



LUDWIG LINK

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Ralph Venhaus on the
importance of clinical
trials

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LUDWIG
CANCER
RESEARCH

LETTER



Clinical trials are admittedly not the sexiest vehicles of biomedical science. Even the snazziest models involve prodigious amounts of paperwork and can drag along for years and years. But they are solid, and reliable,

and—most important—the ultimate test of whether what seems to be a really good idea for a therapy really is all it's cracked up to be. Plus, regulators require them.

Trials are, in short, the *sine qua non* of drug development. Once they have lumbered across the finish line, they provide answers to the questions that really matter to desperate patients and impatient physicians: Does the drug work, and does it work well enough to be worth taking?

Of course, some drugs do and others don't. But all cancer drug trials have one thing in common: they stem from, hands down, the coolest science around. In this issue you'll read about some of the fascinating research Ludwig scientists are doing to advance our understanding and treatment of cancer, and the recognition they have recently received for their contributions at both ends of the cancer research continuum.

We also share an interview with Ralph Venhaus, Ludwig's chief medical officer and director of clinical trials management, who talks about clinical studies and how 'basket studies' are improving and accelerating the development of groundbreaking cancer therapies.

Happy reading!

Sincerely,
Rachel Steinhardt
Director of Communications

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On the cover: Johan Holmberg and Vilma Rraklli of Ludwig Stockholm

TORCH CARRIER

Matthias Ernst was appointed scientific director of the Olivia Newton-John Cancer Research Institute (ONJCRI), the successor to Ludwig's Melbourne-Austin Branch. Matthias is a global authority on gastrointestinal cancer, the fourth most common cancer in the world and the second leading cause of death due to cancer. Matthias brings to this new position more than two decades of experience leading world-class researchers who have helped identify new treatments for colon and gastric cancers.

The new institute will build on the \$250 million Ludwig has already contributed to cancer research in Australia over the last 35 years. Matthias will oversee research programs covering such subjects as cancer and inflammation, tumor targeting, oncogenic transcription, cancer immunobiology, and translational genomics and epigenomics. "I could not be more enthusiastic about this new role and challenge," said Matthias. "I look forward to the opportunity to shape



Matthias Ernst
Ludwig Melbourne-WEHI

and lead the ONJCRI and help it grow into one of Australia's premier cancer research institutes."

The ONJCRI is affiliated with La Trobe University. The La Trobe School of Cancer Medicine has been established at the new institute with Matthias as its inaugural head. Together the institute and the university will undertake collaborative research, train medical researchers and translate research into clinical practice in the hope of improving outcomes for patients.

CAREER TRANSFORMER

Philip Pizzo, former dean of Stanford Medical School, is Ludwig's newest board member. He is currently the David and Susan Heckerman professor of pediatrics and of microbiology and immunology at Stanford University School of Medicine. He is also the founding director of the Stanford Distinguished Careers Institute, an innovative program that helps accomplished professionals in transition contribute to issues of local, national or global importance.



Philip Pizzo
Ludwig Board of Directors

People on the move

In a distinguished medical career spanning more than 40 years, Phil developed an enduring appreciation for how scientific research can help improve human life. “Becoming part of the Ludwig community is an exceptional honor for me,” said Phil. “I have seen many medical breakthroughs in cancer care. Ludwig has contributed a great deal to many of those improvements, and continues to do so today.”

Before joining Stanford, Phil was physician-in-chief of Children’s Hospital in Boston and chair of the Department

of Pediatrics at Harvard Medical School. He also served as the National Cancer Institute (NCI)’s chief of pediatric oncology and head of infectious disease, and as acting scientific director for NCI’s Division of Clinical Sciences. “Phil is a tireless champion of programs and policies to improve the future of science, education and health care,” said Ed McDermott, Ludwig’s president and CEO. “He brings tremendous clinical and research experience to Ludwig and we are fortunate to have him serving on our board.”

CROWDSORCERER

Former Ludwig patent administrator Mona Jhaveri has a new gig. She is the founder, executive director and chair of the board of Sound Affects Life, a nonprofit that hopes to use crowdfunding and the support of musicians to advance new strategies for treating cancer. It will pay particular attention to approaches stuck in the ‘valley of death,’ where, for want of funding, many good ideas falter before they can be translated into new therapies. The organization is dedicated to changing how the war on cancer is fought and financed.

Its mission is to help fill the cancer therapy pipeline by offering individuals the opportunity to directly support specific translational research projects. Sound Affects strategically partners with celebrity and amateur musicians to promote its cause. “I have always wanted to play a part in solving big problems in health care,” said Mona. “Advancing any drug through the development process will always take years of persistent effort, but I believe Sound Affects will make a real difference.”



