LUDWIG INSTITUTE FOR CANCER RESEARCH

LudwigLink

January 2013

THE ENVELOPE, PLEASE ...

It's not just Hollywood celebrities who are worthy of prizes.

Scientists don't devote a lifetime of research to garner a wall of awards, but it's definitely nice to be recognized.

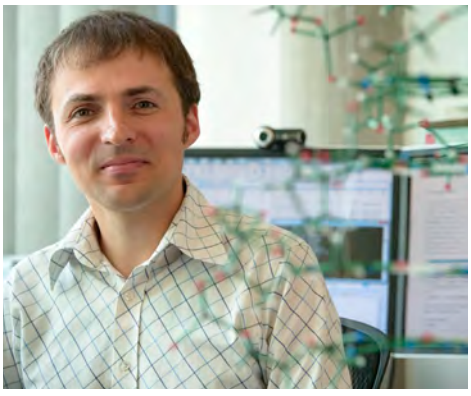
"Awards and prizes are a vote of confidence in me, my lab and my staff and they sustain us during those times that aren't quite as rosy. You have to be sustained during the tough times in order to ultimately make the positive discoveries."

—Peter Ratcliffe, Ludwig Oxford

Ludwig scientists are on a roll and were recently recognized with some of the most prestigious awards in the world of science, including the Horwitz Prize and election to the National Academy of Sciences and the Institute of Medicine.

These awards reflect the invaluable contributions Ludwig researchers have made to advance our understanding of cancer. Their work is a testament to the beauty of science, and shows how discovery can lead to insights into the human condition. All of us are tremendously proud of them and we congratulate them on winning these well deserved awards.

Rachel Steinhardt
Director of Communications



AND THE AWARD GOES TO ...

(find out on the next page)

AND THE AWARD GOES TO ...

Lucy Shapiro

Team elite

Lucy Shapiro is a member and chair of the Ludwig Scientific Advisory Committee, a Virginia and D.K. Ludwig Professor at Stanford University and a recipient of the 2012 Louisa Gross Horwitz Prize, Columbia University's top honor for achievement in biology and biochemistry research. She shares the prize with Richard Losick of Harvard University and Joe Lutkenhaus of the University of Kansas.

Her groundbreaking work has revealed the living bacterial cell as an integrated system. She has shown how the transcriptional circuitry of bacteria is interwoven with the three-dimensional deployment of regulatory and structural proteins and the dynamic organization of the chromosome. This work has completely changed our understanding of these relatively simple cells and contributed biological insights into antibiotic design.

Click here to see Lucy's presentation "Cell Cycle Regulation in a 3D Grid," which she gave on November 20 at Columbia University.

Don Cleveland

Class of 2012

Ludwig San Diego member Don Cleveland has been elected to the Institute of Medicine (IOM). He joins another San Diego member, Web Cavenee, who was elected in 2007. New members to the IOM are elected by active members through a selection process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care and public health.

Don was elected to both the National Academy of Sciences and the American Academy of Arts and Sciences in 2006 for his pioneering discoveries of the mechanisms of chromosome movement and cell-cycle control during normal cellular division, and of the principles of neuronal cell growth during mammalian development. Defects in neuronal cell growth lead to inherited human neurodegenerative disease.

Election to the IOM is one of the highest honors in health and medicine. Established in 1970 by the National Academy of Sciences, the IOM advises Congress and policy makers on important health questions. During the past year, its projects focused on health IT and patient safety, treatment of post-traumatic stress disorder, nutrition rating systems and graphics on food packaging, and studies of environmental factors in breast cancer.

Photo by Rick DeWitt

Alexander (Sasha) Rudensky

Top gun

Election to the National Academy of Sciences, the most prestigious scientific society in the United States, is an acknowledgment by the scientific community that an individual has made truly groundbreaking discoveries. Alexander (Sasha) Rudensky, newly appointed chair of Memorial Sloan-Kettering Cancer Center's Ludwig Center for Cancer Immunotherapy, was elected to the prestigious body in 2012 for his pioneering work in immunology and insights into how immune responses are regulated to prevent autoimmunity.

Since 1863, the nation's leaders have turned to the National Academy of Sciences for advice on the scientific and technological issues that frequently affect policy decisions. The Academy's service to government has become so essential that Congress and the White House have issued legislation and executive orders over the years that reaffirm its unique role.

