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JULY 2014

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LUDWIG CANCER RESEARCH

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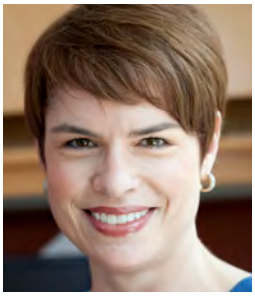
LETTER



Antoine-Augustin Parmentier got one in 1773 for identifying a vegetable that could ease famines, and popularized the potato in France. About a century and a half later, Charles Lindbergh got one for flying from New York to Paris, and revolutionized the business of aviation. More recently, the X Prize Foundation used one to kick off a commercial space race.

A prize is what each of them got. Prizes inspire human achievement at least as much as they celebrate it. And they give the rest of us an opportunity to tip our collective hats to the intrepid, the inspired and the awe-inspiring.

In this issue you'll read about 13 Ludwig scientists who dared to ask big questions. Each of the awards won by our researchers this year recognizes significant contributions to cancer research or therapy. Taken together, they serve as testament to the high caliber of Ludwig research and the dedication of its scientists.

We also asked three young Ludwig researchers from around the world how prizes impact science. See their answers on page 13. And, as always, we set aside a few pages to cover the latest discoveries made by Ludwig researchers who, it would appear, are on their way to more prizes.

Happy reading!

Sincerely,
Rachel Steinhardt
Director of Communications

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On the cover: Xxxxxxx of Ludwig Brussels

CANCER'S WORST ENEMY

Ludwig San Diego's Web Cavenee received the eighth American Association for Cancer Research (AACR) Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research. The award, which he received at the AACR meeting in April, recognizes a true champion of cancer research whose leadership has had a major impact on the field.

Web certainly fits that bill. Though he has made many seminal discoveries, he is perhaps best known for publishing the first direct genetic evidence for the existence of genes that suppress cancer. In giving Web the award, the AACR commended him for his pioneering work in cancer genetics, his leadership in the global fight against one of the most aggressive and intractable cancers, glioblastoma multiforme, and his more than 25 years of service to the organization.

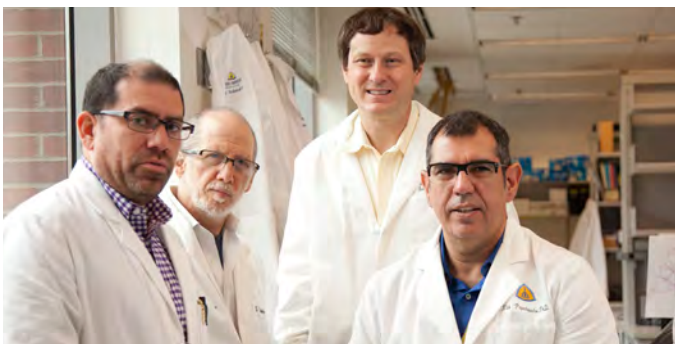
"I am delighted and honored to have been chosen to receive the Margaret Foti Award," said Web. "This is especially gratifying given the stellar group of previous awardees and the many accomplishments of the award's namesake."

Web Cavenee
Ludwig San Diego

TURBOCHARGED TEAM

Ludwig scientists Bert Vogelstein, Ken Kinzler, Victor Velculescu, Luis Diaz and Nick Papadopoulous, members of a research team focusing on malignant brain tumors, received the AACR 2014 Team Science Award, which recognizes an outstanding interdisciplinary research team for its innovative science. They were honored for their groundbreaking work toward the development of new brain tumor diagnostics and treatment, and the translation of discoveries into clinical applications.

Working with researchers from Duke University and the US National Institutes of Health, they were the first to describe the genomes of glioblastoma multiforme, the deadliest type of adult brain cancer. Their work in glioblastoma multiforme has had a huge influence on the race to develop new therapies for this cancer.



Ludwig Johns Hopkins team. Luis Diaz, Bert Vogelstein, Ken Kinzler, Nickolas Papadopoulos, Victor Velculescu (not pictured)

INSPIRED IMMUNOTHERAPIST

Jedd Wolchok of Ludwig MSK received the 2014 Richard and Hinda Rosenthal Memorial Award from the AACR for his groundbreaking contributions to immunotherapy for melanoma. The Rosenthal Award recognizes researchers whose discoveries have notably improved the clinical care of cancer. Jedd's research in immunotherapy and continuing contributions to the field could help turn many currently lethal cancers into largely curable or manageable diseases.

Jedd has also led efforts to establish appropriate standards for evaluating novel immunotherapies in clinical studies. New criteria for evaluating such responses, initially published by Jedd and colleagues in what the AACR describes as a "landmark paper" in *Clinical Cancer Research*, have now become an additional focus for end points in the field's clinical trials. Jedd is the first Ludwig member to be selected for this honor. He received the award during the 38th AACR Annual Meeting in San Diego, where he delivered an award lecture entitled "Realizing the Potential of Cancer Immunotherapy."