Mona Jhaveri

THE ULTIMATE ICE BUCKET CHALLENGERS

Everybody took it. It was this summer's social media sensation. The ice bucket challenge raised awareness of amyotrophic lateral sclerosis (ALS), a progressive neuromuscular disease that is also known as Lou Gehrig's Disease. By mid-September it netted more than \$100 million in donations toward research. [Click here](#) to see Ludwig San Diego challengers, including Don Cleveland and Clotilde Lagier-Tourenne, taking the ice bucket challenge.

Don, team leader of the ice bucket challenge, won an Essey Award, the highest honor granted by the ALS Association's Golden West Chapter. The Essey is awarded annually to members of the ALS community to recognize outstanding efforts in research, philanthropy and public awareness that address the disorder. Don was one of a team of three scientists who collaborated over the past decade on using antisense oligonucleotides to treat ALS.

Antisense oligonucleotides are agents for gene silencing. Don and his colleagues have been developing such molecules to shut down the expression of mutant genes that contribute to ALS. "There's never been a more exciting time for therapy development in ALS," said Don. "We know the mutant genes involved in the inherited form of ALS and we have an idea of how to silence them. We're optimistic that we can change the course of this disease." [Click here](#) to see a newsreel of the 2014 Commitment to a Cure Essey Award winners.



Don Cleveland and Clotilde Lagier-Tourenne take the ice bucket challenge outside Ludwig San Diego.



Don Cleveland, second from left, at the 2014 Commitment to a Cure Essey awards.

THE OTHER ULTIMATE ICE BUCKET CHALLENGER

Clotilde Lagier-Tourenne is the recipient of the sixth International Medicine Paulo Gontijo Award for the most important advance made in ALS by a researcher under 40. The goal of this award is to foster and acknowledge research on ALS. It is sponsored by Brazil's Instituto Paulo Gontijo, which was founded by the physicist and engineer of the same name.

The award recognized Clotilde's research on the role of RNA processing in neurodegeneration, specifically

mutations in the genes for two RNA-binding proteins. The mutations appear to drive ALS by disrupting RNA processing, a step essential to the correct expression of proteins. "I am deeply honored to have been selected for this award," said Clotilde. She will present her research paper, "Identification of Molecular Mechanisms that Drive Neurodegeneration in ALS and Frontotemporal Dementia," during the opening ceremony of the 25th International Symposium on ALS/MND on December 5 in Brussels.

ENGINEER OF IMMUNE RESPONSES

Jedd Wolchok of Ludwig New York has been named one of OncLive's 2014 "Giants of Cancer Care." OncLive, which is the official website of *Oncology & Biotech News*, *OncologyLive* and several other industry publications, created the award program to recognize and celebrate individuals "whose work has helped save, prolong or improve the lives of patients with cancer." Jedd is one of 16 recipients nationwide. He was picked for his leading role in the development and application of checkpoint inhibitors, which are among a new generation of cancer therapies that unleash the immune system to attack tumors. He was particularly recognized for his contribution to the development of ipilimumab, an antibody that undermines immune checkpoints to induce a robust antitumor T cell response.

"Recognition from this esteemed panel of oncology peers is an incredible honor," said Jedd. "We've spent decades figuring out how cancer eludes the immune



Jedd Wolchok
Ludwig New York

response and are now making remarkable progress. With immunotherapy, we can simply treat the patient—and let the patient treat the cancer." [Click here](#) to hear Steven Rosenberg, chief of surgery at NCI, discuss Jedd's research and accomplishments.



Joan Brugge
Ludwig Harvard

IN ALL, AN ACHIEVER

Joan Brugge of Ludwig Harvard is one of this year's recipients of the Susan G. Komen Brinker Award for Scientific Distinction in Basic Science and Clinical Research, the highest award given by the world's leading breast cancer organization.

It recognizes Joan's contributions to our understanding of the cellular processes and pathways involved in normal development of breast cells, as well as the initiation and progression of breast cancer and its response to therapy. "This award is a tremendous honor for me and members of my laboratory," said Joan. "It is gratifying that our work is being recognized by peers in the breast cancer research community and I hope that we and others can build on our findings to make further advances in the treatment of breast cancer." Joan will deliver a keynote lecture on December 10 at the 37th Annual San Antonio Breast Cancer Symposium, a gathering of breast cancer researchers, clinicians and patient advocacy organizations from around the world.

