LudwigLink July 2013

Scientific royalty

Shortly after joining the Ludwig Institute, I was invited to a board dinner where I had the pleasure of sitting next to our new scientific director, David Lane. I remember being particularly intrigued by the "Sir" on his nametag. When was he knighted? Why? We got to talking, and although I never learned the circumstances of his knighthood, I was captivated by his fascination with the Institute, its approach and the achievements that resulted from its independence and flexibility.

At the time, he was particularly excited about a Ludwig discovery, the 806 antibody, which he felt exemplified Ludwig's distinct approach to research. We encourage collaborations of laboratory and clinical research that not only further our understanding of cancer, but also translate laboratory discoveries into candidates for clinical therapy.

When I interviewed David a few weeks ago, this same unbridled enthusiasm for Ludwig was the first thing he shared when asked why he wanted to join the Institute and what makes it stand out from other cancer research organizations. Words like "fleet-footed," "long-term vision," "whole research spectrum," "real impact for patients" and "outstanding science" rolled easily off his tongue.

Click here (password: Ludwig) to listen to David talk about his new role at Ludwig and what he hopes to achieve as our scientific director. You'll also learn more about his research and the opportunities he sees for the future of cancer research. David's passion drives his talent for world-class achievements.

Rachel Steinhardt,
Director of Communications

Sir David Lane

Sitting down with David Lane

An internationally recognized leader in the field of tumor suppressor biology and a strong voice in the battle against cancer, his pioneering research led to the discovery of a tumor suppressor gene, p53, which he named the "guardian of the genome." Knighted for his services to cancer research, he served as Cancer Research UK's first chief scientist. Avrion Mitchinson, with whom he did his PhD in immunology, still refers to him as "the best student I ever had in University College." This gifted scientist is David Lane, the Ludwig Institute's new scientific director. We had a chance to sit down with him and chat about his role.

Why did you want to join the Institute?
Having worked on the Scientific Advisory Committee and the Board of Directors for a number of years, I got to know the Institute very well. And I have to say, it's a pretty amazing organization. I've been able to see firsthand how its scientists carry out outstanding research—all the way from basic to clinical research. Ludwig supports its scientists with long-term funding, which gives them the ability to tackle big problems. They have great resources and the infrastructure to do their research at the very highest level, which accounts for the extraordinary contributions Ludwig scientists have made to cancer research.

What are Ludwig's greatest strengths?
Independence. We choose exactly how we want to spend our resources for the best possible outcome. We support really outstanding science and make sure it gets translated—it doesn't just get stuck in a journal, but is further developed and evaluated so that it has the potential to help patients.

And speed. So often we see an opportunity but it takes years of grant writing before it can happen, whereas at Ludwig, one of our scientists can come to us and say, "This is a fantastic opportunity for a clinical trial," and we can quickly evaluate whether to pursue it. Similarly, if someone comes and says, "This is a piece of equipment we really need; it's really going to transform how

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Sitting down with David Lane

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we're doing our research," we're able to make the decision quickly on whether to buy it or not.

Where do you think Ludwig has a unique opportunity with regard to funding and how it can support research?

The current funding climate for science worldwide is very challenging. And the consequence is that 'the butter is being spread rather thinly'—so individual scientists are competing harder for rather limited funds. And because that results in an extreme level of scrutiny, the type of grants that get funded tend to be the more conservative ones. Ludwig needs to continue to counter those trends. We have great faith and trust in our scientists, and give them enough resources to do outstanding work and sustain that investment so they can take risks. No one can predict what kind of research will ultimately lead to big breakthroughs. The tremendous progress in immune therapy has come from 30-plus years of basic research on the immune system, and nobody could have predicted the impact we are now seeing. So we have to sustain that sort of long-term investment and go for excellence. And when we see excellence, support it. Really nourish our shoots and make sure they flower.

How do you plan to begin at Ludwig and help advance its cancer research programs?

Getting to know everyone well is my number-one priority. There's no substitute for personal contact. I'm a scientist myself, a very active scientist. I love science and I think that puts me in a position where I can understand what people are doing and why they're doing it—while helping people interact with each other and promoting collaboration. Much of the best science comes from unexpected collaboration. Fostering an atmosphere where people feel happy and comfortable working with one another, and making sure they know they are going to be supported, is on my radar.

Will it be tough juggling two roles?

Over the years, I've had to master the art of using my time efficiently, and juggling multiple roles has become second nature to me. I was chief scientist at Cancer Research UK while working with A*STAR—and at one point simultaneously running a biotech company as well as holding a university job.

Much of the best science comes from unexpected collaboration. Fostering an atmosphere where people feel happy and comfortable working with one another, and making sure they know they are going to be supported, is on my radar.

—Sir David Lane,
Ludwig Institute Scientific Director

What are some of the challenges you face?

