7
Stories of Discovery and Impact
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A memorable year

The human papillomavirus or HPV is best known as a cause of cervical cancer in women. Transformative research from the Ludwig Institute for Cancer Research demonstrated that the virus also exhibits long-term, but usually asymptomatic, infection in men. This discovery ultimately helped lead to a recommendation in 2011 that to prevent HPV-caused cancer, men as well as women in the US should be vaccinated.

The entire oncology community welcomed last year’s approval of ipilimumab (marketed as Yervoy) to treat melanoma, the most deadly form of skin cancer. Ludwig research in 2011 has set the stage for clinical trials combining ipilimumab with a vaccine to extend its efficacy.

These are just two of the stories highlighted in this year’s report. We are calling it Seven Stories of Discovery and Impact. Discovery: supporting top-flight scientists around the world with sustained resources and a collaborative culture to enable them to undertake high-stakes research that can change the course of cancer. Impact: providing the necessary assistance and expertise to develop these discoveries, test them in humans and, if successful, ensure they make their way to patients.

Discovery and impact go hand in hand here at the Ludwig Institute for Cancer Research. We couldn’t achieve these results without our tremendous talent. Talent has always defined Ludwig. Our scientists are pioneers who have influenced the direction of research by challenging accepted paradigms and taking their ideas from concept all the way through to treatment.

This collection of stories is a testament to Ludwig science. Each represents the culmination of years of persistent study and incisive experimentation. We are very proud of all this work. After reading this report, we hope you feel our pride is justified.

We are grateful for the generosity of our founder, Daniel K. Ludwig, who endowed the Ludwig Institute 40 years ago, as well as for the support from the governmental, institutional and philanthropic donors who believe in what we do.

Edward A. McDermott, Jr.
President and CEO

Andrew J.G. Simpson
Scientific Director
Tribute to Dr. Lloyd Old

Lloyd Old was just 24 when he wrote down three questions that have since altered the course of cancer research:

**Is there an immune reaction to cancer?**
**If there is, what are the targets?**
**How can you stimulate that immunity?**

These are hugely complicated questions, but in research spanning more than 50 years Dr. Old made seminal discoveries about the relationship between cancer and the immune system. He promoted the development of vaccines that use the body’s ability to fight disease, becoming the acknowledged father of modern tumor immunology. Dr. Lloyd Old died November 28, 2011.

Dr. Old was appointed scientific director and CEO of the Ludwig Institute in 1988 and functioned in those capacities until he stepped down in 2005 to serve as chairman of the Board of Directors, a position he held until 2009.

*In vivo veritas,* Dr. Old’s motto, embodied what many would consider his greatest contribution—his unwavering dedication and commitment to translating basic research in animal models into clinical research in humans. Few scientists have been more instrumental in bringing the study of tumor immunology into the human arena, which in the end is the only arena that really counts.

He was a rare leader who cared as much about the people he worked with as he did for the work itself. Underpinning it all was his abiding concern for those who might benefit from his research—individuals living with cancer.
DIFFERENCE
1
On the trail of a cancer virus
On the trail of a cancer virus

Research on HPV in men leads to a change in US public health policy.

PHOTOS
From left
Luisa Villa
São Paulo, Brazil
Ricardo Brentani
1937–2011
When the US government recommended last November that all boys receive the human papillomavirus (HPV) vaccine to prevent certain types of cancers, Luisa Villa, a Ludwig scientist in São Paulo, Brazil, was not surprised.

Her work helped lead to the decision announced by the US Centers for Disease Control, which guides medical practice across the country. That announcement came as results emerged from an ongoing study she and colleagues at the Moffitt Cancer Center in Tampa, Florida, initiated in 2005, the HPV in Men (HIM) study. In the study, approximately 4,300 men from Mexico, the United States and Brazil are being monitored for infection with HPV.

HPV is best known as a cause of cervical cancer in women. And a vaccine, which Villa also helped evaluate, has been available for girls and women since 2006. But the virus is also associated with penile, oral, head and neck, and anal cancers, which afflict men. Such HPV-associated cancers affect 7,500 men each year in the United States alone.

Until recently, researchers had only a rough idea how prevalent the virus was among men. The HIM study was designed to address this issue. Last February, Villa, who coordinates the Brazilian arm of the study, and her colleagues revealed in The Lancet that about 70 percent of men in the HIM study have the virus—a number in accordance with previous, smaller studies. What’s more, the most oncogenic infections take a while to clear from the body—about 12 to 19 months for infections with HPV16, the strain most commonly associated with cancer.