SICcing BUGS ON TUMORS

Bacteria that thrive in a low-oxygen environment can be used to treat advanced tumors, according to a new study led by scientists from Ludwig Johns Hopkins. In a paper published online in *Science Translational Medicine*, the researchers report that injecting tumors in dogs with *Clostridium novyi*-NT, an engineered and less deadly cousin of the bacteria that causes botulism, shrank or completely eliminated a subset of very advanced tumors. They also tested the treatment in a human patient whose cancer was very advanced, injecting a minute fraction of the dose used in dogs into a single tumor. The treatment dramatically shrank that tumor in the patient, though the patient ultimately died from other metastases.

The bacteria used in the treatment, which find a welcoming low-oxygen environment in the heart of large tumors, destroy cancer cells while sparing normal, well oxygenated tissue surrounding the tumor. "It is not difficult to kill cancer cells," said Bert Vogelstein. "The challenge is killing them while sparing normal cells. I think this approach accomplishes that in principle and has the potential to awaken useful anticancer immune responses." The team plans to conduct an early-stage trial using this bacterium in which they will seek to establish the safety and optimal dosage of the strategy, among other things.

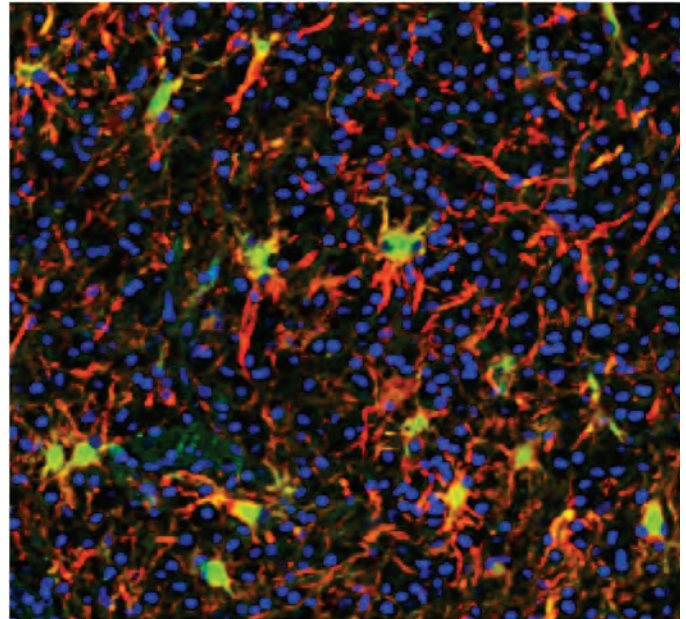


Bert Vogelstein
Ludwig Johns Hopkins

DOUSING THE FLAMES

Inflammation plays a pivotal role in the development of both cancer, which is marked by aberrant cell growth, and neurodegenerative diseases, which exhibit aberrant cell death. Led by Xin Lu, scientists from Ludwig Oxford have identified a mechanism by which these opposed outcomes are linked to the same process. In a [study](#) published in *Proceedings of the National Academy of Sciences USA*, they report that the tumor suppressor ASPP2 serves as a guard against the chronic inflammation that contributes to neurodegenerative disease. “One way that neurodegenerative diseases, such as Parkinson’s disease and Alzheimer’s disease, may be triggered is through the overactivation of inflammatory cells in the brain called astrocytes and microglia,” explained Casmir Turnquist, lead author of the study and recipient of the 2014 Nuffield Department of Medicine Graduate Prize for this work. “ASPP2 activation in response to infection triggers the p53-mediated cell-suicide pathway, thereby contributing to neurodegeneration.”

The researchers demonstrate that STAT1, a cell signaling molecule that is switched on by inflammatory signals, drives the production of ASPP2. “We already know that



Inflammatory astrocytes (red) in brain tissue expressing ASPP2 (green).

ASPP2 plays an important role in suppressing cancer,” said Xin. “Now we know that it also controls the cell’s response to infection and inflammation, and we have connected the dots linking these seemingly unrelated phenomena.”

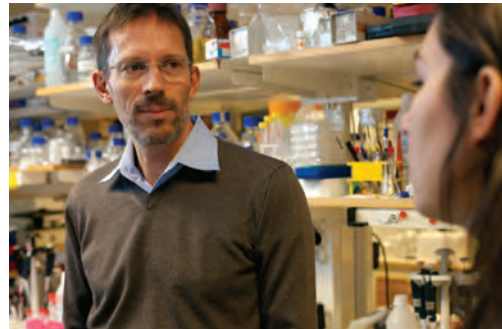
LOSING SOX

Dopamine is a chemical in the brain that affects emotions, movements and sensations of pleasure and pain. Destruction of dopamine neurons in the substantia nigra, the area of the brain that controls motor function, produces the symptoms of Parkinson’s disease, a chronic and progressive movement disorder. Midbrain

dopaminergic neurons are the main source of dopamine in the brain and are essential to cognitive and motor control. In a [study](#) published in *Cell Reports*, a team of Ludwig Stockholm scientists led by Thomas Perlmann report how distinct subtypes of these neurons are generated, including those affected in Parkinson’s disease.