Institutions like Ludwig have really captured the world's attention by showing that cancer can become a treatable disease. We need to continue to do research that deepens our understanding of the disease and discover and develop new therapies to help patients. Our researchers have been and will remain a part of the revolution that shifts cancer from a death sentence into a manageable disease.

Final words of wisdom?

We all need to keep the faith. Science is hard and long and what Ludwig has achieved is just tremendous. Progress over the past 40 years by the entire Ludwig community now provides unprecedented opportunities to translate current discoveries into improved patient care. We are at a pivotal juncture with the potential for significant gains in the near future. And we're going to continue to be one of the leaders in developing new therapies and new approaches to cancer treatment while constantly striving to understand the disease better.

TRIBUTE

Christian de Duve

A scientific giant

His discoveries brought him great intellectual satisfaction, but that was not enough for Christian de Duve. His goal was to use them to conquer disease. His motto was *"mieux comprendre pour mieux guérir,"* or "the better we understand, the better we can cure." de Duve, a Belgian biochemist with a special connection to the Ludwig Institute, died in May at his home in Nethen, Belgium. His discoveries about the internal workings of cells helped give birth to the field of modern cell biology and shed light on genetic disorders. He shared the 1974 Nobel Prize in Physiology or Medicine with Albert Claude and George Palade.

de Duve was a big part of the Ludwig community. In 1978, he proposed that the Ludwig Institute base its Belgian branch within the walls of the International Institute of Cellular and Molecular Pathology, which he founded and was subsequently renamed in his honor. In his very active retirement, he remained involved in Ludwig research and activities.

"I believe Christian's most important contribution to Ludwig was recruiting Thierry Boon," said Benoît Van den Eynde, Ludwig Brussels director. "It was Ludwig's long-term support that allowed Thierry to pursue his ambitious and innovative research, which led to uncovering the first T cell-defined tumor antigen in human beings, and thereby reinvigorated the field of tumor immunology. We will always be grateful to Dr. de Duve for his serendipitous matchmaking."

PEOPLE ON THE MOVE

Leading the charge

Brazil is gearing up for the "biosimilar" boom, and Andy Simpson, Ludwig's former scientific director, is leading the charge. Biologic biosimilars are copycat versions of complex biological drugs, such as the lung cancer drug Avastin, the breast cancer drug Herceptin, and Rituxan, which is used to treat cancer of the lymphatic systems as well as rheumatoid arthritis. Brazil is determined to become an important player in this area, joining a select but growing group of nations becoming manufacturing hubs for biosimilars.

Andy Simpson

The Brazilian government has a key role in supporting the industry by giving grants and loans to biotechnology start-up companies. Two new entities were created by existing Brazilian pharmaceutical companies with support from the Brazilian government to serve this market, Orygen Biotecnologia and BioNovis.

Andy is taking the reins of Orygen as CEO at a propitious moment. Biologics are expected to account for nearly 15 percent of the global pharmaceutical market by **2017**. Andy expects that the first biosimilar monoclonal antibody will be the breast cancer drug trastuzumab, commonly known as Herceptin.

"Biosimilar drugs will be a game changer. They'll go a long way in meeting Brazil's need for affordable health care for its growing population of 200 million, as they offer the very real possibility of providing patients with quality medicines and enhanced treatments at better prices," Andy said. "The government was spending a lot of money importing biological drugs, which was affecting the balance of payments. Now that some of these antibodies are about to come off patent, it is possible to think about producing and manufacturing them in Brazil."

Since biosimilar drugs are never exact copies of the original medicine, establishing appropriate standards for clinical development, manufacturing processes and therapeutic use are the biggest hurdles. Tiny differences in manufacturing mean biological drugs are impossible to replicate exactly. As a result, clinical trials are needed before approval, because there can't be any clinically meaningful differences between the biosimilar and the approved biological product in safety, purity and potency.

Andy, who recently stepped down from the Institute's board of directors to pursue his new responsibilities, brings the right mix of scientific expertise and experience in leading complex projects. Two products, trastuzumab and etanercept, have already been produced in Orygen's pilot plant. Four other projects are under way, as are negotiations with the government for plans to build an industrial plant. This is not an easy feat in Brazil.

"Every start-up has a life of its own. Each project brings unique challenges and opportunities. At Orygen, everyone understands that this is a project of national importance, and there is the same spirit of collaboration and commitment that embodies Ludwig."

Did you know ...?

Nicknamed the silent killer, it spreads rapidly and is seldom detected in its early stages. Symptoms may not appear until it's reached an advanced stage. It has the lowest relative survival rate of all cancers—95 percent of patients die within five years of diagnosis and 74 percent within the first year.

Pancreatic cancer is the 13th most common cancer in the world, with more than 280,000 new cases diagnosed every year. It is more common in men than women, and more prevalent in high-income countries, where rates are increasing.