Those numbers mean that a high proportion of men are at risk for HPV-associated cancer, and that many are probably passing the virus back to their sexual partners. These numbers—along with studies from other groups—helped convince the Centers for Disease Control that vaccinating boys would put a dent in cancer incidence in males, and help prevent transmission of HPV to females.

“We now have a better view of how males are also susceptible to transmission and infection with HPV,” says Villa.

**Counteracting cervical cancer**

Villa’s current work has roots in an HPV program that was established in the early 1980s, when she first joined the Ludwig Institute based in São Paulo.

“Back then we were only just beginning to find some of these viruses in tumors,” she says. Her mentor, Ricardo Brentani, who directed Ludwig’s research efforts in São Paulo from its inception in 1983 to 2005, had just returned from a meeting with his friend Harald zur Hausen, who later won the Nobel Prize for discovering the role of HPV in cervical cancer.

“After his conversation with zur Hausen, Brentani said, ‘Why don’t you look at this; it might be something interesting,’” recalls Villa. “This was the start of a long process.”
Brazil has an especially high incidence of cervical cancer. And, as Villa and her colleagues later discovered, HPV infection rates are also high in the country. This has made the program at São Paulo a hub for studying HPV transmission and testing vaccines.

In the 1990s Villa and colleagues at McGill University in Montreal recruited about 2,500 women for a study that led to a series of groundbreaking findings about HPV biology. For instance, they found out why only some women develop cancer, often years after first contact with the virus. Most women fight off the virus successfully, the researchers found. In a few individuals, however, the infection persists, particularly with high-risk HPV strains, and ultimately increases risk for development of premalignant lesions in the cervix that eventually lead to cancer.

Villa also partnered with Merck to show, in a pivotal 2005 study, that the drug company's HPV vaccine was safe and effective. This work paved the way for eventual approval of the vaccine to combat cervical cancer. More than 530,000 women were diagnosed with cervical cancer worldwide and 275,000 died from the disease in 2008, the year zur Hausen won the Nobel Prize for his work with HPV.

Villa’s work to combat HPV has earned her a reputation as an exacting scientist who has had a significant impact on public health. “Villa’s work was of particular importance for Central and South America, where cervical cancer is still highly prevalent. Her work has been instrumental in providing data crucial to the design, development and approval of vaccines against HPV,” says Harald zur Hausen.
In the coming years Villa and her colleagues will continue to assess the impact of HPV in men, as data from the HIM study continue to emerge. In 2011, results from the HIM study included an analysis of HPV types most associated with genital warts and oral cancer, and an analysis of the association of HPV with number of sexual partners.

In addition to running large human studies, Villa leads an active research program in the molecular biology of HPV infection. She is examining questions such as why infection leads to cancer in some individuals but not others—do susceptible people produce certain molecules in response to infection, and is there something special about their genetic makeup? Do some variants of the virus cause cancer more often than others?

Villa credits the success of her HPV program to the support of Brentani, who passed away last year, seven years after Villa took over his position to lead Ludwig’s research efforts in São Paulo. Villa also credits the long-term vision of the Ludwig Institute, which provided funding through lean years when results were few and far between. “We have always had the infrastructure to run the large projects needed in a very competitive way,” she says.

REFERENCE
INITIATIVE
A scientific community goes after melanoma
Through Ludwig’s community approach, pieces of the melanoma puzzle are being assembled to reveal previously hidden molecular secrets of the disease.
Donata Rimoldi, like most scientists, works within a neighborhood community. Her home base is with a group of Ludwig researchers at the University of Lausanne, but she also works with researchers at neighboring institutions such as the Swiss Institute of Bioinformatics, in the same city, and the University of Geneva, about 40 miles west along Lake Geneva. As the technology needed to do cutting-edge science evolves and becomes more complicated, a community approach is sometimes the only way to accomplish major scientific objectives.

Scientists in Rimoldi’s neighborhood have formed a team to dissect the genetic basis of melanoma, a deadly skin cancer which in 2008 affected almost 200,000 people worldwide, claiming more than 46,000 lives. She and her colleagues undertook a large-scale analysis of the DNA mutations found in melanoma, and showed that mutations in genes called $MAP2K1$ and $MAP2K2$ (mitogen-activated protein kinase) can drive growth of some tumors. The findings were published in December in *Nature Genetics*.