News roundup

The researchers show that expression of Sox6, a transcription factor that plays a key role in the development of the central nervous system, is diminished in Parkinson's disease. They also find that Sox6 promotes development of dopamine neurons in the substantia nigra, which are hit particularly hard by the disorder. These findings could aid the development of stem cell therapies for Parkinson's disease.



Thomas
Perlmann
Ludwig
Stockholm

TARGETING A TUMOR'S SUPPORTERS

An international team of scientists led by Andrew Scott of Ludwig Melbourne has shown that an antibody against the protein EphA3, which is involved in human fetal development but is virtually undetectable in normal adult tissues, potentially targets a variety of solid tumors. The late Martin Lackmann, formerly of Ludwig Melbourne, also led the research. EphA3 is overexpressed in many such tumors. The researchers show that even if cancer cells themselves do not express this molecule, they can thrive through the support of EphA3-bearing cells in their microenvironment.

In a [study](#) published in *Cancer Research*, the researchers report that treatment with an antibody against EphA3, known as chIIIA4, in a mouse model significantly slowed tumor growth. In solid tumors, the team reports, chIIIA4 damaged incipient blood vessels and disrupted the stroma, which cancer cells need to survive.

A “Humaneered” form of the antibody is already being evaluated for blood cancers in clinical trials conducted with Ludwig licensee KaloBios Pharmaceuticals. “Our findings underscore the vital importance of the tumor microenvironment and suggest that antibodies against EphA3 may be effective against a variety of solid tumors as well,” said Andrew.



Andrew Scott
Ludwig Melbourne



Richard Hynes
Ludwig MIT

GROUNDWORK FOR METASTASIS

It's well known that the microenvironment of cancer cells plays an important role in metastasis, but it's less clear how this important niche is generated. In a [study](#) published in *Proceedings of the National Academy of Sciences USA*, a team led by Richard Hynes of Ludwig MIT reveals that platelets and granulocytes, which protect against bleeding and infection, respectively, are recruited to tumor cells to form early metastatic niches that promote a tumor's progression. The recruitment of granulocytes is not induced by tumor-cell-derived signals but by platelet-derived chemokines, signaling molecules that attract immune cells to places where they're needed.

Loss of platelets or granulocytes and prevention of granulocyte recruitment via inhibition of the CXCL5/7 receptor CXCR2 was found to impede metastasis, uncovering a key role for platelet-to-granulocyte signaling in the establishment of metastases. A therapy that prevents such interactions could help undermine metastasis.



Andy Wagner
Ludwig Harvard

BREAKING THE CYCLE

Disrupting the cell cycle is an appealing approach to stopping the uncontrolled growth that defines all cancers. In a [study](#) published in *Molecular Cancer Therapeutics*, researchers from Ludwig Harvard led by Andy Wagner explored how the inhibition of CDK4/6, an enzyme involved in the cell cycle, affects cell proliferation. Increased CDK 4/6 activity inactivates the tumor-suppressor protein retinoblastoma in many cancers, resulting in renewed cell proliferation.

The team found that LEE011, an oral drug candidate designed to inhibit CDK4/6 activity, significantly reduced the growth of well-differentiated and dedifferentiated liposarcomas, the most commonly diagnosed soft tissue tumors. Chemotherapy and other standard treatments have had limited efficacy in treating such fat cell malignancies. The researchers show that LEE011 has robust antitumor activity in mice. They also validate the role of CDK4 in uncontrolled growth of liposarcomas, an effect that derives from its ability to inactivate retinoblastoma. LEE011, a notably selective inhibitor of CDK4/6, is currently under study in clinical trials.

CHANGE AGENT

A team of Ludwig scientists including Ludwig Melbourne's Andreas Behren, Aparna Jayachandran and Jonathan Cebon published a [study](#) online in *Oncotarget* on the role of the protein thrombospondin-1 in epithelial-to-mesenchymal transition (EMT), a reversible process that plays a central role in metastasis. EMT transforms highly structured, sedentary cells into flexible, mobile agents of invasion. The researchers show that thrombospondin-1 is highly expressed and secreted by melanoma cells that have undergone EMT and are invasive and resistant to the drug vemurafenib. Silencing thrombospondin-1 *in vivo* and *in vitro* inhibits invasion of melanoma cells, suggesting that it may be a choice target for drugs to tackle metastasis and drug resistance in melanoma.