Actor Patrick Swayze, best known for his roles in the hit films *Ghost* and *Dirty Dancing,* was diagnosed with stage 4 pancreatic cancer in January 2008. Rumored to have no more than six months to live, he beat those odds but died after a valiant 20-month battle.

But there's good news on the horizon—the five-year survival rate for pancreatic cancer approaches **40 percent** if the cancers are surgically removed while they are still small and have not spread to the lymph nodes.

Ludwig scientist Bert Vogelstein is a member of the Pancreatic Cancer Research Consortium and a scientific advisor of the Lustgarten Foundation, a private, nonprofit foundation dedicated to funding pancreatic cancer research. He and his team developed a gene-based test to distinguish harmless pancreatic cysts from precancerous ones. This may eventually help some patients avoid needless surgery to remove the harmless variety.

AWARDS

Web Cavenee

Bert Vogelstein

Bob Weinberg

First class

Three Ludwig scientists were named as fellows in the inaugural class of the American Association for Cancer Research (AACR) Academy, the most prestigious honor bestowed by the association. They are Web Cavenee of Ludwig San Diego, Bert Vogelstein of Ludwig Johns Hopkins and Bob Weinberg of Ludwig MIT. The AACR Academy was created to recognize and honor distinguished scientists whose major scientific contributions have propelled significant innovation and progress against cancer.

"Each of these researchers has pioneered advancements in cancer research. They have helped to transform the landscape by enhancing the understanding of the underlying causes of cancer and accelerating the development of new tools to defeat it," said Ed McDermott, Ludwig's president and CEO. "We are grateful for the recognition by AACR of the life work of these researchers."

Xin Lu

An excellent fellow

Molecular biologist and Ludwig Oxford director Xin Lu was elected a fellow of the Academy of Medical Sciences in April for her exceptional contribution to science in the UK. With a vision to improve health through research, the academy's mission is to promote medical science and its translation to benefit society. Xin joins David Lane, Ludwig's new scientific director, who is a founding member of the academy.

The honor recognizes Xin's outstanding contributions to the innovative application of scientific knowledge. She discovered the ASPP family of proteins, and her group focuses on understanding how to selectively kill cancer cells. They study the role of ASPP proteins in tumor suppression pathways with the aim of identifying therapeutic targets.

Up to 44 new fellows are elected to the academy each year. They are selected from biological and laboratory sciences, clinical academic medicine and other professions affiliated with medical science. Election to the academy is based on a candidate's outstanding contribution to the advancement of medical science, their application of existing scientific knowledge to innovative health interventions, or their conspicuous service to medical science and health care.

A noble tradition

The Nobel Foundation's new chairman of the board is Ludwig Uppsala's director Calle Heldin.

"I'm pleased and honored by the Nobel Foundation's expression of trust and look forward to this important and exciting assignment. The Nobel Prize has a unique international status and I will do my utmost to contribute to the foundation's efforts to preserve its position and further develop its activities."

Brain trust

It's the most common and deadly form of brain cancer: glioblastoma multiforme (GBM). Life expectancy after diagnosis is 15 months. But the National Brain Tumor Society is determined to change that prognosis. It's launched the Defeat GBM Research Collaborative, an initiative that aims to double the survival rate of deadly brain cancer in just five years.

To achieve this goal, the collaborative will connect leading brain tumor researchers from top cancer institutions across the globe. Projects will be combined and driven by investigator teams with proven track records to significantly improve patient survival. The primary goal is to share data among projects and investigator teams to advance potential therapies along the drug discovery pipeline.

Ludwig scientists Web Cavenee in

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AWARDS

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George Demetri

San Diego and George Demetri at Dana-Farber/ Harvard are two of the senior cancer experts on the Strategic Scientific Advisory Council that will oversee the collaborative. These advisors will chart the strategic direction of research, review achievements and progress, and hold the project teams accountable for attaining key milestones and annual goals over the next five years

Scientific rock stars

Science is cool.

Tech titans want to turn scientists into superheroes, and they're rewarding them each with a $3 million Breakthrough Prize in Life Sciences. The new, international award, similar to the Nobel Prize, rewards scientists who think big, take risks and do research aimed at curing intractable diseases and extending human life. While the prize recognizes researchers at the top of their fields, it's also intended to inspire future scientists.

Three Ludwig scientists were among the eleven recipients of the first Breakthrough Prize in Life Sciences, which is funded by several Silicon Valley entrepreneurs.