Sasha joins three other Ludwig Center directors who are also National Academy of Sciences members: Irving L. Weissman at Stanford University, Bert Vogelstein at Johns Hopkins, and Robert Weinberg at MIT.

Rickard Sandberg

Young gun

The European Molecular Biology Organization promotes excellence in molecular life sciences in Europe. In 2000, it launched its Young Investigator Program, which selects scientists throughout member states to create a network of outstanding life scientists. This highly competitive program has attracted applications from some of the best young group leaders in Europe and neighboring countries.

Rickard Sandberg of Ludwig Stockholm was named a program member in 2012 for his research on single-cell transcriptomics. His work addresses a central challenge of biology: understanding how individual cells process information and respond to perturbations. Transcriptome analysis of single cells helps gauge the extent of cellular heterogeneity.

Rickard will join a network of nearly 300 current and former young investigators that encourages collaboration and organizes meetings within the community. Membership in the program raises the visibility of young researchers in life sciences. Funding to attend conferences, practical training in laboratory management and access to core facilities at European Molecular Biology Laboratory are some of the perks.

Skirmantas Kriaucionis

Ambassador of science

On November 8, Ludwig Oxford scientist Skirmantas Kriaucionis received an award from the Lithuanian Ministry of Education and Science for his discovery of a novel DNA modification. The modified DNA base, 5-hydroxymethylcytosine, is abundant in human and mouse brains and in embryonic stem cells. **The findings** were published in *Science* and have been cited over 400 times to date.

The prize is awarded to Lithuanian scientists working abroad for achievements in physics, biomedical sciences and technology. The Ministry of Education and Science has been granting such prizes since 2006 and, to date, 18 scientists have received them.

The award also encourages Lithuanian scientists working abroad to maintain collaborative links with scientific and academic communities and actively participate in Lithuanian communities abroad. Lithuania couldn't hope for a more perfect ambassador of science. Skirmantas collaborates with the Institute of Biotechnology, Vilnius University and Fermentas, a Lithuanian biotech company. He also participates in British Lithuanian youth community activities.

Bing Ren

Instructions included

The ENCyclopedia Of DNA Elements (ENCODE) project, supported by the US National Institutes of Health (NIH), is tasked with delineating functional sequences in the human genome, such as those that dictate how genes are regulated during development. Recent results from the ENCODE project have revolutionized scientists' understanding of human development and how it can sometimes go wrong. Many scientists believe the work will lead to new treatments for life-threatening diseases such as cancer, and possibly for mental disorders such as schizophrenia. The ENCODE project's goal is to provide the scientific community with information to clarify the role of the genome in health and disease.

Bing Ren, Ludwig San Diego, was awarded an NIH ENCODE grant to lead an effort to comprehensively characterize the epigenetic landscape. Epigenetic events are important mechanisms underlying cancer development and progression.

All the data generated by the ENCODE project will be deposited into public databases as soon as they are experimentally verified. Free and rapid access to these data will enable researchers around the world to pose new questions and gain insights into how the human genome functions.

TRANSITIONS

Joining forces

After 30 years, the Melbourne-Parkville site of the Ludwig Institute closed in December and many of our colleagues transferred their research activities with committed Ludwig support to the Walter & Eliza Hall Institute of Medical Research (WEHI). The move to WEHI was predicated on strong collaborative and collegial links over many years as well as its proximity to the former site. The two groups of researchers not only have shared laboratories but also have collaborated on some of Australia's landmark discoveries in cancer research.

The work conducted at Parkville brought great attention, credit and distinction to the Institute and contributed to making cancer a manageable disease instead of a death sentence, with scientific breakthroughs, productive global collaborations and cutting-edge research. "The move to the WEHI allows us to maintain existing synergies between our laboratories and retain a world-class program in colorectal cancer research," said Matthias Ernst, member and former branch director. "It will provide new and exciting opportunities to continue and build on the research to which everyone at Melbourne-Parkville has passionately contributed over the years."

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—Matthias Ernst

WEHI will celebrate its centenary in 2015 and is affiliated with the University of Melbourne and the Royal Melbourne Hospital. It is home to more than 650 researchers working to understand, prevent and treat diseases including cancer. It is an excellent venue for Ludwig investigators to maximize their research talent and carry forward the mission of "mastery of disease through discovery."

