



# LUDWIG LINK

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LUDWIG  
CANCER  
RESEARCH

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Our leader in Lausanne

LIFE-CHANGING SCIENCE

## LETTER



Disease prevention is a big part of growing up. Kids may not like being stuck with needles, but many keep a stiff upper lip for their vaccinations. They likewise dutifully buckle up in the car and endure the tedium of sunscreen and hats through the summer.

Preventing disease ought to be at least as big a part of our grown-up lives. After all, we have known for some time that prevention, where possible, is the best strategy when it comes to cancer. Cancer deaths could be cut approximately in half if all preventive measures available today were widely implemented. Imagine what we might achieve if we could expand the menu of such measures.

Ludwig plans to help find out. In this issue you'll learn about a project we've launched in partnership with the Conrad N. Hilton Foundation to explore nutritional interventions to forestall colorectal cancer, a leading cause of cancer deaths. In our "Ask a scientist" section, three Ludwig researchers involved in the program weigh in on promising advances and technologies for cancer prevention.

We also have an interview with Ludwig's George Coukos, who shares his plans, hopes and expectations for the new Branch he now leads in Lausanne, Switzerland. All this is in addition to our usual summary of Ludwig discoveries from around the world. You'll notice that our researchers have been as productive as ever.

Happy reading!

Sincerely,  
Rachel Steinhardt  
Vice President of Communications

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## NIXING COLON CANCER: THE HILTON-LUDWIG CANCER PREVENTION INITIATIVE

A cancer prevented does not need to be cured. The assertion is, of course, indisputable. Yet it doesn't appear to have shaped the broad agenda of cancer research over recent decades. Now, a growing number of researchers are looking at how technological advances and a more sophisticated understanding of the molecular biology of cancer might be combined to improve the early detection of various cancers—and the development of lifestyle interventions to prevent their occurrence.

Ludwig researchers are helping to lead such efforts. In January, Ludwig Cancer Research, in partnership with the Conrad N. Hilton Foundation, launched a \$10 million research program to advance dietary interventions and technologies for the prevention of colon cancer, the third most common cancer in the world and among the most lethal. The new effort expands an ongoing collaboration between the two organizations to apply DNA diagnostics to detect the recurrence of such cancers. Ludwig and the Hilton Foundation share a concern that largely preventable cancers represent an increasingly serious public health problem in developing countries. “We are pleased to be partnering again with Ludwig, which brings 40 years of experience advancing research to benefit people globally,” said Shaheen Kassim-Lakha, the Hilton Foundation’s director of international programs.

Colon cancers are clearly not just an issue in economically advantaged countries. “Current estimates are that half of colon cancer cases can be prevented if we have the right strategies in place, and that prevention really is the most cost-effective and sustainable way of reducing the global cancer burden in the long term,” said Bob Strausberg, executive director of collaborative sciences at Ludwig. “Put simply, it costs far less to prevent cancer than to cure it.”

But those advantages will be felt only if evidence-based preventive measures are systematically implemented in health policy, much as they have been for tobacco use in some countries. The Hilton-Ludwig program is thus designed to ensure that its findings inform the development of public health interventions. “Future cancer research needs to be more inclusive of prevention and wellness,” said Shaheen. “By the end of the five-year project, we hope that Ludwig will be successful in identifying a new nutrition-based approach to colon cancer prevention.”

### The power of prevention

Prevention works. Over the past century, childhood deaths from infectious diseases have plummeted with the introduction of vaccines, and deaths from heart disease have declined in step with smoking cessation, diet improvements, and the aggressive detection and treatment of high blood pressure and blood cholesterol. Overall, cancer death rates have declined modestly but steadily.

“Prevention is a tough sell,” observed Bert Vogelstein, codirector of Ludwig Johns Hopkins. “There’s no drama in prevention or preventive medicine. It’s much more exciting to develop a new therapy. When you take a cancer patient and put that patient in remission, even for a few months, that’s dramatic. On the other hand, if you prevent all colon cancers, don’t expect a ticker tape parade. No one’s going to thank you. There’s little excitement in society about the consistent acts that can transform our lives, and this applies to prevention.” Though researchers and clinicians have made significant progress in treating late-stage colon cancers, such treatments are expensive and can cost more than \$250,000 per patient in the US. They are also largely

unavailable in most developing countries. “Prevention and early detection of colon cancer should be a top health priority,” said Peter Gibbs of Ludwig Melbourne. “We expect the end result of this program to lower disease rates across the globe, eliminate health disparities between developed and developing nations, and save precious health dollars.”

There is a strong case to be made for investments in prevention that go beyond the colonoscopy, which has contributed to a decline in colon cancer deaths in wealthy nations. Such measures need to be firmly grounded in science and based on experimental—not just epidemiological—evidence. Epidemiological studies can help identify potentially valuable preventive interventions, but experimental research is needed to establish causal links between these measures and cancer risk reduction.

### Getting the drop on colon cancer

Any screening test is worth only as much as a patient’s willingness to take it. And that’s exactly where, all too often, the colonoscopy runs into trouble. It is the gold standard for colon cancer screening, and there’s ample evidence that it saves lives. But only about half of those in the US who are eligible for the procedure opt to take it. Colonoscopy can also be expensive and, because it is invasive and conducted under anesthesia, has some risks. At the same time, screening tests are critical because signs of colon cancer often appear after it has advanced considerably and is much harder to treat.

