It’s all in the genes

Imagine a new type of treatment in which drugs are tailored to match the genetic origin of a disease in each patient. Instead of prescribing medicine for a particular kind of cancer, such as lung, breast or prostate, doctors could match genetic abnormalities in individuals to a drug designed just for them.

It’s happening, and Ludwig researchers are making great strides in contributing discoveries to the effort. In this issue you’ll read about how a single drug treatment can silence the mutated gene responsible for Huntington’s disease; which gene is a cancer-fighting superhero; and how researchers are getting up close and personal with genes.

The last few decades have brought an enormous and exciting expansion of knowledge about the genetic factors involved in the development of cancer, and Ludwig scientists have advanced this understanding. The tangible benefits of this knowledge are beginning to revolutionize the prevention, detection and treatment of cancer.

Rachel Steinhardt
Director of Communications

P.S. Just a reminder that the 2011 Highlights Report is available online. You can find it here (pdf). If you need additional copies, please ask your branch director or email Susan Andrews at sandrews@licr.org.

PEOPLE ON THE MOVE

SIR DAVID LANE
Knight in shining armor

Sir David Lane, chief scientist at A*Star in Singapore and a Ludwig Scientific Advisory Committee member, received the Cancer Research UK Lifetime Achievement in Cancer Research Prize in July. The award recognized his contribution to the landmark discovery of p53, the most commonly mutated gene in cancer.

The p53 protein was discovered in 1979. Since then, David has dedicated his career to understanding how it protects against cancer. This discovery revolutionized scientists’ understanding of how cells grow and divide, and a highly promising research avenue opened up. Dubbed the ‘guardian of the genome,’ p53 blocks cells with damaged DNA from propagating and eventually becoming cancerous. p53 doesn’t just play a key role in how cells grow and divide; it also influences how they behave, develop and die.

“Decades on from our discovery of p53, we are still making incredible strides in understanding how it behaves and controls cells, and we’re now turning this knowledge into new treatments for cancer,” said David.

p53 guards the body against tumors and is compromised in 50 percent of cancers. It works to prevent cancer by suspending the normal cell division cycle and giving cells time to repair the dings and nicks in DNA that come from everyday environmental assaults. If the damage is too severe to be repaired, p53 triggers cell death.

David’s recent work, which is focused on controlling p53, has identified several promising targets for developing new cancer drugs.

PHIL GREENBERG
Trailblazer

For more than 30 years, Phil Greenberg has been in the vanguard of adoptive immunotherapy, a treatment in which immune cells are transferred to tumor-bearing hosts. It is a potentially powerful tool for treating cancer and infectious diseases such as HIV. His many contributions to the field have opened up important avenues for the immunologic treatment of cancer. Phil is a professor of medicine and immunology at the University of Washington and a member and head of the immunology program at the Fred Hutchinson Cancer Research Center in Seattle. He’s the newest member of Ludwig’s Scientific Advisory Committee, which he joined in July.

Continued on next page
“Ludwig has a long history of supporting the exploration of principles defining the potential interactions between the immune system and cancer, and facilitating studies to translate insights into strategies to treat patients,” said Phil. “As a member of the committee, I look forward to the opportunities not only to help shape the evolution of this effort but also to interact with and learn from the remarkable scientific community that comprises the Institute.”

His research involves isolating and expanding or genetically engineering T cells that can recognize and kill cancer cells and remain functional in the tumor microenvironment with minimal side effects to the patient. His work has demonstrated that adoptive T-cell transfer, which has the ability to restore immunity and eradicate tumors, can produce potent anticancer immune responses, including dramatic remissions in some patients with melanoma, and leukemia.

Every year, melanoma and leukemia claim more than 300,000 lives globally and account for about 4 percent of all cancer deaths. It is estimated that 1.35 percent of people born today will develop leukemia in their lifetime, and existing therapies not only are associated with severe toxicities but also commonly cannot eradicate the disease.

In 2011, Phil received the prestigious William B. Coley Award, which recognizes scientists whose discoveries in immunology or tumor immunology significantly advance immune system–based therapies for cancer.