The project characterizes the Ludwig model for cancer research. Ludwig’s scientists span the globe, converging in places like Lausanne. Ludwig researchers can set up collaborations in almost any scientific neighborhood in the world, leveraging resources and expertise that may not be available at a single institution.

“The global, collaborative aspect of the Institute distinguishes us from many other research institutes,” says Bob Strausberg, who directs Ludwig’s collaborative sciences program.

Where it is needed, the Ludwig Institute can provide an extra push to make projects come alive. The Institute, in this instance, provided targeted funding to support the DNA sequencing that underpins the new findings of Rimoldi and her colleagues.

**Into the genome**

The project began in 2008 with a conversation among genetics researchers at the University of Geneva and Rimoldi and her colleagues in Lausanne.

The Lausanne researchers had stored and cataloged hundreds of melanomas removed from patients over the previous decade. The researchers in Geneva had just installed new state-of-the-art DNA sequencing machines in their labs. Maybe the two groups could collaborate on sequencing melanoma tumors?

“All of a sudden our samples became very precious,” says Rimoldi. “All the previous activity at Ludwig since the 1990s, collecting and cataloging the samples, made this project possible.”

Three years later the group emerged with a comprehensive view of the mutations behind melanoma. Like other researchers before them, the group observed that most melanomas harbor mutations in a key gene, $BRAF$, which transmits molecular signals within cells.
The researchers also observed mutations in additional genes that may drive development of this cancer. These included the genes MAP2K1 and MAP2K2, which operate in concert with BRAF. MAP2K1 and MAP2K2 are mutated in about 8 percent of melanomas, according to the researchers’ analysis of 127 tumors. Moreover, these mutations also seem to drive cancer. For instance, cells with artificially mutated MAP2K1 and MAP2K2 proliferated, much like tumor cells, in a petri dish. The findings suggest that developing drugs targeting melanomas with these MAP2K1 and MAP2K2 mutations could help quell the disease.

Only four months before Rimoldi and her colleagues published their findings, a drug that targets the BRAF protein, called vemurafenib (marketed as Zelboraf), was approved by the US Food and Drug Administration. This drug can dramatically shrink tumors containing BRAF mutations, but unfortunately patients quickly become resistant to the drug and the tumor almost invariably returns. The new findings provide hope for a solution to this problem: drugs targeting the mutated MAP2K1 and MAP2K2 proteins might be used in combination with Zelboraf to help prevent drug resistance and re-emergence of the tumor.

“I appreciated the depths of expertise of my colleagues in areas that I was less familiar with,” says Rimoldi, whose background is in cell biology. “This project could not have come to this conclusion if we had not had all the different parts working together.”

Next steps
Rimoldi’s group is currently collaborating with others in the Ludwig community as part of an initiative focused on melanoma. The initiative is led by Colin Goding in Oxford and Jonathan Cebon in Melbourne, Australia. Based on Rimoldi’s initial results, this community, with Ludwig researchers in Oxford, Brussels, Melbourne, New York and Baltimore, is using advanced sequencing technologies to identify other types of drivers of melanoma. Cebon, for instance, is examining slow-growing tumor cells that are resistant to conventional treatment. These cells may help seed growth of tumors.

Through this community approach, pieces of the melanoma puzzle are being assembled to reveal previously hidden molecular secrets of the disease. The Ludwig Institute is well positioned to apply newly gained knowledge toward improved patient care, such as through clinical studies led by Cebon and Jedd Wolchok in New York (see page 18). The opportunity to perform outstanding discovery science and improve patient care throughout the world is the bond that connects researchers who are part of this initiative.
“The previous activity at Ludwig since the 1990s, collecting and cataloging the samples, made this project possible,” says Donata Rimoldi.

A community approach is sometimes the only way to accomplish major scientific objectives.
CATALYST
3

Putting power into cancer vaccines
Building on their pioneering work in immunotherapy, Ludwig researchers are testing new approaches around the world.
The Ludwig Institute for Cancer Research has long been on the forefront of research harnessing the immune system to fight cancer. Its researchers were there in the infancy of the field, when the first experimental cancer vaccines were developed and cytokines such as tumor necrosis factor were discovered. And they continue their work today in basic research laboratories and in more than 30 ongoing clinical trials to globally hone and test various approaches in people.