Indeed, too many cancers are caught only when they have become incurable. Each year, \$91 billion is spent on cancer drugs worldwide, but most of those medicines are given to patients who have late-stage disease. The newest treatments, created at great expense, can cost \$10,000 a month or more, and typically extend life by only a few weeks or months. Liquid biopsies could help catch

cancers earlier, when they are more treatable with surgery and other therapies, averting much suffering and significant cost.

“

Future cancer research needs to be more inclusive of prevention and wellness,” said Shaheen. “By the end of the five-year project, we hope that Ludwig will be successful in identifying a new nutrition-based approach to colon cancer prevention.

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Bert, Peter and their colleagues are now laying the groundwork for the development of these tests by evaluating the use of liquid biopsies to detect the recurrence of colon cancer. In fact, the team just published the results of one such clinical study (see pg. 12). Their ultimate aim, however, is to develop blood tests that are at least as accurate as the colonoscopy and far less onerous to take.

“When we catch colon cancer early, more than 95% of patients are still alive five years later,” said Peter. “If we catch it after it has grown and spread, treatment doesn’t always work well.” The team hopes that people who shy away from colonoscopies will be happy to take a quick blood test at the doctor’s office. “When it comes to colon cancer, the best test is the one you actually use,” Peter added.





Ludwig Cancer Prevention Meeting 2015

### **Making a difference**

High fiber. Low carb. High protein. Vegetarian. Mediterranean. There's a lot of confusion about what constitutes a good diet, but the idea that diet can influence colon cancer isn't new. Epidemiologists have long suspected that eating a modern Western diet, high in animal protein and fat and low in fiber, increases the risk of colon cancer. But it's unclear what dietary habits are likely to protect people from the disease.

"It's going to be tough asking the public to change their dietary habits," said Alexander Rudensky of Ludwig MSK, "but public perception of cancer as a catastrophic, attention-grabbing disease will ultimately help the implementation of prevention and early detection efforts."

The Hilton-Ludwig program seeks to obtain a firmer grasp on how nutritional changes might aid cancer prevention and how to apply that knowledge to improve public health. Moreover, the findings could be bundled into broadly implemented public health strategies, particularly

in developing countries, where prevention would have the greatest impact in reducing cancer deaths.

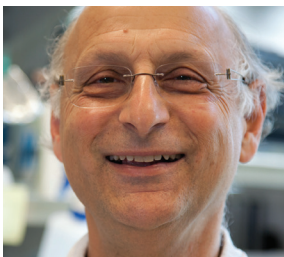
Leveraging its network of cancer prevention researchers and partner organizations, Ludwig is organizing meetings with experts across various disciplines to discuss the project's progress and identify opportunities to collaborate. "Bringing together people from different constituencies, including government, behavioral scientists and other cancer research organizations, allows multiple perspectives to be heard. This enables us to incorporate diverse knowledge and expertise into the research framework and future public health strategies," said Shaheen.

This collaborative approach will likely help ensure that the project's findings and technologies will be transmitted to a broader audience, especially policymakers, businesses and, of course, the public. That, after all, is where the results of the Hilton-Ludwig collaboration will make the biggest difference.

## SWITCHING HATS

Richard Kolodner has been named director of the San Diego Branch. He succeeds Web Cavenee, who will take on a new role at Ludwig as director of strategic alliances in central nervous system cancers. As head of Ludwig's laboratory of cancer genetics, Richard studies how cells ensure the stability of their genomes and repair their DNA to prevent mutations. His work has significantly informed our understanding of the genetic events that drive cancer.

Web will continue to lead our international efforts in adult and pediatric brain cancers. He will spearhead Ludwig's glioblastoma multiforme (GBM) partnerships with the new Global GBM Alliance and the Defeat GBM initiative of the National Brain Tumor Society. Web is known best for his groundbreaking contributions to cancer genetics and his dissection of the role of mutant epidermal growth factor receptors in GBM. He led a Ludwig team involved in developing a targeted antibody against one of those mutants. That antibody has since been adapted by AbbVie and taken into clinical trials for the treatment of GBM.



**Richard Kolodner**  
Ludwig San Diego



**Web Cavenee**  
Ludwig San Diego

## A CLASS OF THEIR OWN

Two Ludwig scientists are among this year's members elected to the American Academy of Arts and Sciences, one of the nation's most prestigious scientific societies and a leading source of independent policy research. Alexander (Sasha) Rudensky is director of Ludwig MSK and chairman of the immunology program at MSK as well. He has contributed enormously to our understanding of the role and regulation of white blood cells known as regulatory T cells. These critical cells suppress immune responses—preventing devastating autoimmunity—but they can also be favored by tumors eager to avoid the attention of the immune system. Aside from his illuminating research in basic immunology, Sasha is working on cancer therapies that target these cells.

