the chromosomes also directs the remodeling of the cell cortex to partition the contents of the mother cell into the two daughter cells during cytokinesis. We are also very interested in centrosomes, which are the major microtubule-organizing centers in animal cells. We want to understand how centrosomes duplicate precisely once per cell cycle, and how centrosomes contribute to cell physiology. A common feature of cancer cells is the presence of extra, or supernumerary, centrosomes, and we would like to know how this misregulation occurs and whether therapies targeting centrosome duplication could enable the selective killing of cancer cells.

What advances do you see in the coming decade as a result of the work you're doing?

One avenue that we are excited about is the result of a collaboration with the Small Molecule Discovery (SMD) group within



Karen Oegema
Ludwig San Diego

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Doing research is essentially like solving a puzzle, and I love the process of trying to solve that puzzle

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Ludwig. Working with the SMD group has allowed us to develop an inhibitor of a key kinase that controls centrosome duplication, which we are calling centrinone. Treatment with centrinone depletes centrosomes from cells. This led to some surprising findings, because we found that cancer cells will continue to divide if you remove their centrosomes, whereas normal cells have a checkpoint that stops them from continuing to proliferate if centrosomes are removed. In ongoing work, we are trying to use this as the basis for a strategy to selectively target cancer cells by combining centrinone with other inhibitors that specifically kill cells dividing in the absence of centrosomes.

What keeps you motivated and excited about your research?

In science you're always trying to figure out how to go from where you are to someplace new. Doing research is essentially like solving a puzzle, and I love the process of trying to solve that puzzle—because there's nothing more exciting to me than tackling a question and eventually getting an answer.

What advice would you give to a young scientist?

Science is a lot like playing in a jazz band or doing improvisational comedy. A lot depends on the interplay between you and the people around you. I would advise that before you accept a job you should meet the people you will be interacting with, and once you are there, get out and really use your environment to help develop the

science that you want to do. The environment you're in is very important. Being at Ludwig has really shaped the type of research my lab is doing. The lab is engaged in curiosity-driven science, and even though it's very focused on solving fundamental cellular questions, the questions we address also have the potential to contribute to the development of cancer chemotherapeutics.

What has been the most exciting discovery of your career?

That's a tough one, but I think it might be the most recent one in which we found, using the inhibitor that we developed in collaboration with the Ludwig SMD group, that normal cells require centrosomes to maintain their commitment to proliferation. This finding was completely unexpected.

Prior to this, the only way to remove centrosomes was to destroy them with a laser or to remove them surgically. The problem with those methods is that the cells have pathways that can regenerate the centrosomes. Thus, you can only remove centrosomes for part of the cell cycle before they are regenerated. What the chemical inhibitor allowed us to do was to suppress the formation of centrosomes so that the cells were unable to form new centrosomes for multiple cell cycles, which revealed that they are essential to the division of normal cells.

Women are three times less likely than men to become scientists. Why is this?

I don't know to what extent women really

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If you look back at historical images of labs, you will see that there were many women working at the bench and making the important observations that drove things forward, and this is even more true today.

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are less likely to be scientists than men. Women have always been interested in science and have always contributed to the endeavor of expanding human knowledge. If you look back at historical images of labs, you will see that there were many women working at the bench and making the important observations that drove things forward, and this is even more true today. However, it is clear that women have been less likely to be the principal investigators that get the credit and represent the science to the world.

With respect to why men have been more prominently at the forefront in presenting scientific findings, I think it results from the same societal issues that have led to the paucity of female CEOs and political leaders. As these societal barriers are reduced, there are other issues that prevent women from assuming leadership positions in science, including the fact that women are likely to be more heavily involved in the lives of their children and more likely to be the ones responsible for organizing family structure and carrying the cultural torch. Having a family and running a lab is wholly consuming and does not leave a lot of time for much else. People who want to maintain a sense of balance in their life either need to find a way to work with their partner, family and friends to achieve this, or accept that they are not going to have the same sense of balance that many of the families around them have. Like most women principal investigators, I do a combination of these things. Ultimately, I am also okay with not

having a balanced life. There are many things that I should do that I don't. With respect to my children, I think the most important thing is for them to see me pursuing and being successful in doing something that I'm passionate about, and for me to work to enable them to be able to develop and pursue their passions as well.