Phil graduated from Washington University with a degree in biology. He received his MD summa cum laude from the State University of New York Downstate Medical Center in 1971. After completing postdoctoral training at the University of California, San Diego, he joined the Fred Hutchinson Cancer Research Center and the division of oncology at the University of Washington in 1976.

“The most beautiful experience we can have is the mysterious—the fundamental emotion which stands at the cradle of true art and true science.”
—Albert Einstein

“Being well rounded is one of the most important aspects of one’s life. Discovering the world from multiple perspectives offers me endless opportunities to enhance and improve my science and art.”
—Rodica Stan

Did you know...?

Ludwig Melbourne-Austin scientist and photographer Rodica Stan melds the two disciplines seamlessly. She grew up in Romania during the dictatorship of Nicolae Ceausescu and dreamed of investigating the world around her. Photography proved an ideal way to capture “permanent memories” to relive and share with family and friends.

Click here to view award-winning photos and read the heartwarming story behind the photograph of the chuckwalla above.
REMINISCING WITH SIR DEREK ROBERTS

“Research ought to be risky”

After serving 14 years on the Ludwig Board of Directors, Sir Derek Roberts stepped down this past June. An engineer who twice served as provost of University College London (UCL), from 1989 to 1999 and later from 2002 to 2003, Sir Derek oversaw several successful projects and expansion during his tenure including the merger of UCL and the Institute of Child Health in 1996. He remains a trustee of the Ludwig Fund, a position he has held since 2002. We had an opportunity to chat with Sir Derek about his tenure on the board and the Institute changes he witnessed during those years.

What is special about being part of Ludwig?

Ludwig embodies several characteristics that make it different from other research organizations. The mission and resources of the Institute have never deviated from the ongoing commitment to innovative basic and clinical cancer research. The Institute has also been extremely successful in identifying outstanding individuals and giving them the freedom to develop their own research initiatives. And it offers an environment that allows its scientists to tackle risky research challenges and fully explore the potential of their work.

With your exposure to research, what do you see as particularly distinct or unique about the Institute?

Research ought to be risky. What struck me right from the very beginning and is particularly important today is the unwavering commitment to innovative research and the stable, long-term funding Ludwig offers its scientists. This allows them to concentrate on their research and not spend all of their time making unsuccessful bids from the traditional funding agencies. Sustained funding has and will continue to lead to fundamentally important advances in the care of patients and will ultimately save lives and improve outcomes.

What is the most important characteristic of an effective board member?

Curiosity. There has to be a willingness to learn coupled with a clear understanding of his or her role and responsibilities on the board. The Ludwig board has three primary roles: to establish policies, approve significant and strategic decisions, and oversee the Institute’s activity. An effective board member has to be open-minded, focus on the Institute’s objectives and strategies, and resist the temptation to micromanage.

What was the most important change in the Institute that you observed during your tenure?

There were two. In the early years under Lloyd Old’s leadership, there was a growing emphasis on clinical research that not all basic research institutions found themselves in a position to undertake. The second was the recognition that the widely dispersed, small-branch model was not sustainable given the available resources. The decision to concentrate the Institute’s research activities was designed to attract leading international scientists; allow the Institute to improve its use of external funding opportunities; and provide adequately equipped, state-of-the-art research facilities for basic research activities.

What advice would you give your successor?

Promote the common vision we share, build on the Institute’s strengths and continue to sustain the superb accomplishments Ludwig has achieved. My successor doesn’t need to be a cancer expert but he or she does need to appreciate that cancers are extremely diverse diseases and Ludwig researchers need the security of predictable, long-term funding. This will allow them to undertake groundbreaking research and advance the frontiers of cancer research.

What will you miss the most?

Serving on the board was both a privilege and an honor. I’ll miss the interaction and camaraderie of the group and the wonderful work and intensity that the board brings to its responsibilities and tasks. The frequent contact I enjoyed with Ed McDermott and Andy Simpson will be the biggest gap in my life.