Sangeeta Bhatia, our other inductee, is a member of Ludwig MIT. A physician and engineer, Sangeeta leads a laboratory that excels in cross-disciplinary research linking engineering to medicine and biology. She and her team develop new platforms for the study, diagnosis and treatment of human diseases, most notably those that enable living cells to interface with synthetic systems. She is applying such technologies to develop new approaches to tissue regeneration, medical diagnostics and drug delivery.



**Alexander (Sasha) Rudensky**  
Ludwig MSK



**Sangeeta Bhatia**  
Ludwig MIT

### A PIONEER

Ludwig Johns Hopkins' Bert Vogelstein has received Johnson & Johnson's 2015 Dr. Paul Janssen Award for Biomedical Research. The award recognizes Bert's seminal contributions to our understanding of how a tumor grows, evolves and progresses, and his many subsequent achievements in cancer genomics. "I am honored to have my laboratory's work recognized," said Bert. "Celebrating science can make a very positive impact in the way people think about problems, not only about scientific problems but problems that occur in our society." Click [here](#) to listen to his acceptance speech.



Bert Vogelstein  
Ludwig Johns Hopkins

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## News roundup

### A DEEPER FOOTPRINT

In mid-June, Ludwig announced the opening of a new Branch in Lausanne that will focus almost exclusively on tumor immunology and the development of novel molecular and cell-based cancer immunotherapies. It will pursue therapies in which a patient's own immune cells are isolated, manipulated, grown and reinfused to achieve a powerful antitumor response. Ludwig Lausanne will not only seek to devise such individualized therapies but also develop the technologies required for their routine, safe and streamlined use.

The Branch will be based at the University of Lausanne (UNIL) and the University Hospital (CHUV). It will work in close collaboration with the new Swiss Cancer Center Lausanne, a multi-institutional partnership involving the

CHUV, UNIL, the ISREC Foundation and the Swiss Federal Institute of Technology. George Coukos, a clinician, researcher and authority on tumor immunology and the development of immunotherapies for ovarian cancer, has been appointed director of Ludwig Lausanne (see Q&A).



George Coukos  
Ludwig Lausanne

## KNOCKOUT COMBOS 2 & 3

It's been a busy quarter for Ludwig Harvard's Stephen Hodi and Ludwig MSK's Jedd Wolchok, who jointly led publications on the results of phase 2 and 3 trials evaluating the combination of checkpoint inhibitors ipilimumab and nivolumab for advanced melanoma. The results of the phase 2 trial were reported at the American Association for Cancer Research Annual Meeting, and those of the phase 3 trial were reported at the American Society of Clinical Oncology Annual Meeting. Both studies were published in the *New England Journal of Medicine*. Though the patient populations and a few particulars of each study differed, both demonstrate that the combination is effective against the deadly skin cancer.

The [phase 2 trial](#) enrolled 142 patients: 72 received ipilimumab plus nivolumab, followed by nivolumab alone, whereas 37 got ipilimumab plus a placebo. The tumors of 109 of these patients had the normal form of the gene *BRAF*, which is frequently mutated in melanoma. Patients with a normal *BRAF* gene have almost no treatment options in advanced stages of the disease. Such patients showed an overall objective response rate of 61% in the ipilimumab plus nivolumab trial. This included a 22% complete response rate. Those with normal *BRAF* who received only ipilimumab had a response rate of 11%, with no complete responses. Patients with *BRAF* mutations had similar outcomes for each of the therapies.

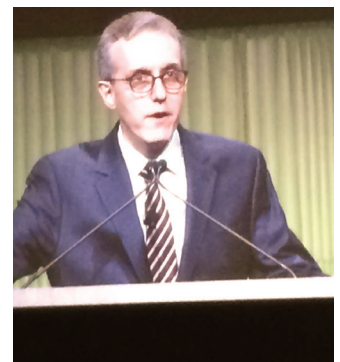
In the [phase 3 trial](#), the median overall progression-free survival (PFS)—the length of time after treatment before the cancer resumed its growth—was 2.9 months for patients who received ipilimumab alone. Those treated with nivolumab had a median PFS of 6.9 months, whereas the combination of the two induced a PFS of 11.5 months. Confirming previous studies, 19% of patients treated with ipilimumab alone and 44% treated with nivolumab had an

objective response to each therapy. The response rate for the combination therapy was 58%.

The researchers also investigated whether the tumors of patients expressed the protein PD-L1, which engages the molecule on T cells that is blocked by the antibody nivolumab. Patients with tumors in which  $\geq 5\%$  of cells expressed PD-L1 had a PFS of 14 months, regardless of whether they were given nivolumab or the combination therapy. In those with tumors expressing less than that amount of PD-L1, the PFS for nivolumab alone was 5.3 months; for the combination therapy, it was 11.2 months. “This finding is very exciting because it could provide physicians with an objective measure to help them decide whether or not to offer a patient the combination treatment, which has a greater likelihood of inducing toxicity, and to do so knowing the expected difference in benefit,” said Jedd.