Studies underway around the world exemplify the multipronged approach of the Institute. In the clinic, for example, Ludwig scientists are combining vaccines with other agents such as drugs that target the immune system. In fact, Ludwig research in 2011 on a newly approved immune-targeting drug, ipilimumab (marketed as Yervoy), has paved the way for clinical trials combining the drug with a vaccine.

**Historical breakthrough**
The new findings build on decades of work by the Institute. In 1991, Ludwig researchers in Brussels published a groundbreaking study in *Science* on tumor antigens, which are cancer-derived molecules that can be targeted by the immune system, directing its destructive power toward a tumor. They found that white blood cells known as cytotoxic T cells can selectively recognize tumor antigens.

“Before this study very few people believed tumor antigens existed,” recalls Benoît Van den Eynde, a Ludwig researcher in Brussels. “This work opened up ways to use tumor antigens to stimulate the immune system to better fight cancer cells.”

Researchers began formulating vaccines based on the newly discovered antigen, known as MAGE, with the idea of stimulating the immune system to attack tumors that express the antigen. The first human trials to test a MAGE vaccine began in the mid 1990s, and showed that the vaccine was safe and induced tumor regression in some patients. Ludwig has since licensed the commercial rights to develop vaccines using MAGE and related tumor antigens to GlaxoSmithKline. The drug company is conducting two large clinical trials in patients with lung cancer and melanoma based on the MAGE-A3 tumor antigen. The vaccine being tested, MAGE-A3.ASCI (antigen-specific cancer immunotherapeutic), has an extra kick because of the addition of an adjuvant, an immune-stimulating substance.

Since the discovery of MAGE, the field has moved forward rapidly. Scientists have discovered many other tumor antigens that are made by a variety of cancers. And they are testing a range of approaches to boost the power of vaccines, such as combining multiple tumor antigens in a single shot, treating patients simultaneously with drugs that target the immune system, and adding adjuvants to the mix.

Ludwig researchers in New York at Memorial Sloan-Kettering Cancer Center are using this multipronged attack in studies of melanoma and ovarian cancer. One of their most recent projects leverages ipilimumab, a drug that shrinks tumors and prolongs the lives of people with melanoma. It was approved in 2011 by the US Food and Drug Administration as the first drug for advanced melanoma in over ten years.
Putting it all together

Ipilimumab is directed against a molecule on immune cells, and seems to act by amplifying the body's existing immune response to melanoma—but it is only effective in some patients.

"Why do some patients have such profound benefit and why do others not respond?" asks Jedd Wolchok in New York, one of many researchers involved in developing and testing the drug. Answering that question is leading the researchers to new ways of making more powerful cancer vaccines.

Last year, Wolchok and his colleagues, including Sacha Gnjatic, another Ludwig scientist in New York, examined the immune response of melanoma patients treated with ipilimumab. They focused on the immune response to NY-ESO-1, another tumor antigen discovered by Ludwig researchers, which is present in 30 to 40 percent of advanced melanomas.

Ludwig researchers found that the likelihood of individuals responding to treatment with ipilimumab depends on the status of their immune system. They learned that patients were nearly twice as likely to benefit from treatment with the drug if their immune system was active against NY-ESO-1. The findings, published in Proceedings of the National Academy of Sciences in October, suggest that an approach combining ipilimumab with a complementary immunotherapy, such as a NY-ESO-1 vaccine, could be powerful. In principle, ipilimumab would boost the immune response, and the vaccine would direct the ramped-up immune system to destroy cancer cells. The study provides experimental support for combination therapies.

The researchers are now laying plans for just such an approach, testing patients with late-stage melanoma with ipilimumab in combination with a NY-ESO-1 vaccine. The vaccine itself will also be superpowered with the addition of adjuvants. Prior research has shown that adding adjuvants to a NY-ESO-1 vaccine can bump up the immune response.

"We are building combinations of therapies," says Wolchok, "to generate tumor regression that has durability."

REFERENCES

Together, Ludwig and CRI formed the Cancer Vaccine Collaborative, which since 2001 has served as a springboard for clinical studies to advance Ludwig’s tumor immunology research.

This collaboration continues to evolve in innovative ways as scientific research advances and the landscape of drug development changes. In December 2010, Ludwig and CRI extended their partnership by creating a new nonprofit venture fund that was established at CRI to raise monies from external donors to support the costs of the clinical investigations undertaken by this initiative.