Titia de Lange

Titia de Lange, a Ludwig Scientific Advisory Committee member at Rockefeller University, was recognized for her work on telomeres, the protective sequences at the ends of our chromosomes. She continues to explore how the loss of these structures leads to cancer and aging. Bert Vogelstein of Ludwig Johns Hopkins discovered many of the genes responsible for human tumorigenesis and devised a model for the pathogenesis of colon cancer that undergirds much of modern cancer research. Bob Weinberg of Ludwig MIT, who studies cancers and how they metastasize, discovered the first human oncogene, a gene that 'goes rogue' after a mutation and drives tumor growth.

NEWS ROUNDUP

Joan Heath

Family ties

What is shorter than your little finger, translucent, and a useful model for biomedical research?

The answer: zebrafish.

The zebrafish attracts researchers investigating many human diseases and new treatments. Zebrafish share many genes with humans. They can develop most of the types of tumors that humans do through the same genetic pathways.

While studying mutant zebrafish embryos, Ludwig researchers in Melbourne, Australia, led by Joan Heath discovered a genetic defect that can halt cell growth and allow cells to evade death. The discovery, reported in ***PLOS Genetics***, has implications for the development of new treatments for diseases including cancer.

The gene *Pwp2h,* which harbored the defect, is required for the proper assembly of ribosomes, the cellular powerhouses that support growth and proliferation. When the gene is mutated, ribosome assembly is disrupted and rapidly dividing cells no longer produce the proteins required to fuel their growth.

Joan and her collaborators studied the effects of the mutated *pwp2h* gene in zebrafish. To the researchers' surprise, intestinal epithelial cells under stress from ribosome failure did not die. Instead, the cells initiated a process known as autophagy to promote their survival.

Currently, there is great interest in developing therapeutics to block ribosome production as a strategy to prevent cancer cells from dividing. The team's zebrafish model of disrupted ribosome biogenesis suggests that this approach requires caution.

"An anticancer treatment that inadvertently promotes the survival of cancer cells through the induction of autophagy would not be desirable," said Joan. "However, our findings in zebrafish have also shown that in cells where ribosome assembly is blocked, the inhibition of autophagy causes rapid cell death. Therefore it is possible that a combination of inhibitors that block ribosome function and autophagy could provide an effective anticancer treatment."

The group has assembled a collection of zebrafish mutants harboring mutations that disrupt the growth and proliferation of the intestinal epithelium. Now that several of these mutants have been cloned, the underlying mutant genes are similarly being evaluated as potential targets for anticancer treatments.

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Checkpoint Charlie

The PD-1 pathway shields tumor cells from destruction by the immune system. It has two components, PD-1, a receptor expressed on the surface of T cells, and PD-L1, which is expressed on both cancer cells and a variety of normal cells. Together PD-1 and PD-L1 suppress the function of T cells, the immune system's attack dogs, so the cells do not recognize and destroy tumor cells.

Ralph Weichselbaum

In a **June 1** study in the *Journal of Immunology*, a team led by Ludwig researcher Ralph Weichselbaum at the University of Chicago explored the effects of radiation and an antibody to PD-L1 in two different mouse models. They treated irradiated tumors in the equilibrium phase, during which the immune system maintains tumor dormancy, with an antibody to PD-L1. The antibody blocked the interaction between PD1 and PD-L1, boosting T cell activity.

Nearly all of the mice whose tumors were induced into the equilibrium phase by radiation were cured with the addition of the antibody to PD-L1. The animals who received radiation alone relapsed 75 percent of the time. "When exposed to localized radiation with an anti-PD-L1 antibody, the tumors moved from the equilibrium phase to complete regression," Ralph said.

When good receptors go bad

Cancer cells are wily, well-traveled adversaries that can sidestep the treatments thrown at them to try and stop them from spreading. In the **April 23** issue of *Cancer Discovery*, a team led by Paul Mischel at Ludwig San Diego reports an important step toward thwarting these crafty cancer cells. They identified a unique mechanism by which glioblastoma cells develop resistance to drugs that target EGFR signaling. EGFR, a protein frequently mutated in lung and colon cancers and glioblastoma, is a major target of therapies. Drugs developed to target this protein work only until the cancer cells adapt to evade the therapy.

So far, most research on this drug resistance has focused on how mutations of other proteins in cancer cells allow them to resist drugs. But Paul and his team have unearthed something unexpected. They found that glioblastoma cells develop resistance to drugs that target EGRF signaling by hijacking the signaling of a perfectly normal cell surface receptor. This receptor, platelet-derived growth factor receptor-β (PDGFR-β), affects vascular development. Targeting both receptors at once, they found, prevents resistance and suppresses glioblastoma tumors in laboratory models.

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It's alive! It's ALIVE!

Can you imagine creating something that has absolutely no chance of surviving, but does anyway?

Ludwig San Diego investigators Chris Campbell and Arshad Desai engineered a mutant yeast cell that they thought had no chance of surviving. But did. Their discovery, published in the **April 25** issue of *Nature*, upends the prevailing model for how dividing cells monitor equal distribution of their chromosomes.