Stephen Hodi  
Ludwig Harvard



Jedd Wolchok  
Ludwig MSK



## MODEL FOR PARKINSON'S

A team led by Ludwig Stockholm's Thomas Perlmann has created a novel mouse model for Parkinson's disease, which is caused primarily by the death of dopaminergic (DA) neurons. The researchers investigated how the controlled removal of the genes *Lmx1a* and *Lmx1b*, which are required for the development of DA neurons, affected mice. Their [study](#), published June 18 in *Nature Neuroscience*, shows that the loss of *Lmx1b* in particular affects dopaminergic neurons in a way that closely resembles their gradual decline, dysfunction and death in Parkinson's disease. "Mice lacking *Lmx1b* genes had many of the same abnormalities you see in various stages of Parkinson's disease, including loss of motor control," said Thomas. Loss of *Lmx1b* affects a cellular process that removes misfolded and malfunctioning proteins from the cell. The researchers are now exploring how exactly *Lmx1b* controls the cell's trash-removal processes. Misfolded proteins may play an important role in cancer and other diseases, so this work is likely have broader implications.

## SECRETS OF A VACCINE

In a [study](#) published online on April 8 in *Science Translational Medicine*, a team of Lausanne researchers, including Ludwig scientists Silvia Fuertes Marraco, Mauro Delorenzi and Daniel Speiser, shows that yellow fever vaccination is an ideal model for how vaccines can be improved to generate long-lasting protective immune memory. Examining data from 41 vaccinated donors, the researchers found in 38 of them a population of unique yellow fever-specific CD8+ T cells that had been maintained at a stable frequency for more than 25 years and were capable of self-renewal.

The cells not only were distinct from T cells of unvaccinated donors, but resembled stem cell-like memory T cells. These long-lasting cells have the capabilities of antigen-specific memory cells yet retain the powerful stem-like characteristics of T cells that have never been exposed to antigen. Studying how long-term immune memory is induced and preserved through vaccination should benefit the development of cancer vaccines and immunizations for intractable pathogens like HIV.

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## A MALIGNANT SIGNAL

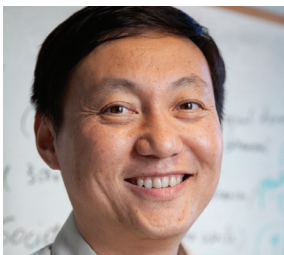
In a [study](#) published online June 4 in the *British Journal of Cancer*, Ludwig Chicago scientists led by Ralph Weichselbaum report a role for autocrine CXCL10/CXCR3 signaling in tumor growth and metastasis. Increased expression of the protein CXCL10 and its corresponding receptor, CXCR3, is associated with advanced human cancers, including melanoma, ovarian cancer and multiple myeloma. Signaling by CXCR3 mediates interactions between tumor cells and the stroma, noncancerous tissue that supports tumors.

Ralph and his team examined the expression and function of CXCL10 and CXCR3, and their signaling pathways, in melanoma cells with differing potential for metastasis. They show that CXCL10/CXCR3 signaling plays a critical role in tumor cell growth, motility and metastasis. The researchers also report that co-expression of this pair of proteins is associated with early disease progression and poor overall survival in patients with melanoma and colon and renal cell carcinomas. "These findings could be used to predict the likely course of disease for a number of cancers," said Ralph. "They also suggest some new targets for the development of drugs to treat metastatic cancers."

## A MYSTERY UNRAVELED

It's tough to produce cells of the intestine, liver and pancreas from stem cells in culture. The process requires the calibrated, sequential application of as many as seven distinct growth factors to coax progenitor cells down the right path and avoid the production of unwanted cell types. In a [study](#) published April 2 in *Cell Stem Cell*, Ludwig San Diego's Bing Ren and his colleagues explain why this is the case. The team mapped the chromosomal changes that take place as stem cells progress to become pancreatic or liver cells. They report that as cells proceed down this path, discrete regions of their chromosomes open up, making the genes encoded at those locations available for reading. Not until particular chromosomal regions have unraveled and exposed their genes can cells respond to a given growth factor.

The details of these findings should aid the development of new stem cell therapies for diseases of the liver and pancreas. "These data powerfully illustrate the potential of recent advances in genomics that have shed light on the physical dynamics of the genome and how the regulation of chromosomal structure affects the biology of the cell," said Bing. He and his team are now investigating whether variations in the chromosomal dynamics they have described play a role in diabetes.



**Bing Ren**  
Ludwig San Diego

## 20/20 HINDSIGHT

Researchers often rely on flow cytometry to capture the range of cells in a tissue sample. But this method, which requires separating out the cells in a given tissue, labeling them with antibodies and fluorescent markers and then counting them, has some obvious limitations. Cells must remain intact, the required antibodies must be available and the tissue must be amenable to such handling. In the May 12 [issue](#) of *Nature Methods*, Ludwig Stanford researchers led by Ash Alizadeh and Maximilian Diehn reported a technique that circumvents such limitations. Their method, dubbed Cibersort, analyzes the RNA present in a slurry obtained from tissue, and then applies a snazzy algorithm to the readout to reconstruct the cellular components of the sample.

Cibersort will be useful to all sorts of biomedical researchers, not least those studying cancer and its treatment. The method should, for example, help researchers probe how different subtypes of immune cells in tumors correspond to patient responses to various immunotherapies. And that's just for starters.