The fund works with partners in industry to access novel immune therapy agents for evaluation in clinical trials. And it is already speeding up progress toward the development of new cancer immunotherapies. In 2011 the fund partnered with Washington, DC-based Oncovir to secure access to a supply of an adjuvant for use in clinical trials.

“Through these partnerships the fund is catalyzing the pace of drug development,” says Jedd Wolchok, head of the CVC and a Ludwig researcher in New York.

Wolchok took the helm of the CVC last year, just before the death of its founder and prior director Lloyd Old, who had also served as scientific director of the Ludwig Institute from 1988 until 2005.

“The CVC was Dr. Old’s brainchild,” says Jonathan Cebon, a Ludwig researcher and longtime CVC member based in Melbourne, Australia. “He felt that there needed to be a very interconnected group of people who were devoted to the advancement of immunotherapy.”
TEAMWORK
Fostering connections across the globe
“We bring together people from all corners of the world to interact, talk and plan,” says Bob Strausberg.
To bring together its researchers from across the globe, the Ludwig Institute sponsors frequent meetings, nurturing scientific relationships that sustain its global approach to cancer research.

“We foster an open conversation,” says Bob Strausberg, who leads Ludwig’s collaborative sciences program. “We bring together people from all corners of the world to interact, talk and plan.”

The biggest meeting in 2011 brought together about 40 researchers in Oxford to discuss the basic mechanisms of cancer biology. After two intense days of talks, discussions and late evenings, new research projects were born.

“I walked away with a document with all the different possibilities of collaborations that I could embark on through that meeting,” says Frank Furnari, a Ludwig researcher in San Diego who studies the molecular basis of glioblastoma, an aggressive type of brain cancer. “Everyone was very willing to share reagents and ideas, because it was our fellow Ludwig Institute members. It was one of the best meetings I have been to.”

Furnari is now using laboratory techniques guided by Ludwig scientists in Oxford to study protein phosphorylation, and is sending cell samples to colleagues in Brussels who are experts at detecting a protein associated with cancer. He has also since sponsored cancer geneticist Érico Costa, from São Paulo, Brazil, in his lab. Even though Furnari focuses on glioblastoma and Costa on breast cancer, they are asking the same question: how do cancer cells communicate to foster growth and metastasis?
The Ludwig Institute typically sponsors one large meeting on a major topic such as cancer biology each year. In 2012, the large meeting focused on cancer stem cells, and took place at Stanford University in Palo Alto, California. The meeting was organized by Irving Weissman, a Ludwig researcher at Stanford. Weissman pioneered studies identifying rare, seemingly unobtrusive cells that can seed the growth of a tumor—now known as cancer stem cells. The meeting aimed to identify promising approaches to prevent stem cells from generating new tumors.

The Institute also regularly sponsors meetings that bring together researchers working on a particular type of cancer or a more defined area of science. Big ideas and projects can also emerge from these smaller meetings. At one such meeting, focused on colon cancer, a major Ludwig initiative was sparked in October 2010 between Bert Vogelstein, a Ludwig researcher at Johns Hopkins University in Baltimore, and a Ludwig clinical researcher, Peter Gibbs, in Melbourne, Australia. Their interactions led to a project that merges basic science and clinical expertise to identify new ways to detect cancer in its earliest stages (see page 43).

“There are not many meetings like that outside of Ludwig,” says Vogelstein. “Ludwig fosters a very personal kind of meeting, where we are encouraged to think big about how we can pool our expertise to do something adventurous that has not been done before.”

No boundaries

To foster interactions among its 700 researchers worldwide, the Ludwig Institute brought on Bob Strausberg in 2009 to oversee its collaborative sciences program.

Strausberg has a long history of setting up international collaborations. In the 1990s, he worked at the US National Institutes of Health to lead the sequencing technology development program for the Human Genome Project, an international endeavor that required close coordination of laboratories worldwide.

Setting up the meetings that help connect Ludwig scientists each year is just one part of Strausberg’s job. Last year he visited with researchers worldwide to find out what they do, what they are thinking about and with whom they might collaborate. His expertise is establishing, facilitating and leading projects with large scientific goals.

Strausberg also connects Ludwig scientists with outside researchers and institutions, and fosters collaborative scientific opportunities, so as to accelerate Ludwig’s research into early cancer detection and prevention.

“We are willing to put in resources to support collaboration,” says Strausberg. “We back up our researchers.”
“Everyone was very willing to share reagents and ideas, because it was our fellow Ludwig Institute members,” says Frank Furnari.