Jedd Wolchok
Ludwig MSK

A NEW CHIEF

José Baselga has been elected President of the AACR and will serve for one year beginning in 2015. Physician-in-chief at Memorial Sloan Kettering Cancer Center and a member of Ludwig's Scientific Advisory Committee, José is a distinguished oncologist and cancer researcher who has brought several transformative breast cancer therapies to the clinic.

He has been actively involved with the AACR for more than 20 years and is the founding editor-in-chief of the organization's scientific journal *Cancer Discovery*. He will work with the AACR board of directors and more than 34,000 members in some 90 countries to further the association's goal of defeating all cancers.

"I am deeply honored to serve as president-elect of the AACR," said José. "Together with the AACR community, I will push forward on multiple fronts, including regulatory science and policy, integration of basic and clinical research, and access to clinical trials for our patient population, with the clear mission of advancing progress in the prevention and treatment of cancer."

José Baselga
Ludwig Scientific Advisory Committee

NONPAREIL CLASS

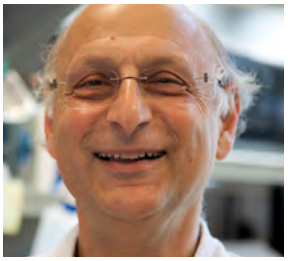
The AACR inducted five renowned Ludwig scientists into the 2014 class of fellows of the AACR Academy at their annual meeting in April: Joan Brugge, Richard Hynes, Ken Kinzler, Richard Kolodner and Irv Weissman.

"It is a great honor to have five Ludwig scientists selected for the class of 2014," said David Lane, Ludwig's scientific director. "Their induction into the academy is testament to the depth of their commitment to science and the profound impact their work has had on cancer research. This is a well-deserved acknowledgment of all they have accomplished as scientific leaders and distinguished researchers in their respective fields. On behalf of the Ludwig community, I extend to each of them our congratulations."

Joan Brugge
Ludwig Harvard

Richard Hynes
Ludwig MIT

Ken Kinzler
Ludwig Johns Hopkins



Richard Kolodner
Ludwig San Diego

Irv Weissman
Ludwig Stanford

OMNE TRIUM PERFECTUM

According to Wikipedia (which, as everybody knows, is always right) the Latin phrase above means "everything that comes in threes is perfect." Alternatively (per Wikipedia), it can be taken to mean "every set of three is complete."

Take your pick. We simply wish to report that the third of a perfectly complete set of meetings, held on April 4 in La Jolla, California, brought together Ludwig leadership worldwide to continue discussing the big issues, and to begin to answer four key questions: What do we do best? How can we make the biggest difference? How can we work together most efficiently? And what frustrates us and holds us back?

The first meeting, held at Ludwig Stanford in 2012, focused on a single, critically important area of Ludwig research—stem cells. Ludwig leaders discussed how each of the network's laboratories might complement the efforts of the others, and identified several promising clinical trial concepts for further consideration. Next, the Oxford retreat, held in September 2013, introduced a broader group to the breadth and scope of Ludwig science and how the network is designed to facilitate scientific progress in both basic and clinical research. "People came away with what was really happening scientifically at each of the components that make up Ludwig Cancer Research and where there might be synergistic opportunities," said Bob Strausberg, head of collaborative sciences.

Major scientific areas that present new opportunities for Ludwig dominated the third meeting. The discussions in La Jolla centered on areas of high priority for developing international teams and the most effective ways the teams might work together toward common goals. "It was more about where there is a broad interest within

Bob Strausberg

> "These meetings have served a very interesting and useful purpose in creating the dialogue for interaction between and among the branches and centers of Ludwig Cancer Research. The power of this group is extraordinary and exploring ways to accomplish things together is resulting in new approaches to big issues of common interest."

Web Cavenee
Ludwig San Diego

the Ludwig community and where we have real interest in building initiatives," said Bob. "Our next steps will focus on how to bring specific ideas to fruition and how Ludwig can really make them happen."

The three meetings might have been perfect, but for Ludwig scientists they were not complete. We will host future meetings to explore opportunities to improve cancer patient outcomes through innovative research approaches, foster new collaborations, and determine how we can achieve transformative advances that will ultimately decrease cancer deaths.

Omne trium perfectum, we say.

> "The Ludwig meetings have been absolutely unique to me in terms of spawning collaborations and new visions. I attribute much of this to the shared Ludwig goal of having a real-world impact on the disease as a priority."