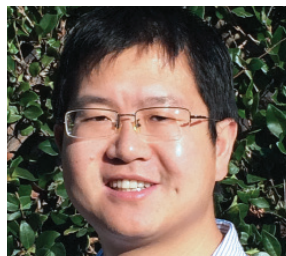
Does being married to another scientist make it easier to have both?

Definitely. Arshad and I are both very involved in the lives of our children and our careers. We also have an amazing nanny who is very central to our lives. Not only does she understand our personalities, but she's instrumental in pulling our lives together. And our kids love her. One advantage of being married to a scientist is that we can both appreciate the challenges of a career in science; it has also helped to drive our science forward. We both find it invaluable to have someone who provides honest strategic feedback on how we can improve the direction of a project.

What's your favorite paper of all the ones you've published?

That's like asking someone to pick their favorite child. I'm not sure you can really do that. For me, my favorite papers are always the ones I am working on now, because you're obsessed with thinking about the experiments that you've done, trying to put them into context, figuring out what they mean and how to tell the story—whereas the ones that you've already published, they're already behind you.

What is the best mentoring advice you ever received?



When I interviewed for a position in Don Cleveland's lab, he told me that in doing research, you may need to be smart or lucky to make discoveries, but the most important ingredient for success is perseverance—inspirational words that stuck with me and have profoundly influenced my research and career.

JIE JIANG

Ludwig San Diego



There are three very memorable ones: Think big, and think outside the box; frame your presentation as a story and explain how it fits into the bigger picture; and go to talks outside your comfort zone—it'll broaden your horizons.

TARU MURANEN

Ludwig Harvard



Only pursue those endeavors that truly engage and appeal to you. Not only will you be more productive but you will enjoy your work more. It's wise counsel when the going inevitably gets rough.

HUI GAN

Ludwig Melbourne

Required reading

Ludwig Brussels

Cancer Immunology Research 2015 February 3

Extensive profiling of the expression of the indoleamine 2,3-dioxygenase 1 protein in normal and tumoral human tissues

Théate I, van Baren N, Pilotte L, Moulin P, Larrieu P, Renaud JC, Hervé C, Gutierrez-Roelens I, Marbaix E, Sempoux C, Van den Eynde BJ.

Ludwig Chicago

Immunity 2014 November 20 STING-dependent cytosolic DNA sensing promotes radiation-induced type 1 interferon-dependent antitumor immunity in immunogenic tumors

Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T, Huang X, Gajewski TF, Chen ZJ, Fu YX, Weichselbaum RR.

Oncotarget 2015 February 28 14q32-encoded microRNAs mediate an oligometastatic phenotype

Uppal A, Wightman SC, Mallon S, Oshima G, Pitroda SP, Zhang Q, Huang X, Darga TE, Huang L, Andrade J, Liu H, Ferguson MK, Greene GL, Posner MC, Hellman S, Khodarev NN, Weichselbaum RR.

Ludwig Johns Hopkins Science 2015 January 2

Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Tomasetti C, Vogelstein B.

Ludwig Melbourne Science Signaling 2014 September 30

Partial inhibition of gp130-Jak-Stat3 signaling prevents Wnt- β -

catenin-mediated intestinal tumor growth and regeneration

Pheesse TJ, Buchert M, Stuart E, Flanagan DJ, Faux M, Afshar-Sterle S, Walker F, Zhang HH, Nowell CJ, Jorissen R, Tan CW, Hirokawa Y, Eissmann MF, Poh AR, Malaterre J, Pearson HB, Kirsch DG, Provero P, Poli V, Ramsay RG, Sieber O, Burgess AW, Huszar D, Vincan E, Ernst M.