Arshad Desai

Chromosomes are made up of DNA, and humans have 23 pairs of them. They carry all the information used to help a cell grow, thrive and reproduce.

"Getting the right number of chromosomes into each cell is absolutely essential to sustaining life," explained Arshad, "but it's also something that goes terribly wrong in cancer. The kinds of mistakes that occur when this process isn't functioning properly are seen in about 90 percent of cancers, and very frequently in advanced and drug-resistant tumors."

Chris Campbell

Chris and Arshad studied the enzyme Aurora B kinase, which regulates chromosome tension to ensure proper cell division. Its location was thought to be central to its role to monitor chromosome tension. But their research shows otherwise. Arshad and Chris found that when Aurora B congregates in a different location, the required tension is still achieved on chromosomes before they are parceled out to daughter cells.

How the protein does this remains unclear, and both scientists are conducting experiments to test various hypotheses.

On-off switch

Many complex diseases have their roots in early human development. Susceptibility to disease is, in part, the result of epigenetic regulation of the genetic blueprint. Epigenetics is the study of changes in gene activity that don't involve alterations to the genetic code but are passed down to at least one successive generation. The great hope for epigenetic research is that with the flip of a biochemical switch, researchers could instruct genes that play a role in many diseases—including cancer—to lie dormant.

A large, multi-institutional research team involved in the US National Institutes of Health Epigenome Roadmap Project published a sweeping analysis in the **May 23** issue of *Cell*. The study details how genes are turned on and off to direct early human development. Led by Ludwig San Diego researcher Bing Ren, the scientists describe how novel genetic phenomena probably play a pivotal role not only in the genesis of the embryo but also in cancer.

The researchers found that modifications to DNA and histone proteins, known as the epigenome, govern the regulation of early embryonic development and tend to be switched off by H3K27me3 histone methylation.

Bing Ren

Modifications that orchestrate later stages of cellular differentiation, when cells become increasingly committed to specific functions, are primarily silenced by DNA methylation. DNA methylation stably alters the expression of genes in cells as cells divide and differentiate from embryonic stem cells into specific tissues.

DNA methylation and H3K27me3 are both involved in the establishment and maintenance of epigenetic gene silencing. While it has long been known that aberrant DNA methylation plays an important role in various cancers, these results suggest that changes to the cell's DNA methylation machinery itself may be important in the evolution of tumors.

"These data are going to be very useful to the scientific community in understanding the logic of early human development," said Bing. "But I think our main contribution is the creation of a major information resource for biomedical research."

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"Our findings highlight the remarkable adaptability of cancer cells and how they harness multiple mechanisms to maintain the growth signals critical to their survival. These results could have implications for our understanding of a wide variety of cancers," said Paul.

The next step is to test in clinical trials how targeting both receptors affects the treatment of glioblastoma. Paul and his colleagues also hope to work with other Ludwig researchers to explore small molecule inhibitors of PDGFR-β and examine whether similar drug resistance mechanisms are found in other cancers.

Rebel with a cause

The most common mutation leading to cancer is in the gene that makes p53, a protein that recognizes and suppresses aberrant cell growth that leads to cancers. A cancer cell starts out as a normal cell, but becomes a 'rebel,' dividing recklessly, invading other tissues, usurping resources and in some cases eventually killing the body in which it lives. If the DNA damage is so extensive that it cannot be repaired, p53 triggers the cell to commit suicide. When p53 is mutated, however, cancers can grow unchecked in the body.

New research reveals how the tumor suppressor p53 is shut down in metastatic melanoma, and how it can be revived. In the **April 25** issue of *Cancer Cell*, a team of researchers led by Xin Lu of Ludwig Oxford describes how p53 is silenced in advanced melanomas by the protein iASPP. In over 50 percent of all human carcinomas, p53 is limited in its antitumor activities by mutations in the protein itself. The researchers explored whether they could restore p53's function in advanced melanomas by checkmating iASPP activation.

"These results demonstrate that functional p53 in melanoma is normally inhibited by two different factors, instead of one, as previously thought. They also

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provide a proof of principle that both of those factors need to be blocked if p53 is to be successfully reactivated in cancer cells," said Xin.

The team treated advanced melanomas in mouse models with two small molecules and the drug vemurafenib, which blocks the action of abnormal proteins that signal cancer cells to multiply and helps slow or stop the spread of cancer cells. With such treatment, advanced melanoma tumors shrank by 75 percent after 28 days of treatment. This work has implications for the treatment of cancers in which p53 is not mutated but is instead functionally silenced; these comprise roughly half of all cancer cases.

Tracking a villain

mTOR. No, it's not a comic book villain.