Ken Kinzler
Ludwig Johns Hopkins

REAL HOPE FOR REAL CHANGE

Ludwig researchers Web Cavenee and Frank Furnari have uncovered a mechanism that drives the growth of an aggressive brain cancer. Published March 1 in *Cancer Research*, the study reveals how a mutated epidermal growth factor receptor named EGFRvIII suppresses a regulator of gene expression, microRNA-9, to jump-start tumor cell proliferation. This occurs because the suppression of microRNA-9 boosts the production of a transcription factor known as FOXP1.

Although FOXP1 is necessary for the proper development of the brain and lung in mammals, the researchers found that elevated expression of FOXP1 in glioblastoma tumors is associated with poor patient survival. They are now working to identify which genes are affected by the enhanced expression of FOXP1, and anticipate that this will yield new drug targets for the treatment of glioblastoma.

Frank Furnari
Ludwig San Diego

OF BIRDS AND MEN

Infecting one tumor with the Newcastle disease virus (NDV), which sickens birds but not people, could boost the effectiveness of cancer immunotherapy, according to research conducted by Ludwig MSK researchers Dmitriy Zamarin and Jedd Wolchok and their colleagues. NDV is being studied as an antitumor agent because it preferentially infects human cancer cells, and kills them pretty effectively. The study, conducted in mice and published March 5 in *Science Translational Medicine*, suggests that administration of an immune checkpoint blockade antibody in combination with this "oncolytic virotherapy" might dramatically enhance antitumor immune responses in patients with a variety of cancers.

NDV was injected directly into one of two melanoma tumors implanted in mice, followed by an anti-CTLA-4 antibody, which releases a brake on the immune system. The combination triggered a potent antitumor response that also led to the destruction of the uninfected tumor. This is notable because oncolytic virotherapy has long been hindered by the immune system's tendency to disable systemically introduced viruses well before they can target tumors. The current study circumvented this problem by injecting NDV directly into the tumor.

The inflammatory immune response induced by viral infection of the tumor, which also exposed cancer antigens to the immune system, was then boosted by checkpoint blockade. As a consequence, even tumors that are typically resistant to immunotherapeutic treatment succumbed to this combined therapy in the mouse model.

Dmitriy Zamarin
Ludwig MSK

Jedd Wolchok
Ludwig MSK

DEVELOPMENTAL DISORDERS

Ludwig Melbourne researcher Joan Heath and colleagues have demonstrated that defects in a process known as minor-class splicing produce severe abnormalities during development. In a study published on February 25 in *Proceedings of the National Academy of Sciences*, they show that the *Rnpc3* gene is required for the rapid growth of organs, including the intestine, liver, pancreas and eye, during zebrafish development. *Rnpc3* regulates protein production through a process called minor-class messenger RNA splicing. Most eukaryotic genomes contain a fraction of minor-class introns with unique sequence elements that are eliminated by their own splicing machinery.

Though the significance of minor-class splicing has eluded researchers for more than 20 years, it was recently linked

to a severe human developmental disorder known as Taybi-Linder syndrome. Joan and her team identified a novel zebrafish mutant with defective minor-class splicing and demonstrated how this pathway shapes the full spectrum of genes expressed during development, explaining its wide-ranging effects. “In the long run, we anticipate that our research will show that minor-class splicing contributes to other diseases that are not fully understood,” said Joan.

Joan Heath
Ludwig Melbourne-WEHI

CLAIRVOYANT

A team of researchers led by Stephen Hodi of Ludwig Harvard and Jianda Yuan and Jedd Wolchok from Ludwig MSK investigated 176 advanced melanoma patients treated with the checkpoint inhibitor antibody ipilimumab at MSK and Dana-Farber/Harvard Cancer Center. They discovered that among patients with late-stage melanoma, those who had relatively higher levels of the protein vascular endothelial growth factor (VEGF) in the blood before treatment with ipilimumab had poorer responses to treatment and lower survival. VEGF’s normal function is to create new blood vessels, and tumors often use the factor to grow and metastasize. The findings were reported in the February 4 online issue of *Cancer Immunology Research*.

The researchers found that 41% of patients with relatively low levels of VEGF before the onset of therapy experienced clinical benefit (including stable disease and partial or complete responses) at 24 weeks after starting the ipilimumab treatment, whereas only 23% of the patients with relatively high levels of VEGF experienced any clinical benefit at that point. Whereas pretreatment VEGF levels had the potential to predict treatment outcomes, changes in VEGF levels during treatment were not linked to treatment outcomes.

Stephen Hodi
Ludwig Harvard

Jianda Yuan
Ludwig MSK

Jedd Wolchok
Ludwig MSK

MAKING HEADWAY

There's new hope for two of the most common cancers worldwide: stomach and bowel cancer. In the February issue of *Molecular Cancer Therapeutics*, Ludwig Melbourne researchers Matthias Ernst, Tracy Putoczki and colleagues show that Janus kinase (JAK) inhibitors could help treat these cancers with fewer side effects. The drugs, which inhibit proteins known as JAKs, reduced the growth of stomach and bowel cancers in preclinical studies.