What was it like being knighted by the Queen?

The family joke is that I only accepted to make my wife a lady. Seriously, I had been to the palace on prior occasions. Before I was given the knighthood, I was awarded the Commander of the British Empire. I also attended a small luncheon with the Queen and the Duke of Edinburgh, a Queen’s Award ceremony on behalf of UCL and a garden party with my wife. So I wasn’t so awestricken by being in the palace as I might have been. Let me just say that I’m more of a Republican than a Royalist.
In a study published in the August 14 issue of *Proceedings of the National Academy of Sciences*, Ludwig Oxford researchers discovered a critical molecular switch that regulates autophagy. They also studied the links between autophagy and a cellular process called senescence that stops cell growth permanently. Study here.

“For some of the recently developed anticancer drugs are potent inducers of autophagy. The new findings may help researchers understand how these drugs can vary dramatically,” said Xin Lu of Ludwig Oxford. “While further study is needed, these findings may in the longer term help doctors to identify patients who are more likely to respond well to autophagic inhibition.”

The researchers identified ASPP2, a tumor suppressor, as a molecular switch that can dictate the ability of a common cancer gene, the RAS oncogene, to either stop or promote senescence. “Our next step will be to identify ways to alter ASPP2 activity at that critical switch point. This could be an effective way to treat cancers with reduced ASPP2 expression and mutated RAS, such as breast and colon cancers,” said Yihua Wang of Ludwig Oxford.

**Forging a new path**

The outcome of certain cancer cases can depend on activated immune cells that somehow manage to infiltrate tumors.

A team led by Ludwig investigator Nicolas van Baren in Brussels has found one of ways these cells can be activated. In an article published in the August 15 issue of *Cancer Research*, they reported the presence of lymphoid structures in melanoma metastases, and showed that B lymphocytes are activated within these structures. The data provide researchers with a new frame of reference in dealing with melanoma.

“Our findings appear as a paradox, because they indicate that the immune system can be very active in the tumor microenvironment, whereas the current view is rather to see this environment as immunosuppressive,” Nicolas explained. “There are two intriguing details. First, the lymphoid structures are present in metastases, but they are never observed in primary melanomas, from which these metastases derive. Secondly, among the antibodies generated we find a type of antibody that is specialized in mucosal defenses, and that we do not expect to observe in skin tumors. Now we must try to demonstrate that the locally generated antibodies are directed at tumor antigens, extend this analysis to local T cell responses and investigate whether the presence of lymphoid structures impacts melanoma progression.”

**Up close and personal**

Sometimes you need to get up close and personal to really see something clearly. Geneticists and biologists have long envisaged the possibility of analyzing profiles of genes at the single cell level, but limitations of available technology meant they had to satisfy themselves with viewing them at a distance.

But now a team of researchers led by Rickard Sandberg of Ludwig Stockholm has shown that a new genomic sequencing method called Smart-Seq enables ‘smarter’ analysis of individual cells. Their findings are published in the July 22 issue of *Nature Biotechnology*.

The team studied tumor cells in the blood system of a patient with recurring malignant melanoma. Once they had identified the tumor cells in a regular blood test, the team used Smart-Seq to analyze their gene expression. This method helped them show that the tumor cells had activated membrane proteins that allow the cells to evade the body’s monitoring system and spread in the blood or lymph.

“While our results are preliminary, we showed that it is possible to do studies of individual, clinically relevant cells. Cancer researchers around the world will now be able to analyze these cells more systematically to produce better methods of diagnosis and therapy in the future,” Rickard said.

**Cancer-fighting superhero**

PTEN is a tumor suppressor gene that boosts the body’s cancer-fighting powers. Mutations in the gene can contribute to the development of cancer, and PTEN mutations have been found in as many as 30 percent of glioblastomas.