It's a molecular pathway that regulates tumor growth, survival and, potentially, cancer drug resistance. Glioblastoma is the most common malignant primary brain tumor of adults and one of the most lethal forms of cancer. It's tough to treat because tumors rapidly become resistant to therapy—and it's very resistant to mTOR-targeted therapy. The mTOR signaling pathway is hyperactivated in nearly 90 percent of glioblastomas and plays a critical role in regulating tumor growth and survival. Therapies that inhibit mTOR signaling are under investigation as drug development targets, but so far results have been disappointing. mTOR inhibitors halt tumor growth but fail to kill tumor cells.

Ludwig researchers Paul Mischel, Web Cavenee and Frank Furnari in San Diego uncovered a molecular mechanism that causes resistance to mTOR inhibitors and identified a novel drug combination that reverses this resistance using low-dose arsenic in mice. Their study was published in the **March 12** issue of *Proceedings of the National Academy of Sciences.*

They explored the role of promyleocytic leukemia gene, or PML, in causing resistance to mTOR inhibitor treatment. They found that when glioblastoma patients are treated with drugs that target the mTOR pathway, PML levels rise dramatically. They also showed that an increase in expression of PML made tumor cells resistant to mTOR inhibitors. If they suppressed the ability of the tumor cells to upregulate the PML protein, the tumor cells died in response to the mTOR inhibitor therapy.

"Current therapy upregulates PML, turning off the mTOR signaling pathway. The tumor cells hide, waiting for the target signal to return," said Paul. "When low-dose arsenic is added, it not only stops the cell from returning, but also shuts down the escape route, killing the tumor cell. These data suggest a new approach for potential treatment of glioblastoma, and we're moving forward to test that possibility in people."

Ask a scientist

What do you believe are the most important benefits scientific research provides to society?

As human beings we have the extraordinary and intrinsic ability to seek the truth and try and understand the world that surrounds us. Research generates knowledge, which not only makes us more complete, but also translates into new technologies, expertise and information that positively affect our everyday quality of life.

—Natalia Sacilotto, Ludwig Oxford

Scientific research has great potential to increase general knowledge and to improve the overall well-being of each individual; it thereby promotes the health of our society. In history, scientific research has repeatedly challenged existing dogmata and thus constantly inspires society to scrutinize our perception of the world.

—Lars Tögel, Ludwig Melbourne

Scientific research provides knowledge and insight into diseases and disease mechanisms, thus providing new strategies for treatment. However, one important factor that is often overlooked is that scientific research provides hope—hope for new cures, hope for better treatments and hope for surviving whatever the future might hold.

—Alexandra Karlén, Ludwig Stockholm

Although the benefits of scientific research are difficult to evaluate, scientific research is the only approach we possess that allows us to accurately detect and also face major challenges, such as environmental changes, emergence of new diseases or societal problems.

—Christian Pecquet, Ludwig Brussels

Q&A WITH JEDD WOLCHOK

A hero who heals others

Celebrated medical oncologist, outstanding researcher, compassionate clinician, accomplished musician: Ludwig's Jedd Wolchok, who was also just appointed as the Lloyd J. Old Chair for Clinical Investigation

Your research yielded fantastic results on a new immunotherapy combination—ipilimumab and nivolumab. Why is this so exciting?

It broke new ground in the treatment of metastatic melanoma and produced durable tumor shrinkage in about half the patients. Ipilimumab is the first in an emerging class of therapies we call "checkpoint blocking agents," which enhance the immune system's ability to identify and kill cancer cells. The approval of ipilimumab to treat advanced metastatic melanoma was a game changer not only for the thousands of people fighting this disease, but also for the entire field of oncology. Now our data indicate that when ipilimumab and nivolumab are given concurrently, they may be more effective against metastatic melanoma than either appears to be alone, as each one impacts the immune system in a distinct but complementary way. So there's renewed hope for patients whose disease has progressed after ipilimumab. Alternative immunotherapies can still work for them.

Who or what was the catalyst for pursuing melanoma research?

Summer of 1984. I had the honor of meeting with Lloyd Old, who was supervising a dozen different labs at Memorial Sloan-Kettering Cancer Center (MSKCC) at the time. He handed me a stack of papers to read and told me to pick the one that resonated, and he'd have me work there for the summer. I had just finished my freshman year at Princeton and the most accessible paper was on a clinical trial on melanoma written by Alan Houghton. As I learned more through the 80s and early 90s and became an oncology fellow at MSKCC, I grew to appreciate what a significant and challenging problem melanoma had become and how there was a desperate need for better answers.

What inspires you most about your research today?

The ability to bring new treatments to people who need them. We now have a spate of new drugs helping more patients than ever before—giving them more time and a better quality of life. I have the extraordinary privilege of trying to help people who are facing a devastating illness. And what more motivation could a person have than to be face to face with someone who desperately needs a better answer? Over the past 17 years, I've been able to change the tenor of the conversation I have with patients. It's gone from "I'm sorry there's nothing we have that works well" to "We have several options that will extend your survival but we're trying to do better than that and that's why you should consider a clinical trial." The advances accrued over the past decade have fundamentally changed the conversations that doctors can have with their patients.

