LUDWIG INSTITUTE FOR CANCER RESEARCH

LudwigLink

July 2012

Inside scoop

All aboard! In this issue, you'll read about the appointments of a new Ludwig member in San Diego and a director in Lausanne, Switzerland, who are recognized global leaders in brain and ovarian cancer, respectively.

Ludwig scientists work locally but collaborate globally. A meeting on stem cells was held at Stanford University, the site of one of our Ludwig Trust Centers, bringing together more than 50 Ludwig scientists. Stay tuned for announcements of new collaborations!

Pioneering research leads to lifesaving therapies, and an Institute goal is to advance novel findings that emerge from its research. This has led to the creation of new companies in six countries. In early May, Ludwig celebrated the launch of its ninth spin-off company, which focuses on cancer immunotherapy.

Three papers in *Nature* and *Cell* presented innovative research from Ludwig scientists in San Diego that examined the 3D structures of chromosomes; tested a technique that allows scientists to read DNA letter by letter; and unveiled how centromeres will help in designing artificial chromosomes.

INSIDE

PEOPLE ON THE MOVE

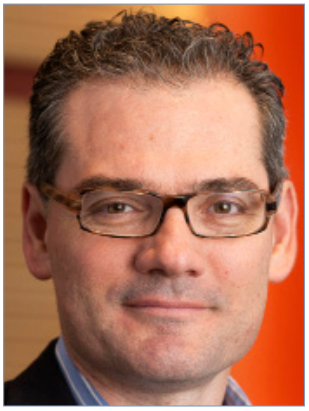
PAUL MISCHEL

Mission: Possible

The diagnosis of a brain tumor is the start of a journey that no one expects to take.

Paul Mischel, who joins us from the David Geffen School of Medicine at the University of California, Los Angeles, is focused on finding new treatments for brain tumors and transforming the care of patients. Brain tumors are very resistant to traditional therapies of radiation and chemotherapy and tend to aggressively recur after these treatments. Paul has recognized the need for new treatment approaches and is developing powerful state-of-the-art diagnostics to guide improved personalized treatment for brain cancer patients. Further, what he's doing in brain tumors may be transferable to other kinds of cancer.

Paul will be the new head of the Laboratory of Molecular Pathology at Ludwig San Diego. He will also hold a professorship in the Department of Pathology at the University of California, San Diego. Paul and his group will officially join the Branch on August 1. There he will continue both his clinical and research work: studying the molecular biology of glioblastomas in the lab and recommending treatments based on those studies in the clinic.



GEORGE COUKOS

Transforming a death sentence

Recent advances are gradually transforming ovarian cancer from a death sentence into a disease women can beat, and George Coukos is at the forefront of turning this disease into a manageable illness.

George, the new director of the Ludwig Center in Lausanne (LICR@UNIL), is a recognized leader in ovarian cancer treatment and research. Prior to his appointment, George was director of the Ovarian Cancer Research Center at the University of Pennsylvania, where he conducted research in the development of novel therapies for ovarian cancer and developed tools for early detection. He is best known for his translational research on the immune system's response to ovarian cancer.

He discovered the first evidence that a spontaneous immune response against a tumor directly affects the clinical course of ovarian cancer, providing a rationale for developing effective immune therapy against this disease. His team has elucidated mechanisms of ovarian cancer immune escape and has developed cell-based and molecular vaccine and T-cell immunotherapy approaches.

NEWS ROUNDUP

Now in 3-DNA

DNA is the hereditary material in humans. Nearly every cell in a person's body has the same DNA. Most of it is located in the cell nucleus. While scientists have developed an understanding of the one-dimensional structure of DNA, until today, little was known about how different parts of DNA are folded next to each other inside the nucleus.

Bing Ren, of Ludwig San Diego, and colleagues described for the first time how different parts of DNA are folded next to each other inside a cell's nucleus in a paper published on April 11 in ***Nature***.