More than 1.7 million people worldwide are diagnosed with these two cancers each year. "This is particularly exciting because clinical trials have already shown that JAK proteins can be safely and successfully inhibited in patients," said Matthias. "We hope this will expedite possible clinical trials and improve the outlook for people with stomach and bowel cancer." JAK inhibitors are already on the market for the treatment of blood disorders and rheumatoid arthritis, and are being investigated in trials for the treatment of other conditions.

Matthias Ernst
Ludwig Melbourne-WEHI

Tracy Putoczki
Ludwig Melbourne-WEHI

DNA DETECTIVES

Ludwig researchers at Stanford led by Maximilian Diehn and Ash Alizadeh have developed a blood test that not only detects the presence of cancer but also can monitor how a patient's cancer responds to various treatments. Dubbed CAPP-seq, for cancer personalized profiling by deep sequencing, the new test can detect tiny amounts of DNA and scan large parts of it to look for mutations that come from tumors. The super-sensitive DNA test can, with greater accuracy than ever before, detect whether there is tumor left in a patient.

This experimental test is specific for lung cancer. The findings, published April 6 in *Nature Medicine*, indicate that tumor DNA could be detected in every patient studied who had lung cancer of stage 2 or higher, and about half the time in patients with stage 1 lung cancer. The researchers are working to improve the lung-cancer test and developing tests for other types of cancer—such as breast cancer, lymphomas, esophageal cancer and pancreatic cancer.

Maximilian Diehn
Ludwig Stanford

Ash Alizadeh
Ludwig Stanford

BREAK REPAIR

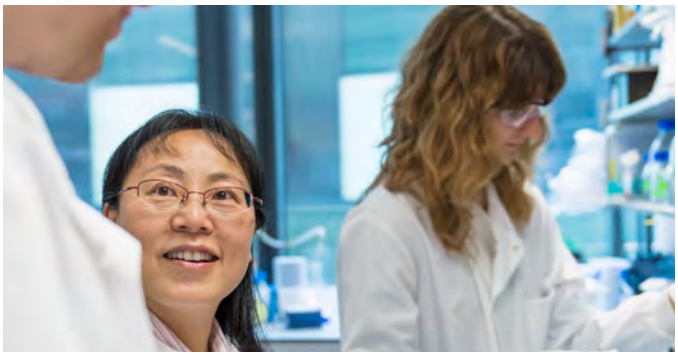
Mistakes cells make while repairing DNA damage can give rise to cancer. Furthermore, many cancer treatments severely damage DNA. So DNA damage repair is a critical component of both carcinogenesis and responses to cancer treatment. In the March 26 issue of *Science Translational Medicine*, Ludwig Chicago researcher Ralph Weichselbaum and colleagues share a method to quantify the efficiency of DNA repair pathways in the context of cancer therapy. They have created a recombinant proficiency score, or RPS, which is based on the expression levels of four genes. They validate the RPS in patients with breast and lung cancers and show that tumors with low RPS are associated with inferior patient survival rates but better responses to chemotherapy. The RPS may help oncologists select which therapies will be effective for individual patients, enabling more personalized care.

> “The RPS may help oncologists select which therapies will be effective for individual patients, enabling more personalized care.”

Ralph Weichselbaum
Ludwig Chicago

THE NUCLEAR OPTION

Every protein needs to get to the right place inside a cell to do its work. Many of the larger proteins imported into the nucleus gain entry through an active transport system that detects a sequence—a molecular bar code of sorts—on such proteins known as the canonical nuclear localization signal. This pathway has been very well characterized. But not all of the proteins that are actively imported through the nuclear envelope carry a nuclear localization signal, and researchers have long wondered how these get inside.



Xin Lu
Ludwig Oxford

Now a team of Ludwig Oxford researchers led by Xin Lu has identified a new pathway by which proteins can be actively shuttled into the nucleus, and named it the RaDAR pathway. This pathway recognizes a specific signal borne by dozens of proteins encoded by the genome. In detecting the novel signal and pathway, the team also explains why a mutant protein accumulates aberrantly in the nucleus of cells in familial melanomas: the mutation, it turns out, confers a signal to the protein so the RaDAR pathway can detect it and shuttle it into the nucleus. The discovery, published on May 22 in *Cell*, could help shed light on molecular dysfunction in several ailments and help scientists better understand the roles many poorly characterized proteins play in cellular life and human health.