Cause for celebration

The HPV Institute in São Paulo, Brazil, celebrated the inauguration of its new laboratories on November 26. The new labs, in the research institute of Santa Casa de São Paulo, are receiving Ludwig support during the transition, as well as support from other Brazilian organizations. Part of the HPV Institute's mission is to contribute to the knowledge of infections and diseases caused by human papillomavirus (HPV).

Ludwig's research presence in Brazil comprises three groups in São Paulo and one in Natal, Rio Grande do Norte.

Luisa Villa, professor at the University of São Paulo and head of the molecular biology laboratory at the Cancer Institute of the State of São Paulo, is the former branch director of Ludwig São Paulo. She has been tapped to coordinate all the research activities at the HPV Institute.

HPV is the most common sexually transmitted infection, and there are more than 40 HPV types. Vaccines can protect males and females against some of the most common types of HPV that can lead to disease and cancer. Luisa is a world expert in the natural history of HPV infection and her work was crucial to the design and development of vaccines against HPV.

Above, Roberto Kalil, head of the research institute of Santa Casa de São Paulo, speaking at the inauguration of the HPV Institute. At left, Luisa Villa

NEWS ROUNDUP

The gatekeeper

Colon cancer is the second most common cancer in women and the third most common in men worldwide. Many patients with advanced or recurrent colon cancer have a poor prognosis, despite the availability of new therapeutic agents that can increase survival time after diagnosis. The *APC* (adenomatous polyposis coli) tumor suppressor gene controls cell growth and death and acts as a "gatekeeper" to prevent tumor development. Mutations in the *APC* gene may result in colorectal cancer.

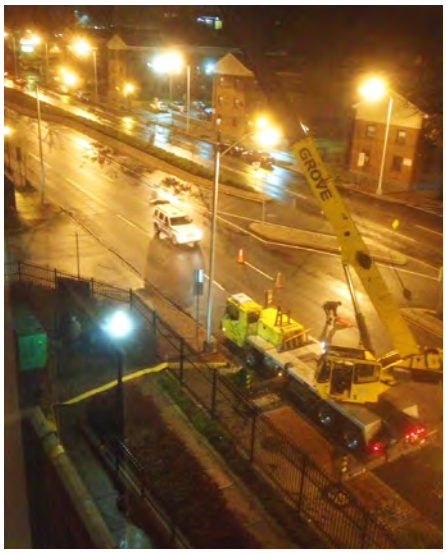
Everyone has two *APC* genes, one on each chromosome 5. Having an altered or mutated *APC* gene increases the risk of developing colon polyps and cancer. APC induces degradation of β-catenin, an essential player in the Wnt signaling pathway, which is required for adult tissue maintenance in bone, heart, muscle, and elsewhere. Mutations in this pathway in adults contribute to degenerative diseases and cancers. Mutant APC genes identified in colon cancers are defective in this activity. Thus, in colon cancer cells, β-catenin levels are elevated which, disrupts Wnt signaling and predisposes the cells to the formation of tumors.

In an October 22 *Oncogene* **study**, Ludwig researchers Oliver Sieber, Peter Gibbs, and Bob Strausberg showed that the mutation is not randomly located within the gene. They found different *APC* genotypes in proximal and distal sporadic colorectal cancers, suggesting that mutations produce distinct Wnt/β-catenin signaling levels that are 'just right' for the formation or production of tumors.

"Our findings suggest that even moderate modulation of Wnt/β-catenin signaling levels could have antitumor effects, and support a rationale for the development of inhibitors of this pathway, which are showing initial promise," said Oliver.

Riggins' Ark: A tale of hurricane heroism

Many heroes go unsung. Though Hurricane Sandy's aftermath was traumatic to say the least, last October's disaster revealed some real-life heroes and extraordinary generosity. Few are familiar with some of Sandy's smallest victims: lab rats. Researchers from Johns Hopkins slogged through thigh-deep storm and sewer water to evacuate lab animals and rescue tissue samples when a flooded sub-basement crippled a cancer research building after the hurricane.



Delivery of an emergency generator to Johns Hopkins the very evening the storm ended. Photo courtesy of Callen Riggins (Greg's son, who came to help and stayed with him to the bitter end of a very long day!)