They have essentially created large-scale maps of how the genome is folding up in embryonic stem cells and differentiated cells. They anticipate that the paper will be a good resource for other scientists studying genome function, providing them with a greater understanding about the basic principles of DNA folding and its role in gene regulation.

"In any biology textbook, when you look at a diagram of how genes are depicted, it is invariably a one-dimensional line. In reality, genes are arranged in such a way that two parts of the gene may be distal to each other linearly, but very close in 3-D," said Bing. "With the knowledge of how DNA folds inside the nucleus, we now have a more complete picture of the regulatory process of genes. That is the primary reason we sought to tackle this problem."

Anchors aweigh

The generation and survival of all organisms depends on the faithful execution of cell division. Cell division depends on chromosome segregation, the step in cell reproduction or division in which chromosomes pair off with a similar chromosome. But cells cannot divide properly without centromeres, the 'anchor points' that control the separation of chromosomes when cells divide. And when centromeres don't work right, the result can be catastrophic. Abnormal cell division and chromosomal instability are hallmarks of cancer cells, especially the most aggressive types. Continued cell division can lead to the formation of tumors.

Arshad Desai, of Ludwig San Diego, and colleagues published a paper in the April 8 issue of ***Nature*** that asks how the chromosomal region knows it's a centromere and how that information is maintained. Understanding centromeres will help in designing artificial chromosomes.

Creating artificial human chromosomes will help scientists better understand what natural chromosomes do and how they do it, and could prove useful in gene therapy. Researchers envision a day when they can slip into a person's cells synthetic chromosomes containing genes that correct or change the course of a disease.

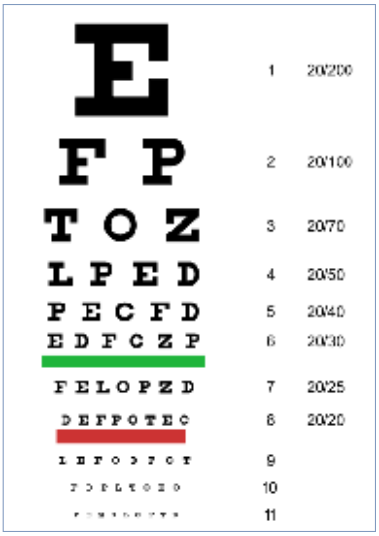
Alphabet soup

Can you imagine reading line 11 of the eye chart at the right without your glasses? How many would you 'guess' right?

One image can change the way we view cancer, and pictures created by new technologies have often catalyzed scientific discoveries.

Two modifications of cytosine, one of the four bases that make up DNA, look almost the same but mean different things. But scientists have lacked a way of reading DNA, letter by letter, and detecting precisely where these modifications are found in particular tissues or cell types.

A team of scientists from the University of Chicago, Ludwig San Diego, and Emory University has developed and tested a technique to accomplish this task. The team used the technique to map 5-methylcytosine and 5-hydroxymethylcytosine in DNA from human and mouse embryonic stem cells, revealing new information about their patterns of distribution. The study revealed that these DNA modifications play major roles in fundamental life processes such as cell differentiation, cancer and brain function.



The results are published in the May 17 issue of the journal ***Cell***.

Pioneering discoveries

iTeos, a spin-off company of the Ludwig Institute and the de Duve Institute at the Université catholique de Louvain, debuted on May 3 to focus on cancer immunotherapy. The Belgium-based company is the ninth company to be formed based on innovative cancer research discoveries licensed from the Institute. It is developing preclinical small molecule immunomodulators that it hopes to combine with existing cancer vaccines initially in pancreatic, lung and colorectal cancers.

"Immunotherapy—boosting the body's natural immune system to fight

cancerous tumors—is the next frontier in life-extending cancer treatment," said Benoît Van den Eynde, a researcher at Ludwig Brussels and cofounder of iTeos. "Effective immunotherapy treatments enable the body's immune system to 're-engage' in destroying tumor cells, thereby potentially creating better patient outcomes with fewer side effects when compared to conventional cancer treatments."