**Ash Alizadeh**  
Ludwig Stanford



**Maximilian Diehn**  
Ludwig Stanford

## MUTANT TARGETS

Rapid proliferation makes cancer cells prone to error in copying DNA. Proteins dedicated to mismatch repair, however, fix many of those errors before they can become mutations. But when mismatch repair genes are themselves mutated, cancer cells of all types accumulate many mutant proteins, which may be recognized by the immune system. Such cancers should be prime candidates for therapies, such as PD-1 blockade, that boost the immune targeting of tumors. A team led by researchers at Ludwig Johns Hopkins tested this idea in a phase 2 clinical trial of patients with advanced colorectal cancer and other metastatic cancers.

The [results](#) of their phase 2 clinical trial, which were published in the *New England Journal of Medicine* and presented at the 2015 American Society of Clinical Oncology Annual Meeting, suggest their hypothesis is correct. Mismatch repair–deficient colorectal cancer patients had an immune-related objective response rate of 40% and an immune-related progression-free

survival at 20 weeks of 78%. For patients with other DNA repair–deficient cancers, these rates were 71% and 67%, respectively. None of the colorectal cancer patients whose tumor cells had intact mismatch repair genes responded to the therapy, and that cohort’s immune-related progression-free survival was only 18%. “Our results will have to be confirmed in a larger trial,” said Luis Diaz, one of the Ludwig investigators, “but we are hopeful that this will have a significant impact on the clinical management of a variety of cancers that would not ordinarily have been considered candidates for PD-1 blockade.”



Luis Diaz  
Ludwig Johns Hopkins

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## A GLOWING SUCCESS

Tumors in the liver are often hard to detect with CT and MRI scans. And many types of cancer, including colon and pancreatic cancers, tend to metastasize to this organ. The earlier the tumors are detected, the better the prospects for the patient. The chances of early detection may soon improve. A team from MIT and University of California, San Diego, including Ludwig MIT scientist Sangeeta Bhatia, published a [study](#) in the May 27 issue of *Science Translational Medicine* describing a rapid, noninvasive way to detect liver cancer.

Their approach employs a harmless probiotic strain of *Escherichia coli* bacteria that, when delivered orally, sets up house preferentially in liver tumors. The researchers engineered it to produce a luminescent signal that can be detected with a simple urine test. The bacteria can help detect tumors barely larger than a cubic millimeter in size, so the approach could enable the detection of liver tumors at relatively early stages, improving the odds of their elimination.

## EARLY WARNING SYSTEM

Tumors often shed genetic material into the bloodstream. As DNA sequencing has become more affordable, many researchers are evaluating the capture and analysis of such circulating tumor DNA (ctDNA) to diagnose and manage cancers. In April, a team led by Peter Gibbs of Ludwig Melbourne and Bert Vogelstein and Ken Kinzler of Ludwig Johns Hopkins published a paper on examining the uses of ctDNA for the diagnosis and management of metastatic colorectal cancer. The [study](#), published in the *Annals of Oncology*, evaluated whether early changes in ctDNA levels could reliably predict the response to therapy in patients with metastatic colorectal cancer receiving standard first-line chemotherapy.

To find out, the researchers sequenced the tumor DNA of 53 metastatic colorectal cancer patients, looking for 1 of 15 genes frequently mutated in this cancer. After matching one mutation to each patient, they then used it to capture and measure ctDNA before and after therapy had started. The team found that a more than ten-fold decline in the level of ctDNA before the second round of chemotherapy corresponded to a significant extension in progression-free survival, as compared with that of smaller declines. The study has, importantly, shown that ctDNA can be reliably isolated and characterized in patients with metastatic colorectal cancer. It has also helped lay groundwork for studies now starting in the Hilton-Ludwig Cancer Prevention Initiative (see pg. 3), which will test whether circulating DNA can be used to detect incipient colorectal cancers and precancerous growths in the colon.

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The team found that a more than ten-fold decline in the level of ctDNA before the second round of chemotherapy corresponded to a significant extension in progression-free survival, as compared with that of smaller declines.

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Peter Gibbs  
Ludwig Melbourne



Bert Vogelstein  
Ludwig Johns Hopkins



Ken Kinzler  
Ludwig Johns Hopkins



## REGARDING PAPPA

Melanoma tends to progress rapidly in pregnant women. A team including Ludwig Melbourne's Jonathan Cebon reports that the expression of pregnancy-associated plasma protein-A (PAPPA), which is expressed by the placenta and found at high levels in the blood of pregnant women, might help explain why.

In a [study](#) published June 30 in *Oncotarget*, the researchers show that PAPPA is widely expressed in melanoma tumors and cells that are preparing to metastasize. They also find that its inhibition curtails the migration of melanoma cells in cell culture and in a metastasis model based on the chicken neural tube. PAPPA makes the human growth hormone insulin-like growth factor (IGF-1) more biologically available to cells. Jonathan and his team find that IGF-1, which can contribute to the growth of tumors, induces changes in melanoma cells that are associated with metastasis. Taken together, they argue, these findings suggest that the PAPPA/IGF-1 axis accounts for the aggressive spread of melanoma in pregnant women and might offer a promising target for the development of new therapies.