When the call went out, the response was swift and well organized. The dean and senior staff at the medical school, including Ludwig researchers Greg Riggins, Bert Vogelstein, Nick Papadopoulos and Otavia Caballero, along with over a hundred Johns Hopkins scientists, physicians and surgeons, quickly saved years of valuable research efforts in the form of samples, cell cultures and lab animals. Many of the researchers formed a human chain and whisked cages with laboratory mice to safety. Irreplaceable documents and one-of-a-kind research samples were also moved safely to other facilities.

"It was really an extraordinary community effort," said Greg. "Of course we were all doing exactly what was necessary to be able to keep our research mission alive, but it was extremely gratifying to know how willing nearly everyone was to pitch in and how well organized the response was to the disaster. I am especially proud of my laboratory team."

Hope for solving a disease puzzle

Parkinson's disease is a fatal neurodegenerative disorder characterized by slowness of movement, shaking, stiffness and, in its later stages, loss of balance. Many of these symptoms are caused by progressive dysfunction and death of neurons in the brain, leading to lack of a chemical called dopamine. About one million Americans have Parkinson's.

The small protein α-synuclein is a major player in the diagnosis of Parkinson's and related disorders. An elevated level of α-synuclein is sufficient to cause Parkinson's. Mutations in the gene for α-synuclein can cause an inherited form of Parkinson's, and expression of normal α-synuclein can increase the risk of developing the disease in sporadic, or nonfamilial, cases. In most cases, α-synuclein aggregates and accumulates inside vulnerable neurons, and is thought to be a crucial component of disease pathogenesis.

A team of Ludwig Stockholm investigators and collaborators from Lund University published a **study** in the December 5 issue of *Science Translational Medicine* showing that α-synuclein disrupts signaling of neurotrophic factors via interference with the nuclear receptor Nurr1. Neurotrophic factors, which play a role in the development and survival of neurons, have significant therapeutic and restorative potential for neurologic diseases.

"This is exciting since it provides an explanation for why neurotrophic signaling strategies have not yet been successful in Parkinson's disease clinical trials. It also suggests that α-synuclein is causing toxicity at least in part by interfering with transcription, something that has not been well studied and

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appreciated in previous studies," said Thomas Perlmann of Ludwig Stockholm.

This work builds on Ludwig studies of Nurr1 and its function in dopamine neurons. When the activity of the *Nurr1* gene is silenced, the neuron becomes dysfunctional. Mutations in *Nurr1* are linked to a rare familial form of Parkinson's. The Nurr1 receptor is essential for development of midbrain dopamine cells that degenerate in Parkinson's, and may be critical in other neurological disorders and a target for the development of drugs for both cancer and/or neurological conditions.

Photo by Rick DeWitt

Jedd Wolchok

Collateral damage

Given the right sort of help, the immune system can destroy entrenched tumors. In the **October 22 issue** of the *Journal of Experimental Medicine*, Ludwig researchers led by Jedd Wolchok in New York described a way to provide that help.

The researchers had previously shown that a treatment of cyclophosphamide, a cancer drug that suppresses the immune system, and OX86, an antibody that activates a molecule named OX40 on T cells, caused tumor regression in mice. So they wanted to see if adding an investigative immunotherapy called T cell transfer would further improve outcomes. In T cell transfer, T cells that target tumors are isolated from patients, manipulated, expanded and then reinfused back into the patients to kill off remaining tumor cells.

"When OX40 is activated on regulatory T cells in the tumor, they get so stimulated that they actually die," explained Jedd. The results were as surprising as they were swift: tumors expressing the Trp1 antigen, a melanoma-associated glycoprotein, didn't just get smaller. They were eradicated. What's more, the combination therapy also destroyed tumors composed of a mix of cells that display the Trp1 antigen and those that do not. This is significant because most human tumors are built from such mixed populations of cells.

Gene hunters

Each cancer has a different blueprint, and scientists recognize that merely identifying pieces of DNA that have a role in the disease is not enough. A more systematic method is needed to identify genes with an essential role in cancer and look for common mutations that can be targeted with drugs or used for disease detection. To develop such a method, scientists at the Ludwig Center at Johns Hopkins have combined detection of cancer DNA in the blood with genome sequencing technology. The resulting test could be used to screen for cancers, monitor cancer patients for recurrence and find residual cancer after surgery.

A report describing the new approach appeared in the **November 28 issue** of *Science Translational Medicine*. To develop the test, the scientists took blood samples from late-stage colorectal and breast cancer patients and healthy individuals and looked for DNA shed from tumors into the blood.