Partners in science

For 60 years, the Brazilian Development Bank (BNDES) has played a fundamental role in stimulating the expansion of industry and infrastructure in Brazil. In July, BNDES announced US$14.8 million in financial support for Recepta, the country's first oncology biotechnology company.

Founded in 2006 as a joint partnership between the Ludwig Institute and Brazilian investors, Recepta develops monoclonal antibodies, proteins produced in a laboratory that can recognize cancer cells and trigger an immune response to destroy them. Recepta has licensed four antibodies from the Institute.

"LICR applauds BNDES' investment in Recepta," said Jonathan Skipper who leads Ludwig's technology development program. "There are tremendous clinical research opportunities in Brazil. It is a country with many talented laboratory and clinical researchers translating science into new therapies that will reach patients."

In March of this year, the U.S. Food and Drug Administration (FDA) granted orphan drug status to Recepta's lead biologics candidate, ReMab 100, for the treatment of ovarian tumors.

The candidate is currently in phase 2 clinical trials. Orphan status is granted to drugs and biologics that treat rare medical conditions affecting a small patient population. It is the first time that the FDA has granted such status to a Brazilian company.

Scientists who lunch

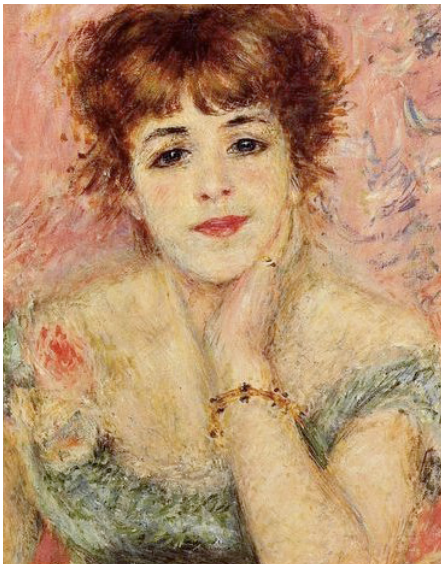
Chromosomes and DNA were on the menu.

At the 15th Annual Women & Science Spring Lecture and Luncheon, Titia de Lange, one of the Institute's Scientific Advisory Committee members, gave a lecture on chromosomes and DNA.

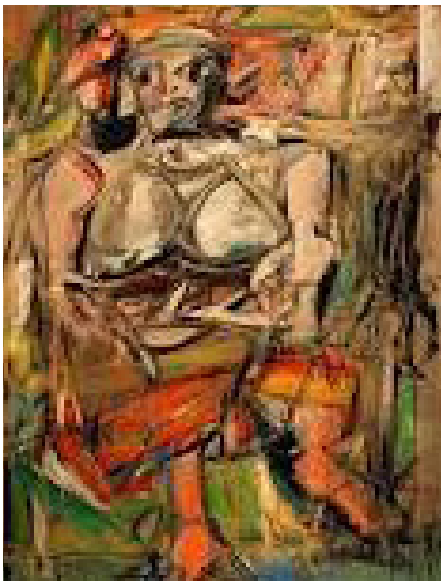
She compared a normal genome to a beautiful Renoir portrait, and argued that the ugliness of a cancer genome could be represented by the distortions of a Willem de Kooning painting.

Titia, the Leon Hess Professor at Rockefeller University, is a world leader in the study of telomeres and their role in cancer. Telomeres have been compared with the plastic tips on shoelaces because they prevent chromosome ends from fraying and sticking to each other, which would scramble an organism's genetic information to cause cancer, other diseases or death. Insights from her work could yield new approaches to cancer diagnosis and treatment.

Women & Science was established in 1997 to encourage leading women in the philanthropic and business circles of New York to embrace science as an interest and philanthropic pursuit. Its purpose is to showcase female scientists and provide a way for women to support those scientists directly.