Jonathan Cebon  
Ludwig Melbourne

## PUZZLE SOLVED

Karen Oegema and Andy Shiau of Ludwig San Diego led a study that settled a 101-year-old debate in cancer biology over whether extra copies of a cellular structure known as a centrosome contribute to the proliferation of cancer cells.

Centrosomes, which are organized by two tiny barrel-shaped structures called centrioles, help promote the assembly of protein filaments called microtubules that are involved in everything from generating and organizing beating cilia to pulling chromosomes apart during cell division. Andy and members of the Small Molecule Discovery Program worked with Karen's team to design a compound they named centrinone, which depletes centrioles from both normal and cancerous human cells. In a June 5 [study](#) in *Science*, the researchers describe how they used centrinone to show that although cancer cells do not need multiple centrosomes, healthy cells require a pair of them to proceed with cell division. With only one centrosome, normal cells hit the pause button, whereas cancer cells keep dividing. This has implications for cancer therapy. "The idea is that if you treat with centrinone, nontransformed cells will stop dividing," said Andy, citing a strategy originally formulated by David Lane, Ludwig's scientific director. "You could then use another drug to kill proliferating cancer cells while sparing the normal cells in the body." Andy and his team are currently developing more drug-like variants of centrinone with the goal of identifying combination therapies that could be tested in clinical studies.



Karen Oegema  
Ludwig San Diego



Andy Shiau  
Ludwig San Diego

## A TUNABLE SIGNAL

An international team led by Christopher Garcia of Ludwig Stanford has discovered that a novel class of molecules called diabodies can, from outside the cell, ‘tune’ the signal sent by a receptor. In a [study](#) published March 12 in *Cell*, they show that a diabody can bind the erythropoietin receptor and stall the uncontrolled growth of cells isolated from patients with myeloproliferative neoplasms, diseases of the blood and bone marrow that can progress to cancer.

The erythropoietin receptor belongs to a class of receptors that transmit signals through the JAK family of proteins. JAK2, which is attached to the erythropoietin receptor, can be mutated in myeloproliferative neoplasms to JAK2V617F, which signals continuously, irrespective of the receptor’s instructions. Garcia and his team show that their diabody alters the geometry of the erythropoietin receptor segment inside the cell so that the manic activity of JAK2V617F is switched off. Further, they show that different diabodies induce different structural changes, affecting how vigorously the JAK2s are activated. Drugs devised from diabodies, they suggest, could help tune the activity of receptors so that pathological signals are blocked while healthy ones are left alone, reducing side effects.



Christopher Garcia  
Ludwig Stanford

## LICENSE FOR SENSITIVITY

Ludwig has entered into an exclusive agreement with Clontech Laboratories, a subsidiary of biotechnology company Takara Bio, for access to the sensitive Smart-seq2 method for single-cell RNA sequencing. This technique, which can comprehensively profile all genes expressed by a single cell, is useful to researchers exploring the differences between cells in tumors and the role of such heterogeneity in drug resistance. But its applications extend well beyond cancer research.

“This method can help researchers identify subtle differences between cell types and RNA sequences in virtually any kind of biological sample,” said Ludwig Stockholm’s Rickard Sandberg, who developed the method. “I’m very pleased to be working closely with Clontech and look forward to seeing how it’s applied across the life sciences.”

### DID YOU KNOW...

The phone you’re carrying around in your pocket has more computing power than was available to NASA when the first men were sent to the Moon. Sadly, it cannot take you to the Moon, but it can help you stay healthy. Want to quit smoking, improve your diet or get off the couch and prep for that 5K run? There is more than one app for that. Have you scheduled a colonoscopy? Well, it turns out there’s now an app for that as well.

It is no doubt needed. Colonoscopies may be the gold standard for colorectal cancer screening, but who looks forward to the dreadful preparations? Unfortunately, there’s no avoiding the big ough of downing glass after glass of nauseating liquid (no app can get around that), but your phone could help keep you on schedule. So allow us to introduce, with a sympathetic shudder, the Colonoscopy Prep Assistant from WellApps. You can get it for free on iTunes and wellapps.com.

The rest, we’re afraid, is up to you.

## Our leader in Lausanne

### **What advice would you give to your younger self?**

Be bold and be courageous in the choices you make—both are key ingredients in a successful career. Dare to follow untraveled paths and don't be afraid of failure. If you don't try, you've already failed. Success is not a given. You have to have the audacity to fly on your own and be willing to take risks.

### **How did you become interested in ovarian cancer research?**

After completing a clinical fellowship in gynecologic oncology, it became very evident to me that it was the side of gynecology that needed the most help. Ovarian cancer is the deadliest form of gynecologic cancer and a particularly challenging problem, and we needed to improve our understanding of this disease and its underlying biology, and the methods to improve prevention and early detection, if we were ever going to attempt to reduce its burden.

In the area of translational research, one of our most important efforts is to develop better ways to interrogate tumors so that we can begin to really understand and learn what happens in patients when things go right and when things go wrong. Our bioengineering research programs



will develop the next generation of immune engineering technologies.

### **What do you consider to be the most exciting development in cancer research today?**

For me and for many others, it has to be the immune therapy revolution. Unlocking the immune system is the big new hope for cancer treatment because in recent years we've seen some truly promising advances in treating certain types of cancer. Along with surgery, radiation and chemotherapy, immunotherapy is becoming a viable avenue of treatment and offers hope to people with cancers that are otherwise difficult to treat.