“Ludwig fosters a very personal kind of meeting, where we are encouraged to think big about how we can pool our expertise to do something adventurous that has not been done before,” says Bert Vogelstein.
UNDERSTANDING
5

The cancer machine
The Ludwig Institute understands that basic research sets the stage for big breakthroughs.
The origins of cancer lie in altered DNA. A tumor typically begins when a single cell in the body loses control and its DNA becomes mutated or altered just enough to set off a tailspin of uncontrolled cell division. The damage accumulates—chromosomes snap, some genes break and other genes ramp up their activity—and the tumor expands.

Few researchers understand the connection between DNA damage and cancer as well as Richard Kolodner, a Ludwig scientist in San Diego.

Several years ago, Kolodner’s group homed in on a set of proteins that help keep DNA intact. These proteins repair certain types of DNA damage, dubbed mismatches. Mismatches can arise when DNA is duplicated during cell division—such as when a cell mistakenly adds an “A” when it should add a “T” to a growing DNA strand. Mutations can result if the damage is not repaired correctly. The repair system, called DNA mismatch repair, is essential for fending off cancer. When this system breaks down, cells can tip toward becoming cancerous.

Kolodner’s research showed in 1993 that defects in mismatch repair underlie a common type of inherited cancer, Lynch syndrome, also called hereditary nonpolyposis colorectal cancer. People with this condition are at extremely high risk of developing a variety of cancers, from colorectal to endometrial cancer. He’s also found that defects in the mismatch repair system often arise in sporadic or noninherited tumors, leading to DNA damage that drives the development of these cancers.
“Drawing a connection between DNA mismatch repair and cancer was a big surprise at the time,” says Kolodner. He explains that researchers had suspected that DNA repair defects might be involved in cancer, but they did not expect the defects would have such a big impact, underlying common forms of cancer and a prevalent form of inherited cancer susceptibility.

Despite its central role in cancer, little is known about how the mismatch repair machinery operates. Kolodner asks, “How do the repair proteins find the error they have to fix? How do they access DNA, which is compacted into a tight structure in the cell?”

In two major studies last year, Kolodner’s group began to answer such questions with research that took a close look at the guts of the repair machine. The interactions among the proteins, like the parts of any machine, are intricate. But the findings boil down to this: certain proteins involved in DNA mismatch repair are associated with DNA as it replicates. That means the proteins are in the right place to find mispaired bases in the DNA as they arise, when the DNA loses its compact structure during replication. “The machinery is there at the right place at the right time,” says Kolodner.

To show this, the researchers genetically tinkered with the machinery in yeast cells, which have a similar repair mechanism to that in people, but are more amenable to experimentation. They attached the repair proteins to fluorescent molecules that glowed when examined under a microscope.

In Cell, they report that the proteins were associated with DNA during DNA replication. In another study, published in Science, the researchers engineered the proteins so they were produced only at certain times during the cell’s life cycle. With this technique, they found that the proteins could operate only during DNA replication.

The findings tie DNA mismatch repair to DNA replication and pave the way for future experiments. The researchers, for instance, have now purified each of the proteins required for DNA mismatch repair and are busy reconstituting the process in a test tube. They are also examining the broken mismatch repair machinery in cancer cells to see if it works in a way that would respond to correction by a drug.

Kolodner’s group is not the only one at Ludwig focused on the basic mechanisms of DNA repair. In 2011, Thomas Perlmann, a Ludwig scientist based in Stockholm, discovered a key component of another major DNA repair machine. It fixes double-stranded breaks, in which both strands of adjacent DNA break, slicing apart chromosomes—a common occurrence in cancer.

Kolodner is grateful that the Ludwig Institute understands that basic research sets the stage for big breakthroughs. “These are very complex, very difficult experiments that take a long time to do and a really long time to do well,” he says of his work on DNA mismatch repair.

“I always feel I am privileged to be at Ludwig, because they provide me with the resources to do experiments to the standard that is required to get to definitive answers,” Kolodner says.
In 2011, Thomas Perlmann, a Ludwig scientist based in Stockholm, discovered a key component of another major DNA repair machine.

“These are very complex, very difficult experiments that take a long time to do and a really long time to do well,” says Richard Kolodner.