Jeanne Samary by Pierre-Auguste Renoir, 1877



Woman I by Willem de Kooning, 1950–1952

REQUIRED READING

San Diego

Nature 2012 Apr 11.
Topological domains in mammalian genomes identified by analysis of chromatin interactions
Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B.

Nature 2012 Apr 8.
An inverse relationship to germline transcription defines centromeric chromatin in C. elegans
Gassmann R*, Rechtsteiner A*, Yuen KW*, Muroyama A, Egelhofer T, Gaydos L, Barron F, Maddox P, Essex A, Monen J, Ercan S, Lieb JD, Oegema K, Strome S, Desai A.

Cell 2012 May 17.
Base-resolution analysis of 5-hydroxymethylcytosine in the mammalian genome
Yu M*, Hon GC*, Szulwach KE*, Song CX, Zhang L, Kim A, Li X, Dai Q, Shen Y, Park B, Min JH, Jin P, Ren B, He C.

**These authors contributed equally to this work.*

Q&A WITH MANJULA DONEPUDI

Senior Manager, Intellectual Property

Most people recognize the term intellectual property, but what exactly does it mean?

It is imagination made real. It is unique. It is Coca-Cola, Lipitor, Spiderman, Netflix.

Intellectual property or IP is an umbrella term referring to commercially valuable creations of the mind. These creations include inventions, artwork, symbols, names and designs. IP protection options include copyrights, trademarks and patents. The appropriate option depends on the work itself. For example, the Institute is mainly concerned with patents which may protect new technological innovations arising from its research.

Ludwig's researchers are potential creators of intellectual property. The rewards provided by the patent system encourage the investment required to test and develop discoveries, producing better and more effective products for consumers.

How did you become interested in this particular field?

Michael Jackson's anti-gravity shoes. Seriously, IP is very exciting. Innovative and creative ideas are at the heart of most successful businesses. Ideas by themselves, however, have little value. They need to be developed, turned into novel products or services and commercialized successfully to reap the benefits of innovation and creativity. In the case of Michael Jackson, music entertainers and dancers are constantly searching for new and interesting elements that can be incorporated into their performances. A patent for his invention gave him an edge in his music videos that made him unique.

A number of celebrities have gone beyond their job description and come up with some truly unique innovations or inventions. Besides Michael Jackson's famous shoes, Walt Disney, Marlon Brando, Steve McQueen, Van Halen and Prince hold patents for some really cool inventions. Intellectual property patents were crucial for turning these innovative ideas and inventions into economic powerhouses. Consider the Walt Disney Company. Founded in 1923, it has evolved into a global leader in family entertainment. This feat wouldn't be possible without patents, trademarks and copyrights.

When I was doing my post doc at MSKCC, I had a lot of interaction with the Office of Technology Transfer, which was responsible for identifying research with potential commercial interest. I learned about the different stages of commercializing a scientific discovery and what it means to take something 'from the bench to the bedside.'

Why is IP important?

Think of IP as a 'power tool' for economic growth. In 2011, the value of intellectual capital in the U.S. economy was estimated at approximately US $8.1 trillion to $9.2 trillion.

U.S. President Barack Obama summed it up best in a speech last year: "We're going to aggressively protect our intellectual property. Our single greatest asset is the innovation and the ingenuity and creativity of the American people."

The patent system remains a powerful innovation engine for economies around the world. Patents are intended to better society in the long run by motivating companies and individuals to innovate; after the patent expires, society will have free access to the technology. Technologies and creations that have changed millions of lives would probably not exist today if

inventors were not given patent protection as an incentive to create things that spur economic growth. Patent protection spurred the development of products and services we couldn't imagine living without—Facebook, microwaves, Google, cell phones, Amazon, smoke detectors.

Why does the Institute patent its intellectual property?