A WINNING COMBINATION

Checkpoint inhibitor therapy is a high point in the history of cancer immunotherapy. And Ludwig has been one of its champions and innovators. Over the last few years, in collaboration with 4-Antibody, Ludwig has developed several monoclonal antibody checkpoint modulators (CPMs), which boost the ability of immune cells to target cancer and other diseases by helping a patient's own immune system fight cancer. "Combining Ludwig's expertise in immuno-oncology translational research with the technology developed by 4-Antibody has allowed us to create viable CPM antibodies directed against key checkpoint targets," said Jonathan Skipper, head of technology development.

Jonathan Skipper

With the recent acquisition of 4-Antibody by Agenus, three CPMs developed by Ludwig and 4-Antibody will advance into preclinical development—two antibodies that bind and activate the protein GITR, which boosts T cell responses to cancerous and infected cells; and a CTLA-4 monoclonal antibody that unlocks a braking mechanism the body imposes on the immune system. Working together, the organizations plan to advance the portfolio of CPMs as single agents and in combinations. Programs are also underway for the discovery and development of other CPM antibodies, including OX40 agonists and LAG-3, TIM-3 and PD-1 antagonists.

Are prizes good for science?

Scientific discoveries should be recognized and celebrated. Prizes increase public awareness, portray scientists as heroes and highlight science as a career path. For the recipients, prizes may also provide money for 'no strings attached' research, allowing the pursuit of risky and cutting-edge ideas in an increasingly challenging funding climate.

AARON NEWMAN
Ludwig Stanford

From departmental-level awards right up to a Nobel Prize, any opportunity to have your research formally recognized and rewarded is valuable. The $3 million Breakthrough Prizes inaugurated by Silicon Valley's elite aim to "celebrate scientists as heroes," which is gratifying for those who give so much of themselves to science as a career.

KATHERINE WOODS
Ludwig Melbourne

In general, yes. Prizes do have the potential to be controversial. However, they serve as recognition of the work and achievements of a scientist or group of scientists. Science prizes can also help increase public awareness of the work that is being recognized.

NICHOLAS ROBERTS
Ludwig Johns Hopkins

The ideal doctor

How did you become interested in medical research?
I've always had an interest in science and, particularly, medicine. Growing up on a farm, I was able to observe the entire circle of life. My mother was a nurse, and through conversations with her as a youngster I had exposure to hospitals and what happens in them. One of the things that always impressed me was the way my mother spoke about doctors and the respect she had for them. But the most important reason was and continues to be my passion to help people and prevent needless suffering.

How important were the places you trained as a young scientist?
It's not the places but the people you train with that are most important. The people I worked with not only inspired me and showed me how to do the research basics, including planning projects and writing grants and papers, but also encouraged me along my scientific journey. They gave me invaluable guidance when times were difficult and helped me work out where I wanted to go and to identify what I wanted to do in the future.

Can you give an example?
Bill Robinson was a visiting professor from Denver whose interest in melanoma sparked my initial interest in that disease. He was an inspirational person and had a passion for research that I carry with me to this day. Bill was also a true mentor and a wise counselor. I learned a lot just by observing him and how he interacted with people.

Peter Gibbs
Ludwig Melbourne-WEHI

You pioneered a cancer treatment called SIRT, which was hailed a global lifesaver. Can you explain what it is and why it was so effective?
SIRT is an interesting therapy. It was originally developed in Melbourne, Australia, and I got involved with it early on. It's a one-off treatment where tiny radioactive beads, about one-third the width of a human hair, are injected directly into the liver via a catheter inserted into an artery near the groin. The beads lodge in the liver and release a radiation dose over a number of days to shrink the

> "Bottom line, it's not the places but the people you train with that are most important."

tumors. The effect is confined to the liver so adjoining tissues are not damaged. It's a local form of radiation treatment that can be safely combined with chemotherapy, and the two together are potentially quite a powerful combination. We're finishing up an international phase 3 clinical trial and the results will be reported mid next year. This study is particularly relevant to the hundreds of thousands of people worldwide who develop liver metastases each year, who need treatments that more effectively target these liver tumors.

Can you tell us a little bit about your collaboration with Ludwig Johns Hopkins and the impact your joint efforts have had on cancer detection and prevention?
It's a terrific collaboration and the most exciting thing I'm doing at the moment. The development of noninvasive methods to detect and monitor tumors continues to be a major challenge in oncology, and together we're exploring the utility of circulating tumor DNA as noninvasive cancer biomarkers for colorectal cancer screening and treatment. This has great potential as a more effective and patient-friendly method for the detection, monitoring and treatment of colorectal cancer, and indeed most types of cancer. Together it's a great partnership, which I believe is going to start having a big impact on patients in the near future.