Jonathan Cebon
Ludwig Melbourne

KEEPING PEACEKEEPERS PEACEFUL

Different types of cells retain their unique characteristics and distinct functions as they divide, even when their identity can be altered by external signals. But not much is known about the molecular mechanisms by which cells stick to their lineages. In a [paper](#) published online in *Cell*, Alexander Rudensky of Ludwig MSK and his team examine how regulatory T cells (T_{reg} cells), which suppress immune responses and protect the body from fatal autoimmunity, retain their identity. These cells are defined by their expression of a transcription factor known as FoxP3.

The researchers show that an unexpressed stretch of DNA in the gene encoding FoxP3 maintains the identity of these cells as they divide. It does so, they find, by serving as a sensor for an immune factor



Alexander Rudensky
Ludwig New York

named interleukin-2 that promotes T_{reg} cell growth, and by counteracting inflammatory signals that lead to the loss of T_{reg} cell identity. Such loss can turn these peacekeepers into cellular assassins and contribute to chronic inflammation. The researchers suggest that this novel mechanism of identity maintenance may represent a general way in which cellular lineages are maintained.

UNLEASHING INNATE IMMUNITY

Ludwig and the Cancer Research Institute have entered into an agreement with VentiRx Pharmaceuticals to conduct a clinical trial with motolimod, the company's leading immune-oncology agent, by combining it with other immunotherapy agents available to Ludwig and the Cancer Research Institute through their industry partnerships. Motolimod is a novel Toll-like receptor 8 agonist that activates multiple components of the innate immune response, the immune system's first line of defense.

Previous studies have shown that when motolimod is given in combination with certain chemotherapies, it enhances immune responses within the tumor microenvironment. "Ludwig's mission is to conduct basic, applied and clinical research to support the swift development of game-changing cancer therapies, and motolimod holds considerable promise as a cancer drug, particularly as a component of combination immunotherapies," said Jonathan Skipper, Ludwig's executive director of technology development.



Jonathan Skipper

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Ludwig's mission is to conduct basic, applied and clinical research to support the swift development of game-changing cancer therapies...

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Did you know...

DID YOU KNOW...

You are not just a person.

You are an ecosystem – or, looked at another way, a giant vehicle for microbes. Within you, and nestled in every nook of your body surface, are numerous bacteria, fungi and viruses. The bacteria in our intestinal tract alone weigh about as much as a brain – three pounds— and we carry around with us about 100 trillion of them wherever we go.

They're not freeloaders, either. In fact, a good many species pay their rent by keeping us alive and in good health. They do so in countless ways – shaping everything from brain development to metabolism to immunity – and scientists are just beginning to work out exactly how they do this.

What most of us do know, however, is that many other bugs are not quite as benevolent. It falls on the immune system to figure out which ones are alien or out of control, how to respond and when to dial down that response. The cells and molecules of the innate immune system are on the front lines of that perpetual campaign. Innate immune cells survey the body for molecular patterns of suspicious intruders using specific receptors. When they detect such patterns, they initiate an attack and sound the alarm, recruiting the rest of the immune system to the fray. The inflammatory milieu in which all this unfolds is tightly regulated: Whereas brief inflammatory responses are essential to fending off a microbial invasion, chronic inflammation can promote disease, notably cancer.

That's where Mads Gyrd-Hansen and his team at Ludwig Oxford come in. His lab focuses on the innate signaling molecules that help orchestrate the inflammatory response and explores how loss of that control promotes cancer. A recipient of a fellowship from the Wellcome Trust and a grant from the Danish Research Council, Mads has recently been studying signaling by NOD receptors, which detect molecular patterns carried by bacteria that have snuck into cells and are likely to cause disease.

"Understanding how the immune response induces and controls inflammation is essential to understanding a wide variety of diseases and disorders," said Mads. "If we are to develop new drugs in the future to better treat human diseases, we need to understand the basic principles of how these processes work."



Mads Gyrd-Hansen
Ludwig Oxford

A patient's best friend

Why are clinical trials so important for cancer research?

Bottom line: The only way to find out if a new cancer treatment works is to test it in cancer patients through clinical trials. Clinical trials are the last component of a long drug research and development process that usually starts with discovery and involves extensive preclinical testing in cell culture and animal studies. All of the standard, recognized cancer treatments we have today are a result of this research and development process.