It's critical to our mission. We're committed to what we call translating or advancing our research into experimental cancer therapies to benefit patients. The Institute patents its intellectual property to ensure that Ludwig discoveries have a chance to make their way through testing and attract interest from commercial partners willing to invest in the successful development of these discoveries. Their returns allow us to fund further research. Without patent protection, investment in the development of technological innovation would not be forthcoming, and it's very unlikely that an innovation would ever make its way to patients.

Can you give a description of your typical work day?

Every day is different. We deal with issues related to science, business and law. An investigator might call to let us know that she has a paper on a new discovery ready, or she's going to give a presentation or poster session. Publication is essential for Institute scientists and must not be impeded, but a patent is only valid if filed before public disclosure of the patented invention. Therefore, we need to act fast to review the proposed disclosure to determine if there's something that might be commercially useful. If it is and there's something new that requires patenting, we research other potential uses to ensure the new discovery is broadly protected.

To drive innovation, patents must be used and we seek to license them to a commercial entity that will invest the resources to translate and move it into the clinic. An example is Ludwig's MAGE-A3, a tumor-specific antigen expressed in a variety of cancers that was in-licensed to GlaxoSmithKline for further development. The company is in the midst of phase 3 trials testing its vaccine candidate against metastatic melanoma (DERMA study) and non-small cell lung cancer (MAGRIT study). Clinical design details of the studies that will ultimately involve thousands of patients were reported at the 2011 meeting of ASCO (American Society of Clinical Oncology).

IP is exciting because we're privy to cutting-edge science and our work has a direct impact on making a discovery available to ultimately benefit patients. An ongoing challenge is making an assessment of the true scale and importance of new discoveries and subsequently moving the research from the laboratory into practice. At the end of the day, knowing that we are contributing to the scientific mission of the Institute and that Ludwig scientists get the best out of their discoveries is the ultimate reward.

You have a Ph.D. in biochemistry from the University of Illinois. As a graduate student, did you ever seriously consider another career?

No. Science hooked me at a young age. My father was a chemist and I loved spending Saturdays in the lab with him. A chemistry lab is a very cool place for a kid. He had a unique talent for putting a 'human touch' on chemistry, showing me why helium balloons float, salt melts ice and every snowflake is unique.

When not working, what do you do?

I have two young children who keep me pretty busy. When I'm not spending time with them I'm at my neighborhood yoga studio trying to advance my yoga practice. I've also started to learn Spanish.

Is there anything else you'd like to share with the readers?

I'm a classically trained singer and dancer and studied the flute. My sister and I performed professionally and had a half-hour radio segment on All India Radio. It's pretty heady stuff when you're young. We became well known in the Indian community in Canada and the U.S., which led to a two year gig in college hosting a TV show called Sounds of India. A future dream is to channel my inner coffeehouse chanteuse, learn to play the guitar and sing in small cafés.

Click below for a couple of Manjula's song bites:

LUDWIG AROUND THE WORLD

Still hopelessly devoted

Almost two decades ago, actor and singer Olivia Newton-John overcame a battle with breast cancer, and today she is an inspiration to millions of people battling the disease. She tirelessly promotes the importance of early detection. Her personal triumph over cancer led to her partnership with Austin Health and the creation of the Olivia Newton-John Cancer and Wellness Centre on the Austin campus in her hometown of Melbourne, Australia, where the Institute's Melbourne-Austin Branch has just moved.

On June 22, Newton-John attended the opening ceremony of the first stage of the A$189 million center. She had been working on the project since 2003. "I am so excited to finally share with you the realization of a dream that began 20 years ago with my own cancer journey. It is humbling to know that so many of you have cared so much and shared my vision," said Newton-John during her remarks. The facility brings together three elements: the research of the Ludwig Institute, cancer services provided by Austin Health and a focus on wellness to ease the stress and side effects of cancer treatment. The remaining research facilities, inpatient wards and palliative care unit will open in mid 2013.