With immunotherapy, we've entered a new era of cancer therapy by enabling the immune system to continuously monitor against the reappearance of 'foreign' cancer cells. So the ability to reprogram the immune system is changing the paradigm in cancer treatment. Harnessing the natural ability of our immune system to eliminate malignant cells represents the most promising anti-ovarian cancer strategy since the development of chemotherapy. We now have the tools to shape the way we treat cancers in a way we haven't before. I think there is no doubt in the oncology community that immunotherapy is here to stay and will continue to make a significant impact—in much the same way that chemotherapy, molecular targeted therapies, radiation therapy or surgery have done—as we optimize the technology and the medical science behind it.

**Can you tell us about the research you'll be pursuing at the Lausanne Branch?**

We will continue to study the human tumor microenvironment and develop a variety of new immunotherapeutic strategies, including more personalized approaches using cell-based technologies. We know that immune-based approaches have succeeded in other lethal cancers, such as melanoma. I believe that successful immunotherapy approaches will depend on the ability of re-engineered T cells to travel into the tumor environment, and we

are developing ways to engineer immune cells to better recognize tumor cells and then to kill them. Our ultimate goal is to translate these discoveries to the clinic.

**What made you decide to assume the leadership role at the new Ludwig Lausanne Branch? Why did you decide take on this challenge?**

My passion for immunotherapy and Ludwig's long history in Lausanne and its expertise in cancer immunology made my decision easy. Ludwig has invested more than 200 million Swiss francs in its research efforts in Lausanne, and there is a cadre of experienced cancer immunologists on the ground. This puts the new Branch in an unparalleled position to guide the field in bringing the next generation of cancer immunotherapies to patients.

**What are you hoping to achieve in Lausanne?**

We aspire to be one of the world's leading programs in cancer immunotherapies. I think we can achieve this by creating a vibrant environment within the Branch that offers our researchers access to the clinical pathway as well as cutting-edge technology and engineering. This will ultimately give patients access to innovation. The most important goal is to foster the creation of groundbreaking translational research programs and accelerate our discoveries into results that will have a positive impact on the future treatment of human cancer.



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Harnessing the natural ability of our immune system to eliminate malignant cells represents the most promising anti-ovarian cancer strategy since the development of chemotherapy.

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This is a big, bold vision—and one I deeply believe we can achieve. We have a common and unified goal for the organization and we're going to work very hard to ensure a collaborative, open environment and leverage the talent of our scientists and clinicians in order to avoid the 'silo' culture that tends to hinder progress in cancer innovation.

Critical to our success is the government and multi-institutional support from the Lausanne University Hospital (also known as the CHUV), University of Lausanne, the ISREC Foundation and the Swiss Federal Institute of Technology. We'll be based at the University of Lausanne and the CHUV and operate in close collaboration with the new Swiss Cancer Center Lausanne.

**You have been grappling with ovarian cancer for almost 25 years. Are we making any headway in detecting or preventing it?**

Persistence is in my DNA. Worldwide, ovarian cancer is the seventh most common cancer in women and the five-year survival rates haven't changed much in the past 30 years. Right now, we don't have any ovarian cancer screenings that have been proven accurate enough to use in the general population. Nor do we have guaranteed ways to detect it or to prevent it other than surgical removal of the ovaries and the fallopian tubes.

Since our ultimate goal is to prevent cancer, it's very important we focus our efforts in detecting tumors early enough to save lives by finding ways to train the body's own immune system to kill cancer cells. With immune-based approaches, we're finally making progress and getting some momentum going.

**You've been quoted as saying that you always set yourself five-year goals. What are they now?**

Make the promise of immunotherapy a reality for more patients. I'm very optimistic that treatment advances in immunotherapy will mean that cancer cure rates could rise from 50% to 75%. We're going to achieve this by developing innovative and transformative approaches and moving them as rapidly as possible into the clinic.

Translational research is interpreted many ways, but true translational research has a direct impact on the way we manage patients. The key word is "impact." The eyes have to be really focused on a specific problem, and we need to assemble the teams and approaches that will make a dent in this problem. So it's imperative that we work closely with our partner institutions to ensure that both the research environment and the clinical environment are completely integrated, which will allow us to achieve these ambitious goals.

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## What advance(s) will have the biggest impact on improving cancer prevention?



Cancer is a complex disease resulting from the interaction between environmental and genetic factors. While epidemiological studies identifying environmental risk factors and developing effective preventive intervention are important aspects of cancer prevention, the biggest impact on improving cancer outcomes will likely come from advances in early detection of precancerous or cancerous lesions.

**JEANNE TIE**  
Ludwig Melbourne



Understanding how nutrition affects inflammation and immunity and the impact this has on the microbiota—the microorganisms that inhabit our organs. Our recent discoveries on how dietary products influence the cross-talk between microbiota and the host immune system provide promising new therapeutic strategies for enhancing cancer prevention and increasing anticancer immunity.