The investigators applied whole-genome sequencing to DNA in blood samples and compared sequences among cancer patients and healthy people. The scientists then looked for telltale signs of cancer in the DNA, such as dramatic rearrangements of the chromosomes or certain changes in chromosome number.

"This approach uses the power of genome sequencing to detect circulating tumor DNA in the blood, providing a sensitive method that can be used to detect and monitor cancers," said Victor Velculescu at Ludwig Johns Hopkins.

This research is supported in part by the Conrad N. Hilton Foundation, which funded a group of Ludwig investigators and collaborators to investigate metastasis, the direct cause of nearly all cancer deaths.

Additional research will focus on determining how the new test could help doctors make decisions about treating patients. For example, a blood test could identify certain chromosomal changes and guide physicians to prescribe particular anticancer drugs or consider patient enrollment in clinical trials for drugs that target specific gene defects.

Teamwork

Over the past decade, discoveries in basic cancer research have provided many insights, reagents, drugs and clinical protocols with potential to significantly improve cancer outcomes. Nowhere is this potential more striking than in research on cancer immunotherapy, which can provide clinical responses in even the most challenging cancers.

To translate new developments in basic immunology into patients with cancer, MedImmune teamed up with Ludwig and the Cancer Research Institute (CRI) to test anticancer combinations in the clinic.

This is MedImmune's most expansive collaboration with an academic partner to date. Clinical trials will evaluate combinations of cancer immunotherapies, including three MedImmune compounds in different stages of development. The MedImmune agents belong to a class of drugs that modulate checkpoints of the immune system, thereby increasing the body's immune response to cancer.

"This collaboration is an innovative way to advance immunologic therapies and uncover optimal treatments for patients with cancer," said Edward Bradley, senior vice president and head of MedImmune's Oncology Innovative Medicines Unit. "By joining forces in the early stages of clinical development, MedImmune can leverage the extensive experience and synergy of these premier cancer research institutions to expand its portfolio of clinical-stage immune-active molecules."

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Did you know...?

Alfred Nobel's will stipulated that his fortune be placed in a fund destined to honor "those who, during the preceding year, shall have conferred the greatest benefit on mankind."

Ludwig's Thomas Perlmann is one of five members of the Nobel Committee for Physiology or Medicine responsible for selecting candidates from names submitted by invited nominators. He has the daunting task of assessing the qualifications of the candidates, with the assistance of appointed expert advisers.

Two pioneers of stem cell research shared this year's prize. John Gurdon from the United Kingdom and Shinya Yamanaka from Japan were awarded the prize for discovering that mature cells can be converted into pluripotent stem cells, which can become any other type of cell in the body.

John Gurdon, left, shown here in a photograph with Thomas, was the first to clone an animal, a frog, in 1962. The technique would eventually give rise to Dolly the sheep, the first cloned mammal.

"This year's Nobel Prize awards a discovery that has fundamentally changed the way we view cell development. One could say that the awarded scientists have discovered the reset button of somatic cells. By reprogramming somatic cells into induced pluripotent stem cells we now have entirely new tools that will greatly enhance our understanding of human disease, including cancer."

—Thomas Perlmann

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Ludwig and CRI will carry out the trials through their joint Cancer Vaccine Collaborative network of clinical immunologists and oncologists, and Ludwig's clinical trials team will manage the studies. Funding will be provided by CRI's Cancer Vaccine Acceleration Fund. The first trial is slated to start in mid 2013.

Think globally, treat locally

Tumor metastasis, in which cancer cells migrate from their tissue of origin and colonize elsewhere in the body, accounts for over 90% of cancer deaths.

Scientists from the Ludwig Center at the University of Chicago hypothesized over 15 years ago that an intermediate state of tumor spread or metastasis exists between patients with extensive metastasis and patients whose disease stays confined to one local tumor with no spread. The scientists termed this intermediate state oligometastasis or metastasis limited in number and location. They then demonstrated that some patients with oligometastasis can be cured with therapies, including surgery and radiotherapy that are directed locally at the metastasis.

In a **paper** published December 10 in *PLoS ONE*, Ludwig investigators led by Ralph Weichselbaum, in collaboration with Yves Lussier at the University of Illinois, took the research a step further. They analyzed patients with lung metastasis who underwent surgical resection with curative intent. They found that some patients were cured, some developed rapid metastasis, and some developed metastasis at a very slow rate of progression. They then asked themselves what accounted for these radical differences in patient outcomes.