Ludwig MIT

Nature 2014 October 16 CRISPR-mediated direct mutation of cancer genes in the mouse liver

Xue W, Chen S, Yin H, Tammela T, Papagiannakopoulos T, Joshi NS, Cai W, Yang G, Bronson R, Crowley DG, Zhang F, Anderson DG, Sharp PA, Jacks T.

Ludwig New York

New England Journal of Medicine 2014 December 4 Genetic basis for clinical response to CTLA-4 blockade in melanoma

Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahli C, Liu C, Harbison CT, Wang L, Ribas A, Wolchok JD, Chan TA.

Ludwig Oxford

Nature Cell Biology 2014 November 16

ASPP2 controls epithelial plasticity and inhibits metastasis through β -catenin-dependent regulation of ZEB1

Wang Y, Bu F, Royer C, Serres S, Larkin JR, Soto MS, Sibson NR, Salter V, Fritzsche F, Turnquist C, Koch S, Zak J, Zhong S, Wu G, Liang A, Olofsen PA, Moch H, Hancock DC, Downward J, Goldin RD, Zhao J, Tong X, Guo Y, Lu X.

Cancer Research

2015 February 15 Interaction between p53 mutation and a somatic HDMX biomarker better defines metastatic potential in breast cancer

Grawenda AM, Møller EK, Lam S, Repapi E, Teunisse AF, Alnæs GI, Børresen-Dale AL, Kristensen VN, Goding CR, Jochemsen AG, Edvardsen H, Bond GL.

Proceedings of the National Academy of Sciences USA 2015 March 3 iASPP, a previously unidentified regulator of desmosomes, prevents arrhythmogenic right ventricular cardiomyopathy (ARVC)-induced sudden death

Notari M, Hu Y, Sutendra G, Dedeić Z, Lu M, Dupays L, Yavari A, Carr CA, Zhong S, Opel A, Tinker A, Clarke K, Watkins H, Ferguson DJ, Kelsell DP, de Noronha S, Sheppard MN, Hollinshead M, Mohun TJ, Lu X.

Ludwig San Diego

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The chromosome axis controls meiotic events through a hierarchical assembly of HORMA domain proteins

Kim Y, Rosenberg SC, Kugel CL, Kostow N, Rog O, Davydov V, Su TY, Dernburg AF, Corbett KD.

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2015 January 15 A urokinase receptor-Bim signaling axis emerges during EGFR inhibitor resistance in mutant EGFR glioblastoma

Wykosky J, Hu J, Gomez GG, Taylor T, Villa GR, Pizzo D, VandenBerg SR, Haseley Thorne A, Chen CC, Mischel PS, Gonias SL, Cavenee WK, Furnari FB.

Nature 2015 February 19 Integrative analysis of haplotype-resolved epigenomes across human tissues

Leung D, Jung I, Rajagopal N, Schmitt A, Selvaraj S, Lee AY, Yen CA, Lin S, Lin Y, Qiu Y, Xie W, Yue F, Hariharan M, Ray P, Kuan S, Edsall L, Yang H, Chi NC, Zhang MQ, Ecker JR, Ren B.

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Chen K, Yang D, Li X, Sun B, Song F, Cao W, Brat DJ, Gao Z, Li H, Liang H, Zhao Y, Zheng H, Li M, Buckner J, Patterson SD, Ye X, Reinhard C, Bhathena A, Joshi D, Mischel PS, Croce CM, Wang YM, Raghavakaimal S, Li H, Lu X, Pan Y, Chang H, Ba S, Luo L, Cavenee WK, Zhang W, Hao X.

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Pan Y, Volkmer JP, Mach KE, Rouse RV, Liu JJ, Sahoo D, Chang TC, Metzner TJ, Kang L, van de Rijn M, Skinner EC, Gambhir SS, Weissman IL, Liao JC.