**NICK ARPAIA**  
Ludwig MSK



Advances in secondary prevention will have a great impact in cancer prevention, leading to long-term survival and even cures. Effective early detection of cancer requires the development of noninvasive, sensitive, specific and cost-effective tests. Digital genomics-based tests are on the forefront of this approach. The genetic information derived from such tests can also provide opportunities for adjuvant therapies tailored to the individual.

**NICK PAPADOPOULOS**  
Ludwig Johns Hopkins

## Required reading

### Ludwig Brussels

**PLoS One 2015**

**April 8**

**microRNA-155, induced by interleukin-1 $\beta$ , represses the expression of microphthalmia-associated transcription factor (MITF-M) in melanoma cells**

Arts N, Cané S, Hennequart M, Lamy J, Bommer G, Van den Eynde B, De Plaen E.

### Ludwig Chicago

**British Journal of Cancer 2015**

**June 4 [Epub ahead of print]**

**Oncogenic CXCL10 signalling drives metastasis development and poor clinical outcome**

Wightman SC, Uppal A, Pitroda SP, S Ganai S, Burnette B, Stack M, Oshima G, Khan S, Huang X, Posner MC, Weichselbaum RR, Khodarev NN.

### Ludwig Johns Hopkins

**New England Journal of Medicine 2015**

**June 25**

**PD-1 blockade in tumors with mismatch-repair deficiency**

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhajee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA.

### Ludwig Lausanne

**Science Translational Medicine 2015**

**April 8**

**Long-lasting stem cell-like memory CD8+ T cells with a naïve-like profile upon yellow fever vaccination**

Fuertes Marraco SA, Soneson C, Cagnon L, Gannon PO, Allard M, Maillard SA, Montandon N, Rufer N, Waldvogel S, Delorenzi M, Speiser DE.

### Ludwig Melbourne

**Annals of Oncology 2015**

**April 7 [Epub ahead of print]**

**Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer**

Tie J, Kinde I, Wang Y, Wong HL, Roebert J, Christie M, Tacey M, Wong R, Singh M, Karapetis CS, Desai J, Tran B, Strausberg R, Diaz LA Jr, Papadopoulos N, Kinzler KW, Vogelstein B, Gibbs P.

**Oncotarget 2015**

**June 30**

**Pregnancy-associated plasma protein-A links pregnancy and melanoma progression by promoting cellular migration and invasion**

Prithviraj P, Anaka M, McKeown SJ, Permezel M, Walkiewicz M, Cebon J, Behren A, Jayachandran A.

### Ludwig MIT

**Science Translational Medicine 2015**

**May 27**

**Programmable probiotics for detection of cancer in urine**

Danino T, Prindle A, Kwong GA, Skalak M, Li H, Allen K, Hasty J, Bhatia SN.

### Ludwig MSK

**New England Journal of Medicine 2015**

**July 2**

**Combined nivolumab and ipilimumab or monotherapy in untreated melanoma**

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD.

**New England Journal of Medicine 2015**

**May 21**

**Nivolumab and ipilimumab versus ipilimumab in untreated melanoma**

Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, Shaheen M, Ernstoff MS, Minor D, Salama AK, Taylor M, Ott PA, Rollin LM, Horak C, Gagnier P, Wolchok JD, Hodi FS.

### Ludwig San Diego

**Cell Stem Cell 2015 April 2**

**Epigenetic priming of enhancers predicts developmental competence of hESC-derived endodermal lineage intermediates**

Wang A, Yue F, Li Y, Xie R, Harper T, Patel NA, Muth K, Palmer J, Qiu Y, Wang J, Lam DK, Raum JC, Stoffers DA, Ren B, Sander M.

**Nature Reviews Cancer 2015 May 15**

**Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma**

Furnari FB, Cloughesy TF, Cavenee WK, Mischel PS.

**Science 2015**

**June 5**

**Reversible centriole depletion with an inhibitor of Polo-like kinase 4**

Wong YL, Anzola JV, Davis RL, Yoon M, Motamedi A, Kroll A, Seo CP, Hsia JE, Kim SK, Mitchell JW, Mitchell BJ, Desai A, Gahman TC, Shiao AK, Oegema K.

### Ludwig Stanford

**Cell 2015**

**March 12**

**Tuning cytokine receptor signaling by reorienting dimer geometry with surrogate ligands**

Moraga I, Wernig G, Wilmes S, Gryshkova V, Richter CP, Hong WJ, Sinha R, Guo F, Fabianar H, Wehrman TS, Krutzik P, Demharter S, Plo I, Weissman IL, Minary P, Majeti R, Constantinescu SN, Piehler J, Garcia KC.

**Nature Methods 2015**

**May 12**

**Robust enumeration of cell subsets from tissue expression profiles**

Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, Hoang CD, Diehn M, Alizadeh AA.

### Ludwig Stockholm

**Nature Neuroscience 2015**

**June 18**

**Dopaminergic control of autophagic-lysosomal function implicates Lmx1b in Parkinson's disease**

Laguna A, Schintu N, Nobre A, Alvarsson A, Volakakis N, Jacobsen JK, Gómez-Galán M, Sopova E, Joodmardi E, Yoshitake T, Deng Q, Kehr J, Ericson J, Svenningsson P, Shupliakov O, Perlmann T.

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