"With these findings, we are now able to use microRNA expression to characterize oligometastasis and ultimately better select patients with tumor metastasis for curative interventions," said Ralph. "Understanding the molecular basis of tumor metastasis will allow for the targeting of specific biological processes to treat patients with more advanced tumor spread."

Q&A WITH PETER RATCLIFFE

Member, Oxford Branch

Peter Ratcliffe, who was appointed Ludwig's newest member in July, has transformed scientists' understanding of how cells react to oxygen levels. We had a chance to catch up with him and chat about his work.

How did you get interested in this area of research?

I'm a kidney specialist by training and became interested in how the kidneys respond to oxygen in order to regulate erythropoietin (EPO), a type of hormone that helps produce red blood cells. When the body is deficient in EPO, red blood cells can't be produced, and a lack of EPO can indicate a kidney problem.

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

My laboratory works on understanding how cells in the body detect how much oxygen is available to them, and especially how they respond to a lack of oxygen. This has led to a better understanding of the development of diseases such as cancer and pulmonary or cardiovascular disease, where lack of oxygen plays an important role. We're working to better understand these pathways and how they might be manipulated to treat these diseases.

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

The research has great potential for the development of new treatments for cancer and heart disease. I still continue to look after patients in the hospital, those who will hopefully in time benefit directly as a result of this research. Many major pharmaceutical companies are developing drugs that inhibit the oxygen sensing system and mimic hypoxia (low oxygen). The hope is that this will be beneficial for one or more of the diseases that encompass low oxygen delivery.

You've stated that China is a crucial partner in research collaborations. What are the dynamics at play?

China offers major opportunities for collaborations not only because the government has recently made substantial investments in science and technology but also because of the country's size and relative genetic homogeneity of the population. Predisposition to disease is different in Europe and China, and if we're going to address disease mechanisms as they are occurring in the human race, we need to engage with other countries. Also, it's increasingly important to become involved in

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"Working on a problem gives me a sense of the spine-tingling excitement one feels in trying to unravel something no one knows. In research there is a real thrill in discovery."

—Peter Ratcliffe

international research collaborations in order to share experiences and knowledge, and benefit from the cross-fertilization of ideas across the international landscape.

At this point in your career, what prompted you to accept your appointment as a member?

It was an exciting opportunity to extend my existing research program, which is well aligned with the aims and vision that Ludwig Oxford is currently undertaking. I hope it will allow me to add value both to the work I'm doing and to Ludwig itself.

You have received a number of prestigious awards and prizes. Which meant the most to you and why?

They all mean a lot to me. I'm an active researcher, which means I address questions to which we don't know the answers. Inevitably in that process, many negative answers are uncovered. Putting it simply, a large amount of what goes on in my lab doesn't work. So these awards and prizes are a vote of confidence in me, my lab and my staff and they sustain us during those times that aren't quite as rosy. And that's important, because you have to be sustained during the tough times in order to ultimately make the positive discoveries.

Are you a proponent of open access? Is it a positive factor in scientific research?

Yes and yes. It's an important aspect of research findings and there's no question that one of the most fundamental components of human civilization is the ability to transfer large amounts of data and knowledge efficiently between one individual and another.

Greater access to scholarship serves the strategic goals of greater international impact and collaboration. Even though most open-access systems charge authors publication fees and give readers free online access to the full text of the articles, I believe that scientific collaboration, advancement and utilization will be facilitated by free access to information.

Of course, for researchers, a big question is how much they have to set aside from grants to pay for open-access publication. But I believe the benefits outweigh this drawback as the research process can be accelerated through data sharing, and for researchers it brings increased visibility, usage and impact of their work.

Did you ever consider another career path?

I'm always considering other career paths. Seriously, I can't really identify how or why I got into medical research. To me, science remains a unique profession, one that gives me the opportunity to earn support for and pursue my ideas. Working on a problem gives me a sense of the spine-tingling excitement one feels in trying to unravel something no one knows. In research there is a real thrill in discovery and in the immense satisfaction in simply gaining an understanding of the problems you've spent months and sometimes years grappling with. Most researchers are addicted to it.

What keeps you motivated and excited about your research?