What is the biggest obstacle that you have had to overcome in your career?

Balancing how much time and energy I have to do the very important job of taking care of sick patients while paying the appropriate amount of attention to the science. In my world they are both so important and finding that balance is extraordinarily difficult. I see patients one day a week and take care of inpatients two weeks a year. But even though clinic is just once per week, people can be sick on the other days and I need the temporal space to help them. If I were seeing patients in the clinic every day, I would not have enough time or capacity to do science, whether that's clinical, basic or translational science. You need cognitive

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space. You need creative space. There are precious few places like the Ludwig Center at MSKCC that allow a physician to define their clinical practice and give people that space to really try to succeed in both worlds.

Can you explain what immunotherapy is and why it holds so much promise?

Cancer can be recognized by our own immune systems as something foreign and dangerous that can be gotten rid of like an infection. And immunotherapy is an intervention that aims to recruit a patient's immune system to do just that. Immunologists have long hypothesized that specific interventions could stimulate and 're-educate' patients' own immune systems to attack their cancer. Immunotherapies are designed to help activate the immune system by blocking the 'stop sign' that prevents immune cells from destroying cancer cells. Malignant cells are able to proliferate because of driver mutations but also because they hide from the body's immune system. Sometimes the body doesn't recognize them as foreign and it doesn't fight them, or the tumors actively thwart an immune response as a means of survival. The goal is to get the patient's defenses up so cancer is recognized as an invader, and it gets controlled as an infection would.

With immunotherapy, we've entered a new era of cancer therapy. It's helped us turn advanced cancer into a chronic rather than an acutely deadly disease by enabling the immune system to continuously monitor against the reappearance of 'foreign' cancer cells.

If you were just named magic czar of all of cancer in the United States, what would you change about the system to move research from bench to bedside faster?

Money. We need more of it devoted to scientific and medical research. The lack of knowledge and lack of effective drugs are obstacles we've overcome. We have collaborative and collegial relationships with industry. Contracted research is a thing of the past and we're now undertaking collaborative research to advance our goals. Too much time and energy is expended on the constant need to secure funding. And unfortunately much of the time spent on it doesn't bear fruit.

Scientists want to make progress and eliminate the dependence on writing grants. Ludwig understood this four decades ago. I think it's a big reason why its reach and impact have been so phenomenal. The secret is to identify promising scientists it has confidence in who will make a difference in cancer research, and to put the resources behind them. Instead of worrying about money, all I have to worry about is the next great experiment. Or the therapy or clinical trial. It's a much more effective use of my time. With this model, Ludwig was ahead of the curve. It's a wonderful feeling, knowing that all of the projects I am working on right now will continue to develop and grow over the next five years.

Worldwide deaths from melanoma have reached almost 73,000 a year. What steps can be taken to reduce this number?

Use sunscreen and stay out of the tanning bed. There's no such thing as a safe tan. And getting one—whether artificially or from the sun—is unhealthy, increasing an individual's risk of developing cancer. In fact, people who begin tanning younger than age 35 experience a 75 percent higher risk of melanoma.

You and Dr. Old shared a love of music as well as both being accomplished musicians. What instrument do you play?

Tuba. I play in a group called the Brooklyn Wind Symphony, a community-based organization. The majority of its members are music teachers who are looking for a way to hone their performing skills. We perform and raise money and support for a public high school in Brooklyn that is a magnet school for the performing arts. We commissioned a new work, Requiem, by David Maslanka, which was performed on June 15. We're actually the first group from New York to win a performing spot at the Midwest Clinic, an international band and orchestra competition, which will be held in Chicago this December. It's the World Cup of wind bands and quite an honor.

Click here to listen to *Rolling Thunder* by Henry Fillmore

REQUIRED READING

Ludwig Lausanne

Immunity 2013 April 18
MicroRNA-155 is required for effector CD8(+) T cell responses to virus infection and cancer
Dudda JC, Salaun B, Ji Y, Palmer DC, Monnot GC, Merck E, Boudousquie C, Utzschneider DT, Escobar TM, Perret R, Muljo SA, Hebeisen M, Rufer N, Zehn D, Donda A, Restifo NP, Held W, Gattinoni L, Romero P.

Cancer Research 2013 April 30
(Epub ahead of print)
Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T cell rejection function in tumors
Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G.

Clinical Cancer Research 2013 May 6
(Epub ahead of print)
TIE-2 and VEGFR kinase activities drive TIE-2-expressing monocytes immunosuppressive function in human breast tumors
Ibberson M, Bron S, Guex N, Faes-Van't Hull E, Henry L, Ifticene-Treboux A, Lehr HA, Delaloye JF, Coukos G, Xenarios I, Doucey MA.