This all began when I was visiting Baltimore in 2010, when Bert presented his initial data around circulating DNA in patients undergoing liver resection. I felt it showed enormous promise for helping people with colorectal cancer from early-stage right through to end-stage disease. That stimulated the initial conversation, and collaboration was a natural next step. We started with one protocol, generously supported by Ludwig, and have been able to leverage that initial investment with funding from a wide range of sources, such that we now have seven colorectal studies up and running, covering the spectrum from screening right through to optimizing care of people with advanced cancer. We've also begun work in pancreatic cancer. For each of the studies in Melbourne, we're collecting the data and the samples and sending them over to Bert's lab for analysis; then we work together to understand the results. They have been fantastic collaborators.

Besides the time difference, what are the challenges in collaborating with other Ludwig researchers?
The biggest challenge is the distance. Teleconferencing and videoconferencing are viable options, but it would be great to be able to meet more frequently, particularly face-to-face, and spend more time together looking at the data. But our trips to the US are frequent enough and the work continues to move forward, with lots of e-mails back and forth.

How soon before blood tests become routine and we are able to detect early signs cancer?
That's a very difficult question to answer. The initial data we have are very promising

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The development of noninvasive methods to detect and monitor tumors continues to be a major challenge in oncology, and together we're exploring the utility of circulating tumor DNA as noninvasive cancer biomarkers for colorectal cancer screening and treatment.
”

and I would expect in the next five years that measuring circulating DNA will become a standard part of managing patients with early-stage through late-stage colorectal cancer. Most exciting for me is the possibility, within the next ten years, that patients will be given a routine blood test to screen for cancer as part of their annual physical. It would be a real breakthrough because the data so far indicate that if a doctor can detect an abnormality in the bloodstream it means there's a very high chance of that person having an early cancer hiding somewhere. It's a safe, noninvasive and very promising initial screen to detect cancer in someone who wouldn't otherwise have any symptoms. A blood-based test could be transformative in how we screen patients for colorectal cancer and potentially many other cancer types where early diagnosis is critical; it would save lives and result in major savings of health care dollars.

How effective is screening for colorectal cancer?

Very, with recent data indicating that the rate of colorectal cancer in the US has declined 30% on the basis of screening. Colonoscopies are the 'gold standard' for colorectal cancer screening. They can detect the disease at an early stage when it's most curable—and even prevent it by finding polyps before they become cancerous. In the US, uptake of screening is pretty good: Roughly more than half of all Americans older than 50 are getting screened. In Australia it's terrible, with

only 5% or 10% of the eligible population being screened. There are lots of factors at play, but I think patients often resist or delay having colonoscopies because of the preparation, discomfort or fear of pain. Or maybe it's just the yuck factor.

How important is the 'celebrity factor' in increasing awareness of screening?

In the US, screening jumped dramatically when Katie Couric had a colonoscopy on air on the "Today" show in 2002. So the celebrity factor is definitely a big driver in promoting awareness of a disease. In Australia there aren't any celebrities who've come out and said they've had colorectal cancer. Entertainers like Olivia Newton-John and Kylie Minogue had breast cancer and were very open about coming forward and promoting

> "A blood-based test could be transformative in how we screen patients for colorectal cancer and potentially many other cancer types where early diagnosis is critical ..."

mammograms and screenings, which stimulated interest in these preventive measures. But the few celebrities I've come across with colorectal cancer are very reluctant to mention it in public, and the media report it as abdominal or stomach cancer—never bowel cancer.

Colorectal cancer incidence rates have declined, but why haven't survival rates?
In the US the number of colorectal cancer deaths is declining, which is great news, but elsewhere in the world it's actually increasing. And in parts of Asia it's increasing dramatically. In places where it used to be number five or six in terms of cancer incidence, it's now number one. These countries have adopted some of the bad bits of the West—sedentary lifestyle, poor food choices, smoking—and it's showing up as a spike for colorectal cancer more than any other tumor type. To make matters worse, many of these countries don't have any screening programs, so many patients are being diagnosed very late.

In difficult times, what motivated you to continue with your research?
The number one driver is the potential impact on patients. That's something I've always been very focused on. Through the work we're doing with circulating tumor DNA and screening, we can make a huge difference by diagnosing cancers earlier and stopping people from dying of cancer rather than focusing on keeping someone with advanced cancer alive a little bit longer. Some of the work we're doing is getting to the point of presentation and publication, and I think it was quite exciting at the American Society of Clinical Oncology meeting this year when the stage 2 circulating tumor DNA data was presented for the first time.

How do you balance your commitments to work and family?
Conflicts are ongoing because the work you're doing is never finished. There're always things that need to get done. Deadlines never disappear. You get past one and then another one comes up. You always have this false sense that maybe you'll get past this crisis or this hurdle and free time will open up, but inevitably it doesn't. You have to plan and make time for the things that are important—especially family—as you go along and not just wait for opportunities to come up.