A study published on August 28 in *Proceedings of the National Academy of Sciences*, coauthored by Ludwig researchers Web Cavenee, Frank Furnari and Paul Mischel and former Ludwig researcher Tim Fenton, found that modification of PTEN affects sensitivity to a potential glioblastoma treatment.

continued on next page
Resetting the clock
With a single drug treatment, researchers led by Don Cleveland at Ludwig San Diego can silence the mutated gene responsible for Huntington’s disease, slowing and partially reversing progression of the fatal neurodegenerative disorder in animal models. The findings were published in the June 21 issue of Neuron.

Huntington’s has one known cause and no cure. It’s a disorder passed down through families in which nerve cells in certain parts of the brain degenerate. The disease is caused by the mutation of a single gene, which results in the production and accumulation of toxic proteins in the brain. It affects roughly 30,000 Americans, and those diagnosed develop uncontrolled movements frequently accompanied by psychiatric problems.

A one-time injection of a new DNA-based drug treatment known as ASO (short for antisense oligonucleotide) blocked the activity of the gene whose mutation causes Huntington’s disease. As a result, the researchers could slow and partially reverse the progression of the fatal neurodegenerative disorder. A single dose silenced the damaged gene for months and led to partial reversal of disease symptoms. The benefit persisted at least nine months after the dosage.

“These findings open up the possibility that a very short-term treatment can lead to a long-term benefit, including partial reversal of the disease course,” Don said.

Despite years of research, glioblastoma, the most common and deadly brain cancer in adults, continues to outsmart treatments targeted to inhibit tumor growth.

Biologists and oncologists have long understood that a protein called the epidermal growth factor receptor, or EGFR, is altered in at least 50 percent of patients with glioblastoma. Yet patients with glioblastoma either have upfront resistance or quickly develop resistance to inhibitors aimed at stopping the protein’s function, suggesting that there is another signaling pathway involved.

Previous research indicates that PTEN may be turned off in some cancer patients, disabling its function and potentially causing the resistance to EGFR inhibitors.

The Ludwig team identified two types of enzymes responsible for turning off the brakes of PTEN, the fibroblast growth receptor and SRC family kinases. By understanding how these enzymes disable the suppressor function of the gene, scientists may be able to target different molecules that can intervene to stop resistance.

“The more we understand, the better we can conceive of ways to restore PTEN function in tumor cells and stop resistance to EGFR inhibitors in patients with glioblastoma,” said lead author Tim Fenton, who conducted this research while at Ludwig San Diego and is currently at the UCL Cancer Institute.
COMPANY NEWS

TCMetrix

Starting a business is no joke

“Jump off a cliff and assemble an airplane on the way down.”

—Reid Hoffman, LinkedIn co-founder

That’s what four enterprising Ludwig scientists have done in creating TCMetrix, a start-up company that evolved from a former tetramer facility in Lausanne, Switzerland, that serviced Ludwig’s global cancer vaccine programs. A competitive advantage of the company is its close ties to the Cancer Vaccine Collaborative, a joint program of Ludwig and the Cancer Research Institute, which has conducted more than 40 cancer vaccine and immunotherapy clinical trials over the last decade involving over 1,000 patients. For many years the TCMetrix team has reliably supplied these international user groups with quality reagents at no charge; the team hopes to continue to serve them as future customers.

The company will begin to commercialize technologies developed by the tetramer facility and provide researchers in clinical and basic sciences with innovative, state-of-the-art T-cell monitoring reagents of the highest quality—think the Swiss watch of the tetramer industry.

Right now it’s offering 300 off-the-shelf and custom-made reagents. All reagents are provided with quality control data and recommended instructions for applications and storage.

Since becoming operational, TCMetrix has established an international network of academic and biopharma clients.

To learn more about this exciting new venture, click here.

RELATED READING

Brussels
Cancer Research 2012 August 15
Neogenesis of lymphoid structures and antibody responses occur in human melanoma metastases
Cipponi A, Mercier M, Seremet T, Baurain JF, Théate I, van den Oord J, Stas M, Boon T, Coulie PG, van Baren N.

Stockholm
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Oxford
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San Diego
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Stanford
Clonal evolution of pre-leukemic hematopoietic stem cells precedes human acute myeloid leukemia

*These authors contributed equally to this work.