I call them Sunday morning moments. These are thrilling moments precipitated by a call from a postdoc on a Sunday morning to tell me the results of an experiment. It means that the experiment was done on a Saturday, the result was read on Sunday morning and it was positive, hence the call to me. When this occurs it's a heady moment and that's what I'm addicted to – probably akin to what an athlete feels winning a gold medal at the Olympics.

It's also a rare occurrence as most of the results from the experiments are negative, so they usually wait and tell me on Monday morning.

How can young scientists make the most of the institution at which they find themselves? What advice would you give to a young scientist?

Be confident in your ideas. Look for areas where you can seriously challenge existing wisdom. Don't follow mainstream ideas and don't be afraid to think outside the box. If you have a novel idea or approach, test it out; see if it fits the evidence. If it does, go with it. Think about what other people in the field are working on and try to do something that is unique where there is an unmet gap and focus on that. The important thing is you believe that the problem you're addressing is tractable and that its importance will become apparent once the solution is gained.

REQUIRED READING

Brussels

Cancer Research 2012 November 1
Tryptophan catabolism in cancer: beyond IDO and tryptophan depletion
Platten M, Wick W, Van den Eynde BJ.

Ludwig Center at Dana-Farber/Harvard

The Lancet 2012 November 21 (Epub ahead of print)
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial
Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; on behalf of all GRID study investigators.

Ludwig Center at The University of Chicago

PLoS ONE 2012 December 10
Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs
Lussier YA, Khodarev NN,* Kelly Regan K,* Kimberly Corbin K,* Li H,* Ganai S, Khan SA, Gnerlich J, Darga TE, Fan H, Karpenko O, Paty PB, Posner MC, Steven J. Chmura SJ, Hellman S, Ferguson MK, Weichselbaum RR.
**These authors contributed equally to this work.*

Ludwig Center at Johns Hopkins

Science Translational Medicine 2012 November 28
Detection of chromosomal alterations in the circulation of cancer patients with whole-genome sequencing
Leary RJ, Sausen M, Kinde I, Papadopoulos N, Carpten JD, Craig D, O'Shaughnessy J, Kinzler KW, Parmigiani G, Vogelstein B, Diaz LA Jr, Velculescu VE.

Melbourne-Parkville

Oncogene 2012 October 22 (Epub ahead of print)
Different APC genotypes in proximal and distal sporadic colorectal cancers suggest distinct WNT/β-catenin signalling thresholds for tumourigenesis
Christie M, Jorissen RN, Mouradov D, Sakthianandeswaren A, Li S, Day F, Tsui C, Lipton L, Desai J, Jones IT, McLaughlin S, Ward RL, Hawkins NJ, Ruszkiewicz AR, Moore J, Burgess AW, Busam D, Zhao Q, Strausberg RL, Simpson AJ, Tomlinson IP, Gibbs P, Sieber OM.

New York

Journal of Experimental Medicine 2012 October 22
Induction of tumoricidal function in CD4+ T cells is associated with concomitant memory and terminally differentiated phenotype
Hirschhorn-Cymerman D, Budhu S, Kitano S, Liu C, Zhao F, Zhong H, Lesokhin AM, Avogadri-Connors F, Yuan J, Li Y, Houghton AN, Merghoub T, Wolchok JD.

San Diego

Proceedings of the National Academy of Sciences USA 2012 November 20
Bioinformatic identification of genes suppressing genome instability
Putnam CD, Allen-Soltero SR, Martinez SL, Chan JE, Hayes TK, Kolodner RD.

Stockholm

Developmental Cell 2012 November 13
Mechanistic differences in the transcriptional interpretation of local and long-range shh morphogen signaling
Oosterveen T*, Kurdija S*, Alekseenko Z, Uhde CW, Bergsland M, Sandberg M, Andersson E, Dias JM, Muhr J, Ericson J.
**These authors contributed equally to this work*

Science Translational Medicine 2012 December 5
a-Synuclein–induced down-regulation of Nurr1 disrupts GDNF signaling in nigral dopamine neurons
Decressac M, Kadkhodaei B, Mattsson B, Laguna A, Perlmann T, Anders Björklund, A.

Uppsala

Developmental Cell 2012 September 11
Mig6 is a sensor of EGR receptor inactivation that directly activates c-Abl to induce apoptosis during epithelial homeostasis
Hopkins S, Linderoth E, Hantschel O, Surarez-Henriques P, Pilia G, Kendrick H, Smalley MJ, Superti-Furga G, Ferby I.