What would you like to accomplish in the future?
Early diagnosis and treatment are crucial in fighting cancer. Once cancers show clinical symptoms, it's often too late. The earlier we get them, the better the chances of recovery. Current screening methods can detect cancers at a very early stage and save thousands of lives each year. They can be the difference between life and death, particularly with bowel cancer. I'd like to develop a new screening test to detect cancer with a far greater impact. That really would be a major breakthrough in cancer diagnostics.

“Through the work we're doing with circulating tumor DNA and screening, we can make a huge difference by diagnosing cancers earlier and stopping people from dying of cancer …”

You're the lead investigator on the ASPREE study. Can you explain what this is and what you expect it to accomplish?
Aspirin in Reducing Events in the Elderly (ASPREE) is a five-year international randomized clinical trial designed to determine whether the benefits of aspirin outweigh the risks in healthy people aged 70 and older. Early data suggest that aspirin can markedly reduce the risk of many cancers, including colorectal cancer, by 30 to 40%. There are lots of other reasons to take aspirin: it can reduce the risk of heart attack, stroke, dementia and other diseases of aging. But the big question has always been what's the risk-benefit ratio, as aspirin can cause bleeding in the stomach as well as bleeding in the brain, which can cause a stroke. Initial results of the study will be available in 2018, and I'm hoping we can definitively see a reduction in the risk of colorectal cancer and multiple cancers as well, potentially opening up aspirin as a routine preventive medication.

If aspirin is really a wonder drug, shouldn't we all be taking it every day to ward off potential illnesses?
You have to remember that aspirin is a drug and with any drug there are side effects. In recent years, there've been a number of studies showing that over the long term it can reduce the risk of cancer, but the mechanisms by which it does this are still unclear. We know inflammation plays an underlying role in cancer development and aspirin helps reduce inflammation. Other research has

shown that aspirin's ability to reduce blood clotting could play a role in its cancer-fighting abilities. I think many of these questions will be answered in the next decade or so as the results of multiple ongoing clinical trials become available.

Who or what would inspire you if you were 21 again?
People. People who've achieved great things. People who've done it in a way that I admire. People who've been collaborative. People who've shared and worked as a team. They're the ones who inspire me much more than individuals who've done it by themselves. People who work in areas that many others think don't show much promise for success, but with persistence and ongoing self-belief, over time they achieve great things and have a fantastic story to share. That's inspirational. It's those stories of success and the impact of those research stories that motivate and inspire the younger generation to take a bold path and start something new and potentially turn it into something that makes a difference.

As you get older, one of the sadder things is that there aren't as many people above you to inspire and guide you, to offer you help and advice. You're increasingly on your own. Tony Burgess, someone I greatly respect and admire, is still a source of wise counsel, and it's very helpful to have people like him around to act as a sounding board to bounce ideas off. It's essential to have those types of people around you to mentor you, even if they don't have an in-depth understanding of the issues. Being able to seek their advice and help at times when you're not quite sure what to do is invaluable.

Is there anything else that you'd like to share?

Ludwig's support and connections have given me the freedom to pursue unique opportunities and conduct my research without deadlines or the need for immediate results. Many of my colleagues don't have this luxury. Unlike industry and other organizations, Ludwig isn't looking for short-term gains: they encourage all of their researchers to step back and ask how they can make the biggest impact.

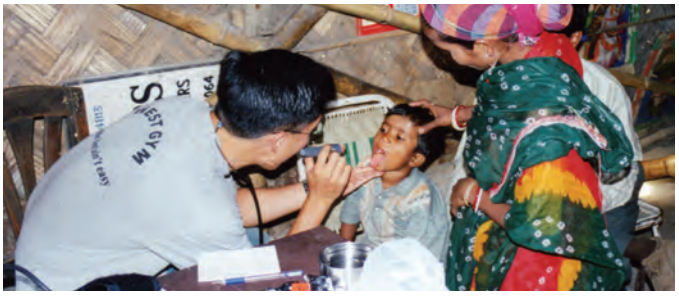
DID YOU KNOW…

Hippocrates urged doctors to "sometimes give your services for nothing…and if there's an opportunity to help someone in financial straits, to give full assistance to them."

Ludwig Melbourne's newest hire, physician scientist Elgene Lim, seems to have taken this advice to heart. Awarded the 2010 Fulbright Victoria and 2011 National Health and Medical Research Council postdoctoral fellowships, he spent four years at the Dana-Farber Cancer Institute and Harvard Medical School under the mentorship of Eric Winer and Myles Brown. There he researched underlying cancer biology and novel approaches to treat breast cancers, and established a platform of patient-derived breast cancers in mice that has now become a core facility at Dana-Farber.

But—apropos of the bit about Hippocrates—he has also made impressive contributions to global health. Elgene has spearheaded multiple medical relief efforts in India, including in the state of Odisha and the slums of Calcutta. In 2009, building on previous efforts, he led a multidisciplinary team of doctors, dentists and teachers from Melbourne to work among tribal groups of Odisha in partnership with local doctors. This is a long-term endeavor with a goal to establish a culturally appropriate and economically viable model of cancer and health care. He has also volunteered as a physician to asylum seekers in Melbourne, who face many barriers in accessing health care in Australia.