Here at Ludwig, we are primarily involved with phase 1 and early phase 2 clinical trials, which test a new drug or treatment first in a small group of cancer patients to initially evaluate safety and appropriate doses before going into larger trials to determine its actual efficacy. We also investigate a drug's mechanism of action or biomarker profile in such trials. Every trial we perform is the result of a discovery that investigators believe indicates a viable concept for a new treatment. Eventually, all cancer treatments must prove to be effective and have an acceptable safety profile in appropriately designed and conducted clinical trials with a larger number of patients before they can be made widely available to the general patient population.



Ralph Venhaus, Ludwig's chief medical officer and director of clinical trials management

Why are so few patients enrolled in clinical trials?

While the majority of children with cancer do participate in clinical trials, the participation rate of adults is still extremely low – only about 3% overall. Many clinical trials have to be closed owing to a lack of patients.

This is unfortunate but can be explained. There are a lot of barriers to patient recruitment. Probably the biggest hurdle is that most of the trials are concentrated in the big academic centers, but the majority of patients are treated outside these centers and often don't even know

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While the majority of children with cancer do participate in clinical trials, the participation rate of adults is extremely low.

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about clinical trials. Oftentimes, a patient's physician isn't aware of trials in their geographic area or they might not have the time to discuss the possibility of a trial with the patient. Patients and their doctors also worry that participation in a trial might be too great a burden for patients and their families. And there's even the issue of medical liability.

And patients themselves often don't want to be a test subject for an experiential treatment. They're afraid they might get a placebo and not receive any treatment at all, or that participation in a trial is a last ditch effort. However, when a placebo is indeed used, it's often given together with the best standard treatment available; this ensures that the patient receives an active treatment and allows us to compare standard treatment alone to standard treatment with the new treatment. The use of placebos without a standard treatment is only ethically acceptable in patients who would not receive any standard treatment at all – for example, during a period of time when a patient is closely monitored by their doctor, but no specific medical treatment is indicated until symptoms develop or change.

The elderly is another population that is underrepresented, as physicians are more apt to refer middle-aged or very young patients to a clinical trial. Elderly patients are more likely to have medical histories that make them ineligible to participate in a trial, as they often suffer from other physical ailments in addition to cancer.

All this results in too many trials chasing too few suitable patients in too few treatment locations. And you end up with a fairly large number of trials that can't be completed due to lack of enrollment.

These are major issues, but Ludwig is being proactive about them. In our trials, we take great care not to unreasonably restrict the enrollment criteria for patients. For example, we do not generally use age as an exclusion criterion, as long as the patient appears healthy enough to tolerate the treatment. We are also reaching out to smaller community hospitals and treatment centers, where the vast majority of patients receive their standard of care. It's a way for us to engage some of the 97% of patients who might otherwise not have access to a trial.

What do you think about trials that test multiple drugs?

These so-called 'basket studies' are a great idea because they allow you to efficiently match patients whose cancer has a specific target for treatment with drugs, irrespective of the type of cancer they have, thus accelerating the development of new targeted therapies. They also speed enrollment, allowing many screened patients to enter the study, which means the investigators will get answers faster on whether experimental drugs work. These studies give patients the best chance for treatment of a deadly disease because everyone gets some type of therapy. So instead of starting with multiple clinical trials, you start with one trial—the basket—

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In our trials, we take great care not to unreasonably restrict the enrollment criteria for patients. For example, we do not generally use age as an exclusion criterion, as long as the patient appears healthy enough to tolerate the treatment.

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in patients with different cancer types, allowing patients to enroll in cohorts or groups suited to their specific tumor indication.

Finding the right basket to put them in is done by genetic profiling, evaluation of biomarkers or other selection criteria. Having many drugs and treatment baskets available under the cover of a single study is an efficient way to keep overhead low, patient recruitment high, data collection and analysis efficient, and patients interested and focused.

What is most gratifying about your job?

The patients. We know that patients have benefited from the clinical trials we've been involved with. At the end of the day, it's gratifying to see something work, which allows patients to live longer and enjoy a reasonable quality of life.

It's heartening to hear stories like the one about the patient with stage 4 melanoma whose life expectancy was 10 to 15 months before the trial. This patient is still alive 10 years later. That's what it's all about.

Tell us a little about your work prior to joining Ludwig in 2002?

I was educated in Germany and received my bachelor's degree in chemistry from the University of Dortmund and my medical degree from the University of Heidelberg. During my five years in medical school, I had the advantage of working almost full-time as an emergency medical technician in hospital emergency rooms and intensive care units, which gave me



invaluable experience. After medical school, I specialized in anesthesiology and intensive care and became board certified. All together, I spent 10 years in emergency rooms, operating rooms and intensive care units. I loved the work, but after some 4,000-plus anesthesiological procedures in windowless rooms, I jumped at the opportunity to join ASTA Medica as a jet-setting clinical pain researcher learning how to do clinical trials. This is what brought my family and me to the United States in 1990, where I founded and directed the company's US medical affairs department. It was here that I first became involved in cancer trials, which eventually became more and more the focus of my work.