Ludwig Melbourne

PLoS Genetics 2013 February 9
Autophagy induction is a Tor- and Tp53-independent cell survival response in a zebrafish model of disrupted ribosome biogenesis
Boglev Y, Badrock AP, Trotter AJ, Du Q, Richardson EJ, Parslow AC, Markmiller SJ, Hall NE, de Jong-Curtain TA, Ng AY, Verkade H, Ober EA, Field HA, Shin D, Shin CH, Hannan KM, Hannan RD, Pearson RB, Kim SH, Ess KC, Lieschke GJ, Stainier DY, Heath JK.

Ludwig MSKCC

New England Journal of Medicine
2013 June 2 (Epub ahead of print)
Nivolumab plus ipilimumab in advanced melanoma
Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, Burke MM, Caldwell A, Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M.

Ludwig Oxford

Cancer Cell 2013 April 23
(Epub ahead of print)
Restoring p53 function in human melanoma cells by inhibiting MDM2 and cyclin B1/CDK1-phosphorylated nuclear iASPP
Lu M, Breyssens H, Salter V, Zhong S, Hu Y, Baer C, Ratnayaka I, Sullivan A, Brown NR, Endicott J, Knapp S, Kessler BM, Middleton MR, Siebold C, Jones EY, Sviderskaya EV, Cebon J, John T, Caballero OL, Goding CR, Lu X.

Ludwig San Diego

Cancer Discovery 2013 March 27 (Epub ahead of print)
De-repression of PDGFRβ transcription promotes acquired resistance to EGFR tyrosine kinase inhibitors in glioblastoma patients
Akhavan D, Pourzia AL, Nourian AA, Williams KJ, Nathanson D, Babic I, Villa GR, Tanaka K, Nael A, Yang H, Dang J, Vinters HV, Yong WH, Flagg M, Tamanoi F, Sasayama T, James CD, Kornblum HI, Cloughesy TF, Cavenee WK, Bensinger SJ, Mischel PS.

Proceedings of the National Academy of Sciences USA 2013 March 12
PML mediates glioblastoma resistance to mammalian target of rapamycin (mTOR)-targeted therapies
Iwanami A, Gini B, Zanca C, Matsutani T, Assuncao A, Nael A, Dang J, Yang H, Zhu S, Kohyama J, Kitabayashi I, Cavenee WK, Cloughesy TF, Furnari FB, Nakamura M, Toyama Y, Okano H, Mischel PS.

Cell Metabolism 2013 May 22
(Epub ahead of print)
EGFR mutation-induced alternative splicing of max contributes to growth of glycolytic tumors in brain cancer
Babic I, Anderson ES, Tanaka K, Guo D, Masui K, Li B, Zhu S, Gu Y, Villa GR, Akhavan D, Nathanson D, Gini B, Mareninov S, Li R, Camacho CE, Kurdistani SK, Eskin A, Nelson SF, Yong WH, Cavenee WK, Cloughesy TF, Christofk HR, Black DL, Mischel PS.

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(Epub ahead of print)
A tale of two approaches: complementary mechanisms of cytotoxic and targeted therapy resistance may inform next-generation cancer treatments
Masui K, Gini B, Wykosky J, Zanca C, Mischel PS, Furnari FB, Cavenee WK.

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Tension sensing by Aurora B kinase is independent of survivin-based centromere localization
Campbell CS, Desai A.

Current Opinion in Cell Biology
2013 March 2 (Epub ahead of print)
Genome organization and long-range regulation of gene expression by enhancers
Smallwood A, Ren B.

Ludwig Stanford

Proceedings of the National Academy of Sciences USA 2013 May 20
Anti-CD47 antibody–mediated phagocytosis of cancer by macrophages primes an effective antitumor T-cell response
Tseng D, Volkmer JP, Willingham SB, Contreras-Trujillo H, Fathman JW, Fernhoff NB, Seita J, Inlay MA, Weiskopf K, Miyanishi M, Weissman IL.

Science 2013 May 30
(Epub ahead of print)
Engineered SIRP variants as immunotherapeutic adjuvants to anticancer antibodies
Weiskopf K, Ring AM, Ho CC, Volkmer JP, Levin AM, Volkmer AK, Ozkan E, Fernhoff NB, van de Rijn M, Weissman IL, Garcia KC.

Ludwig University of Chicago

Journal of Immunology 2013 June 1
Radiation-induced equilibrium is a balance between tumor cell proliferation and T cell-mediated killing
Liang H, Deng L, Chmura S, Burnette B, Liadis N, Darga T, Beckett MA, Lingen MW, Witt M, Weichselbaum RR, Fu YX.