Elgene currently leads translational breast cancer research at Ludwig Melbourne, with a focus on hormone signaling in breast cancer and the evaluation of novel therapies in patient-derived breast cancer mouse models. He has established an endocrine breast cancer research clinic to study recurrence patterns of the disease in these patients and long-term systemic effects of hormonal therapies, and to evaluate novel therapeutic and lifestyle intervention strategies.



Required Reading

Ludwig Brussels

Proceedings of the National Academy of Sciences USA
2014 March 4

Local immunostimulation leading to rejection of accepted male skin grafts by female mice as a model for cancer immunotherapy

Bourdeaux C, Lurquin C, Jacquemart I, Lethé B, Brasseur F, van Baren N, Baurain JF, Dyson J, Van Snick J, Uyttenhove C, Boon T.

Clinical Cancer Research
2014 April 21

A short treatment with galactomannan GM-CT-01 corrects the functions of freshly isolated human tumor–infiltrating lymphocytes

Demotte N, Bigirimana R, Wieërs G, Stroobant V, Squifflet J-L, Carrasco J, Thielemans K, Baurain J-F, Van Der Smissen P, Courtoy PJ, van der Bruggen P.

Ludwig Chicago

Science Translational Medicine
2014 Mar 26

DNA repair pathway gene expression score correlates with repair proficiency and tumor sensitivity to chemotherapy

Pitroda SP, Pashtan IM, Logan HL, Budke B, Darga TE, Weichselbaum RR, Connell PP.

Ludwig Harvard

Nature Genetics
2014 May 4
(Epub ahead of print)

Dystrophin is a tumor suppressor in human cancers with myogenic programs

Wang Y, Marino-Enriquez A, Bennett RR, Zhu M, Shen Y, Eilers G, Lee J-C, Henze J, Fletcher BS, Gu Z, Fox EA, Antonescu CR, Fletcher CDM, Guo X, Raut CP, Demetri GD, van de Rijn M, Ordog T, Kunkel LM, Fletcher JA.

Ludwig Lausanne

Nature Medicine
2014 May 4 (Epub ahead of print)

Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors

Motz GT, Santoro SP, Wang LP, Garrabrant T, Lastra RR, Hagemann IS, Lal P, Feldman MD, Benencia F, Coukos G.

Ludwig Melbourne

Proceedings of the National Academy of Sciences USA
2014 February 25

Minor class splicing shapes the zebrafish transcriptome during development

Markmiller S, Cloonan N, Lardelli RM, Doggett K, Keightley MC, Boglev Y, Trotter AJ, Ng AY, Wilkins SJ, Verkade H, Ober EA, Field HA, Grimmond SM, Lieschke GJ, Stainier DY, Heath JK.

Molecular Cancer Therapeutics
2014 February

Therapeutic inhibition of Jak activity inhibits progression of gastrointestinal tumors in mice

Stuart EC, Buchert M, Putoczki T, Thiem S, Farid R, Elzer J, Huszar D, Waring PM, Phesse TJ, Ernst M.

Ludwig MSK

Science Translational Medicine
2014 March 5

Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy

Zamarin D, Holmgaard RB, Subudhi SK, Park JS, Mansour M, Palese P, Merghoub T, Wolchok JD, Allison JP.

Cancer Immunology Research
2014 February 4

Pretreatment serum VEGF is associated with clinical response and overall survival in advanced melanoma patients treated with ipilimumab

Yuan J, Zhou J, Dong Z, Tandon S, Kuk D, Panageas KS, Philip Wong P, Wu X, Naidoo J, Page DB, Wolchok JD, Hodi FS.

Nature Immunology
2014 April 13

Inflammation-induced repression of chromatin bound by the transcription factor Foxp3 in regulatory T cells

Arvey A, van der Veeken J, Samstein RM, Feng Y, Stamatoyannopoulos JA, Rudensky AY.

Ludwig San Diego

Cancer Research
2014 Mar 1

Suppression of microRNA-9 by mutant EGFR signaling upregulates FOXP1 to enhance glioblastoma tumorigenicity

Gomez GG, Volinia S, Croce CM, Zanca C, Li M, Emnett R, Gutmann DH, Brennan CW, Furnari FB, Cavenee WK.

Ludwig Stanford

Nature Medicine
2014 April 6
(Epub ahead of print)

An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage

Newman AM, Bratman SV, To J, Wynne JF, Eclov NC, Modlin LA, Liu CL, Neal JW, Wakelee HA5, Merritt RE, Shrager JB, Loo BW Jr, Alizadeh AA, Diehn M.