I'm an entrepreneur at heart, and my next move was to Coley Pharmaceutical Group in Wellesley, Massachusetts, a privately held biotechnology company that was later taken over by Pfizer.

I was the third employee and tasked with establishing and leading their worldwide clinical research operations. In my three-year stint at Coley, I was primarily involved in developing innovative products that stimulate the immune system via TLR-9.

I assembled a rather large team of 30 researchers and we completed over 10 studies in that time period. It was through our immunology work that I first met Lloyd Old and Eric Hoffman. In 2002, they asked me to join Ludwig as head of clinical affairs and oversee the expansion of its clinical research capabilities. Four years later, I assumed responsibility for regulatory affairs also, and in 2010 became director of clinical trials management and chief medical officer.

How did you become a motorcycle enthusiast?

As a small kid, I loved the BMW bikes the cops rode in postwar Germany – white with blue “Polizei” emblazoned on them. As a big kid in college, a ride down the Autobahn on the back of a friend's bike got me hooked, and I got my first one a few months after that ride. And it's still my favorite way to commute to the office!

Do you have any other secret hobbies or passions we should know about?

At home, in New Hampshire, I do all my

own landscaping and I am an expert in building retaining walls, so front loaders and backhoes are a big part of my weekends and vacations. I also do my own carpentry, plumbing and electrical work, which is good because I bought a piece of property in Virginia on a lake several years ago that I'm now developing. Nevertheless, despite my strong affiliation with construction work, I do intend to hold on to my day job.

How did you become an anesthesiologist?

I guess childhood experiences had a profound effect on me. The city I was born in – Hagen, in the Westphalia region – was in ruins after the war, and many of the buildings had been completely destroyed. My preschool was right across the street from the Catholic Marienhospital, and since there was no fence separating the school from the hospital, I would run over every time an ambulance would arrive with a patient. There were no emergency ramps, so patients had to be hand carried on stretchers up the stairs. I witnessed a lot during the three years I spent there. I distinctly remember one day when they brought in a patient who was in agonizing pain. He repeatedly cried out to the emergency technicians, “Please, give me anesthesia. Please, give me anesthesia.” More than anything, I wished I could do something for him. That must have stuck in my brain and I consider myself very lucky to have been able to live my dream and to pursue a profession that I'm still passionate about after all these years.

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At the end of the day, it's gratifying to see something work, which allows patients to live longer and enjoy a reasonable quality of life.

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What motivated you to pursue a career in science?



Simply put, it was my curiosity—how are we made and what are the invisible processes that keep our bodies alive? Also I owe much to my teachers and mentors, who have helped me stay focused and on the right track throughout my career.

MATOUS HRDINKA
Ludwig Oxford



I like challenges and clinical research brings me a new one on a daily basis. I wanted a career where my contributions would make a difference and pharmacovigilance is an exciting field that is continually evolving. It's an integral part of the drug development process, specifically providing critical oversight of a drug's safety.

GARY O'DONNELL
Ludwig Clinical Trials Management



Expanding ideas and considering the method to test a hypothesis is a fascinating process. When the idea is validated, accumulated failure is gone and it encourages me to proceed to the next step. Curiosity and getting excited by new findings have helped me overcome practical issues such as getting grants, so far.

KAORU KAHATA
Ludwig Uppsala

Required reading

Ludwig Brussels

Science 2014 August 21

Innate lymphoid cells regulate intestinal epithelial cell glycosylation

Goto Y, Obata T, Kunisawa J, Sato S, Ivanov II, Lamichhane A, Takeyama N, Kamioka M, Sakamoto M, Matsuki T, Setoyama H, Imaoka A, Uematsu S, Akira S, Domino SE, Kulig P, Becher B, Renauld J-C, Sasakawa C, Umesaki Y, Benno Y, Kiyono H.

Ludwig Chicago

Journal of Clinical Oncology 2014 August 4

[Epub ahead of print]

Learning while caring: medicine's epistemology

Hellman S.

Ludwig Harvard

Molecular Cancer Therapeutics 2014 Jul 15

[Epub ahead of print]

Antiproliferative effects of CDK4/6 inhibition in CDK4-amplified human liposarcoma *in vitro* and *in vivo*

Zhang YX, Sicinska E, Czaplinski JT, Remillard SP, Moss S, Wang Y, Brain C, Loo A, Snyder EL, Demetri GD, Kim S, Kung AL, Wagner AJ.