Ludwig has been actively engaged in research in Australia for 35 of its 41-years in existence, and has invested over A$250 million of its own resources in the scientific base of the country. "We extend a special salute to the Victorian government and the planners for their foresight in incorporating a state-of-the-art laboratory within the Olivia Newton-John Cancer and Wellness Centre and making it available to the Institute," said Ed McDermott, Ludwig president and CEO, during the opening day ceremonies. "New laboratories will provide fantastic facilities for Ludwig researchers in the Melbourne-Austin Branch, permitting us to expand our research activities and enhancing our ability to attract and recruit top-flight scientists," said Andrew Scott, Ludwig Melbourne-Austin.

The new Ludwig lab at the Olivia Newton-John Cancer and Wellness Centre

From left: Ed McDermott, Andrew Scott, Andy Simpson at the new Branch location

On the threshold of something big

In 1921, a group of Syrian and Lebanese immigrant women founded the Ladies' Beneficent Society with the goal of building a hospital to provide quality medical care to the residents of São Paulo, Brazil. Less than a decade shy of its centennial, the Hospital Sírio-Libanês (HSL) has made a name for itself, not only in Brazil but throughout Latin America, as a center of excellence for cancer research and treatment.

On April 13 and 14, HSL hosted the Intersections First International Cooperative Cancer Symposium in São Paulo to celebrate a new strategic partnership with the Ludwig Institute and Memorial Sloan-Kettering Cancer Center and the opening of a new Molecular Oncology Center led by Ludwig scientist Anamaria Camargo. The two-day event brought together leading oncologists from Brazil and around the world to celebrate the opening and share their research. The newly established center will be jointly funded by Ludwig and HSL. It combines Ludwig experience in cancer genomics research and new drug development with the clinical oncology excellence of HSL.

The assembly of cancer experts presented work on personalized medicine, targeted therapy and translational research, with glimpses of how these topics will affect current and future cancer treatment and prevention.

MEETING NOTES

We are family

A strong community is a critical component of scientific success. Collaborating across disciplines and institutions, sharing resources and data, and integrating findings and insights are keys to successful research and discoveries. In an ongoing commitment to fostering a collaborative network, the Ludwig community came together in May for a stem cell meeting hosted by the Ludwig Trust Center at Stanford University. It was attended by more than 50 Ludwig researchers from around the world who study various aspects of cancer development and cellular heterogeneity.

"The meeting was a huge opportunity to engage and build a much more interactive community. One of Ludwig's goals is to find ways of bringing people together to share information, improve communications and extend Ludwig researchers' networks through collaborations," said Bob Strausberg who oversees Ludwig's collaborative sciences program.

Today, collaboration helps expand scientific reach, allowing researchers to tap into resources for new, innovative approaches to research problems, technologies, reagents and ideas. Scientific research has become increasingly complex, and Ludwig can facilitate collaborations with its resources—its network of leading scientists and focus on technology development, with expertise in clinical trials management, antibody and small molecule development and in-house intellectual property experts.

"To make the Ludwig community vibrant, we need to meet periodically in order to share ideas, explore alternative directions in research and identify new uses of technology," said Andy Simpson, Ludwig's scientific director. "I've found that the most productive interactions are the ones you can't predict."

Did you know ...

Bob Marley, legendary Jamaican singer, songwriter and guitarist died at the age of 36.

From metastatic melanoma.

Across the globe, more than 46,000 people will die from melanoma this year and 200,000 will be diagnosed with the disease.

Two internationally renowned Ludwig scientists who work in this field were recognized this spring by the Melanoma Research Alliance.

Cebon

Jonathan Cebon received an Established Investigators Award and research grant in April and Jedd Wolchok was honored at the inaugural Leveraged Finance Fights Melanoma benefit in May at Bryant Park Café in New York. Funds raised at the event go to raise awareness about melanoma.

Wolchok