REFERENCES


TRANSLATION
6
Crossing the drug development divide
Few basic scientists have the expertise to make a drug-like compound, test it in animals and begin the initial steps toward validating the concept in human studies.
There is a stage in the research process that many basic scientists have trouble crossing. They may understand the intricacies of how a cell behaves or how molecules malfunction during disease, and may be brimming with ideas of how to fix them to generate new treatments. But they can’t get their ideas out the laboratory door. Few have the expertise to make a drug-like compound, test it in animals and begin the initial steps toward validating their concepts in human studies. Good ideas often languish.

That’s where Andy Shiau and his group come in. In 2009 the Ludwig Institute hired Shiau and chemist Tim Gahman, who have extensive experience in commercial drug discovery and development, to help its researchers take their ideas from concept to exploratory treatment. Shiau and Gahman are based in San Diego, where they work with other researchers, from pharmacologists to synthetic chemists. As part of the Hilton Ludwig Cancer Prevention Initiative, the group collaborates with Ludwig scientists to create small molecules that could act like drugs, helps test them in biological assays and in animals, and assesses whether discoveries might be worth turning into treatments. The group’s work also bolsters basic research at the Ludwig Institute, since many of the ideas and reagents it generates are used in the laboratory to help advance scientific findings.

In 2011, their work began to bear fruit. “Last year was great for us,” says Shiau. “We were able to kick some of these projects into high gear.” The researchers tout one early success: developing an agent that may lead to a drug to fight glioblastoma, the most common and most lethal brain cancer in adults. The work began with basic research by scientists at Ludwig who showed that MELK, a protein produced in excess in glioblastomas, helps propel the development of these tumors. Published in 2008, the research indicated that blocking expression of MELK reduces the ability of glioblastoma cells to proliferate and form new cancers. MELK was beginning to look like a good drug target. The next step was to develop an agent that could inhibit its function.

The group’s work also bolsters basic research at the Ludwig Institute, since many of the ideas and reagents they generate are used in the laboratory to help advance scientific findings.
Shiau's group stepped in. Along with Greg Riggins, a Ludwig scientist in Baltimore, the researchers identified a small molecule that shuts down MELK. They have shown that the agent stops the growth of brain tumor cells in a petri dish, setting the stage for testing in animals.

If successful, their research has the potential to lead to tests in people. To get to that stage, Shiau's group has the expertise to craft drugs that will meet the standard for evaluation in human trials by working with in-house experts and outsourcing many other aspects of the work, such as compound synthesis and toxicology studies.

Such drug-development work is often done by pharmaceutical and biotechnology companies. But it would have been hard to get industry interest in the MELK project, given that the science is just emerging, says Web Cavenee, a Ludwig scientist in San Diego. Now Shiau and his collaborators are taking the work to a new level. "Our goal is to do drug discovery that is smart, cost effective and nimble, and in a way that will lead to treatments that will help people," says Cavenee.

Other projects include developing an inhibitor against another cellular molecule, PLK4, which is involved in regulating proper cell division. An inhibitor has the potential to put a wrench in the growth of cancer cells.

Shiau and Cavenee say that the openness of an Institute like Ludwig enables researchers to collaborate effectively on projects like these. The Institute provides opportunities for basic scientists to think about the next step in their research—translating their discoveries to the clinic and ultimately to patients living with cancer.

Says Shiau, "It is sort of this magic blend of ingredients."
“Our goal is to do drug discovery that is smart, cost effective and nimble, and in a way that will lead to treatments that will help people,” says Web Cavenee.

The Institute provides opportunities for basic scientists to think about the next step in their research—translating their discoveries to the clinic and ultimately to patients living with cancer.
CONNECTION
7
Pathway to prevention
Two Ludwig scientists imagine a future in which a blood test could detect signs of early tumors.
When Peter Gibbs finally managed to meet Bert Vogelstein, at a Ludwig-sponsored meeting in October 2010, he did not know how their encounter would go. Still, he knew it was a great opportunity. Although the researchers worked as part of the Ludwig community on different continents, and their research branched out in different directions, they both studied colorectal cancer, the topic of the meeting.

Neither scientist imagined the meeting would spark a collaboration that would draw millions of dollars in funding from outside the Institute, and that could have a major impact on cancer detection and treatment.

Gibbs, a Ludwig scientist in Melbourne, Australia, is a clinician. He sees patients regularly and knows how to run human studies. Vogelstein, a Ludwig scientist based at Johns Hopkins University in Baltimore, is a self-described “lab rat” known for his seminal research discoveries on key cancer genes. In their many years studying cancer, the researchers had never crossed paths.