Ludwig Johns Hopkins

Science Translational Medicine 2014 Aug 13

Intratumoral injection of *Clostridium novyi*-NT spores induces antitumor responses

Roberts NJ, Zhang L, Janku F, Collins A, Bai RY, Staedtke V, Rusk AW, Tung D, Miller M, Roix J, Khanna KV, Murthy R, Benjamin RS, Helgason T, Szvalb AD, Bird

JE, Roy-Chowdhuri S, Zhang HH, Qiao Y, Karim B, McDaniel J, Elpiner A, Sahora A, Lachowicz J, Phillips B, Turner A, Klein MK, Post G, Diaz LA Jr, Riggins GJ, Papadopoulos N, Kinzler KW, Vogelstein B, Bettingowda C, Huso DL, Varterasian M, Saha S, Zhou S.

Ludwig Melbourne

Oncotarget 2014 Jul 30

Thrombospondin 1 promotes an aggressive phenotype through epithelial-to-mesenchymal transition in human melanoma

Jayachandran A, Anaka M, Prithviraj P, Hudson C, McKeown SJ, Lo PH, Vella LJ, Goding CR, Cebon J, Behren A.

Clinical Cancer Research 2014 July 29 [Epub ahead of print]

Molecular pathways: IL11 as a tumor-promoting cytokine-translational implications for cancers

Ernst M, Putoczki TL.

Cancer Research 2014 August 15

Targeting EphA3 inhibits cancer growth by disrupting the tumor stromal microenvironment

Vail ME, Murone C, Tan A, Hii L, Abebe D, Janes PW, Lee FT, Baer M, Palath V, Bebbington C, Yarranton G, Llerena C, Garic S, Abramson D, Cartwright G, Scott AM, Lackmann M.

Ludwig MIT

Proceedings of the National Academy of Sciences USA 2014 July 29

Platelets guide the formation of early metastatic niches

Labelle M, Begum S, Hynes RO.

BMC Cancer 2014 July 18

Extracellular matrix signatures of human primary metastatic colon cancers and their metastases to liver

Naba A, Clauser KR, Whittaker CA, Carr SA, Tanabe KK, Hynes RO.

Ludwig New York

Cell 2014 August 14

Control of the inheritance of regulatory T cell identity by a cis element in the Foxp3 locus

Feng Y, Arvey A, Chinen T, van der Veen J, Gasteiger G, Rudensky AY.

Ludwig Oxford

Proceedings of the National Academy of Sciences USA 2014 July 8

STAT1-induced ASPP2 transcription identifies a link between neuroinflammation, cell polarity, and tumor suppression

Turnquist C, Wang Y, Severson DT, Zhong S, Sun B, Ma J, Constaninescu SN, Ansoorge O, Stolp HB, Molnár Z, Szele FG, Lu X.

Ludwig San Diego

Cancer Discovery 2014 August 4

Greater than the sum of its parts: single-nucleus sequencing identifies convergent evolution of independent EGFR mutants in GBM

Gini B, Mischel PS.

Trends in Endocrinology and Metabolism 2014 July 25

mTORC2 in the center of cancer metabolic reprogramming

Masui K, Cavenee WK, Mischel PS.

Clinical Cancer Research 2014 September 15
[Epub ahead of print]

Tumor suppressive miR-148a is silenced by CpG island hypermethylation in IDH1 mutant gliomas

Li S, Chowdhury R, Liu F, Chou AP, Li T, Mody RR, Lou JJ, Chen W, Reiss JK, Soto H, Prins RM, Liao LM, Mischel PS, Nghiemphu PL, Yong WH, Cloughesy TF, Lai A.

Ludwig Stockholm

Cell Reports 2014 August 21

Sox6 and Otx2 control the specification of substantia nigra and ventral tegmental area dopamine neurons

Panman L, Papathanou M, Laguna A, Oosterveen T, Volakakis N, Acampora D, Kurtsdotter I, Yoshitake T, Kehr J, Joodmardi E, Muhr J, Simeone A, Ericson J, Perlmann T.

Ludwig Uppsala

PLoS One 2014 August 18

Fine-tuning of Smad protein function by poly(ADP-ribose) polymerases and poly(ADP-ribose) glycohydrolase during transforming growth factor β signaling

Dahl M, Maturi V, Lönn P, Papoutsoglou P, Zieba A, Vanlandewijck M, van der Heide LP, Watanabe Y, Söderberg O, Hottiger MO, Heldin CH, Moustakas A.