When Vogelstein gave his presentation at the Ludwig meeting on the Johns Hopkins campus, Gibbs sat up in his seat. Vogelstein’s group was making fast progress on developing a novel technology to detect signs of colon cancer in blood samples, based on measuring the presence of DNA from tumors. Such a biomarker indicates the presence of cancer.

“Putting our clinical and scientific expertise together really works very well. The combination is powerful,” says Peter Gibbs.
Vogelstein also had preliminary results from a small pilot study. In that study, he looked for cancer DNA in the blood of patients who had undergone surgery for advanced metastatic cancer that had spread to the liver. Patients with the highest levels of the biomarker were most likely to experience recurrence. Such information could potentially help doctors make decisions about treatment strategies. But the findings were preliminary, and Vogelstein needed more patients.

Vogelstein explained that his pilot studies, like many done by other researchers, were not enough. The field needs “definitive studies,” he says, that “must show beyond question that the markers are useful for clinicians and can guide treatment decisions.”

Gibbs knew he had what Vogelstein needed—access to hundreds of patients who could be enrolled in prospective protocols, with a structure in place to collect and store their tumor and blood samples for analysis, combined with comprehensive data on their treatment and outcomes. “It became obvious both of us should work together,” says Gibbs.

The research underway is a first step to finding biomarkers that can detect tumors before they develop in the first place. With that goal in mind, the scientists are already designing additional studies to look at DNA biomarkers in earlier stages of colorectal and pancreatic cancer—work that has drawn the financial support of multiple Australian funding bodies and the Conrad N. Hilton Foundation.

Vogelstein and Gibbs imagine a future in which people who have developed early tumors could be flagged by detection of a biomarker in their blood. Then they could be treated with conventional surgery and chemotherapeutic agents, which nearly always cure patients as long as the cancers haven’t widely spread when detected.

“The fundamental idea is that we are not likely to conquer cancer simply by treating advanced cancers, which is what the majority of directed cancer research is now aimed at,” says Vogelstein. “Maybe we can do what has been done with other diseases and rely on prevention and early detection approaches.”

Vogelstein and Gibbs acknowledge that such an approach is many years in the future. But both give credit to Ludwig for enabling them to take steps to make that possibility come alive.

“We would not have met unless both of us had had that Ludwig connection,” says Gibbs. “Putting our clinical and scientific expertise together really works very well. The combination is powerful.”
“The fundamental idea is that we are not likely to conquer cancer simply by treating advanced cancers, which is what the majority of directed cancer research is now aimed at,” says Bert Vogelstein.

Although the researchers worked as part of the Ludwig community on different continents, and their research branched out in different directions, they both studied colorectal cancer, the topic of the meeting.
Financials

Total Institute funding
- 60.7% Ludwig Institute funding (US $74.1 million)
- 35.5% External sources (US $43.4 million)
- 3.8% IP revenue (US $4.7 million)

External funding by source
- 18.4% Government organizations
- 9.8% Universities and hospitals
- 4.2% Philanthropic
- 2.8% Industrial
- 0.3% Other
- 60.7% Ludwig Institute funding

External funding by continent
- 12.5% Australia
- 11.6% North America
- 10.6% Europe
- 0.7% South America
- 0.1% Other
- 60.7% Ludwig Institute funding
- 3.8% IP revenue
Highlights

2011 PUBLICATIONS
299 primary research articles
60 reviews, book chapters
and/or commentaries

PATENTS ISSUED
460 US patents issued to date
105 European patents issued to date
16 patents issued in 2011

CLINICAL TRIALS
31 ongoing investigational clinical trials globally with compounds derived from Ludwig research,
18 managed by the Institute
42 ongoing product development programs based on IP or technologies from the Institute
8 ongoing commercial phase 3 trials incorporating Ludwig technology

START-UP COMPANIES
As of 2011, Ludwig launched 9 start-up companies in 6 countries
Leadership

AS OF JULY 2012

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Head  
San Diego, CA, USA
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<td>Benoît Van den Eynde, MD, PhD</td>
<td>de Duve Institute at the Université catholique de Louvain</td>
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<tr>
<td>Lausanne, Switzerland</td>
<td>George Coukos, MD, PhD</td>
<td>University of Lausanne</td>
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<td>Ludwig Trust Center Johns Hopkins University</td>
<td>Bert Vogelstein, MD and Kenneth Kinzler, PhD (Co-directors)</td>
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