



**2014
RESEARCH HIGHLIGHTS**

LIFE-CHANGING SCIENCE

**LUDWIG
CANCER
RESEARCH**

WELCOME



Edward A. McDermott Jr.
President and
Chief Executive
Officer



**Sir David Lane,
PhD**
Scientific
Director

Cancer is a bit of a paradox. We think of it primarily as a taker of lives yet, intrinsically, it is life in excess—proliferation run amok, a chaotic, malign parody of the real thing.

We say this not to philosophize, or to dehumanize a devastating illness, but to make a point. Take a step back and you'll notice that in decoding the mad logic and addled circuitry of the tumor and its constituent cells, researchers are indirectly probing the puzzle of life itself. This is not an easy puzzle to solve. Thus the solution to cancer, as our founder Daniel K. Ludwig pointed out, depends on collaboration across borders and disciplines, over many years. It requires unflagging effort, with the best scientific minds attacking the problem, in concert, and from multiple angles.

We have sought in this 2014 Research Highlights report to illustrate how Ludwig's researchers are doing just that. You will read here about how our scientists advanced the engineering of mice and cells to model the generation of cancers, identify cancer cells' vulnerabilities and capture the complex biochemical changes induced within them by targeted therapies. You will learn about how they're charting the elegant choreography of cell division, the generation of drug resistance and the wholesale transformation a malignant cell undergoes as it prepares to colonize another organ in the body.

It is our mission to ensure that such research ultimately benefits cancer patients. So you will also discover here how a Ludwig scientist's hunch culminated in the birth of a biotech company and the development of a pair of promising candidate immunotherapies. You will read

about how our researchers' discoveries could improve the use and efficacy of cancer immunotherapy and how they're working to expand the number of cancers that can be treated with an existing targeted therapy.

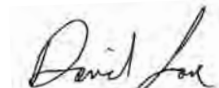
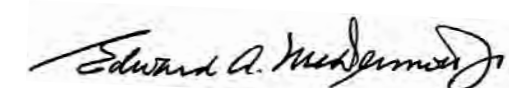
This report does not try to capture all of Ludwig's life-changing science but to offer up just a sampling of discoveries made in Ludwig laboratories around the world. To learn more about what we've accomplished, we invite you to visit our website (ludwigcancerresearch.org). For news about Ludwig and our partners, and other important developments in cancer research, you can now follow us on LinkedIn, Twitter and Facebook.

You will not be disappointed. Ludwig's pioneering, decades-long exploration of the immune system's interaction with cancer and the efforts of our researchers to harness it to treat the disease are now bearing fruit as a parade of immunotherapies enter clinical trials and obtain regulatory approval. These advancements are converging with a renaissance in our understanding of the molecular and cell biology of cancer, which is in turn fueling the development of more effectively targeted therapies and sophisticated diagnostic tests. We are, in other words, in the midst of a revolution in cancer research and care in which Ludwig scientists are playing a leading role.

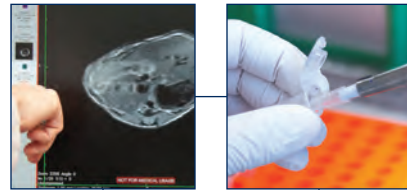
With that in mind, we hope you enjoy the Ludwig 2014 Research Highlights report.

Warm regards and happy reading,

Ed and David



MAKING DISCOVERIES

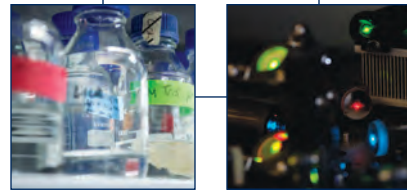


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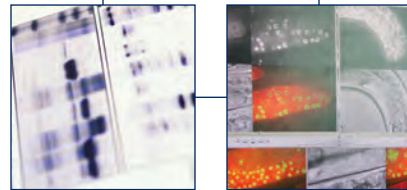


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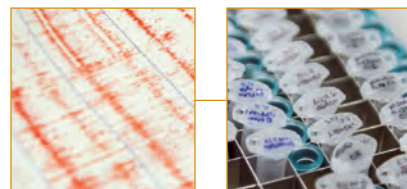
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MAKING
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Exploration of a family of proteins exposes a malfunction that drives metastasis and illuminates a new pathway to the cell's nucleus.

XIN LU

ASPPS' TRACKERS

ALL XIN LU WANTS TO KNOW IS THIS: How do cells—deaf, mute and sightless as they are—sense external stimuli and respond to those signals?

“This is our big-picture question,” says Lu, director of Ludwig Oxford.

It certainly is big—in fact, it's a question at the heart of the cancer conundrum. How do cells in various states of health differently interpret signals that invite them to divide, change shape, perform various tasks or travel to another place?

Lu's pursuit of the answer has led her on a fascinating scientific chase, tracing the molecular circuitry that transmits biochemical signals from the membranous shell of the cell to the inner sanctum of its nucleus, which houses the genes that decide its fate.

For years, she and her colleagues have focused their quest on the ASPP family of

proteins, which shuttle throughout the cell to relay messages. “They are like hubs for molecular signaling,” says Lu.

In 2014, Lu's team reported in *Nature Cell Biology* how one of those proteins, ASPP2, stabilizes an association between proteins that help connect cells lining inner body cavities, keeping them rigidly structured and in place. They also showed how mutations of ASPP2 which destabilize that link spur metastasis. In a second study published in *Cell*, Lu and her colleagues reported how ASPP proteins are directed into the nucleus by a unique molecular code—and so described a previously unknown and widely used nuclear import pathway.

Lu, who was born in China, is also something of a hub. She connects researchers across the globe: the lead postdoctoral researchers on the two studies, Yihua Wang and Min Lu (no relation), were recruited from top universities in China, with which Xin Lu has established strong research collaborations.

Going mobile

Lu's previous work has shown how ASPP proteins modulate distinct molecular signals involved in the suppression of cancer. For instance, ASPP2 binds the tumor suppressor p53, known as the "guardian of the genome," thus activating it to suppress tumor growth. In their 2014 study, Wang, Lu and their colleagues report that ASPP2 plays a key role in the epithelial-mesenchymal transition (EMT)—a catch-all term for the changes a cell undergoes as it shifts from a settled into a mobile state—and in its reverse, mesenchymal-epithelial transition (MET).

The researchers found that ASPP2 contributes to MET in the development and maintenance of kidney tubules, which filter waste out of the blood stream. Conversely, loss of ASPP2 expression dramatically promotes EMT. The team showed in a mouse model that breast cancer cells expressing low levels of ASPP2 metastasize furiously to the brain, and that this can be reversed by the expression of ASPP2 in those cells. Poor ASPP2 expression in breast and liver tumors taken from patients, the team discovered, is correlated with notably lower patient survival.

Probing the molecular dynamics of ASPP2's role in EMT and MET, the researchers found that ASPP2 stabilizes the association between two proteins, E-cadherin and β -catenin, that form the junctions between epithelial cells. This prevents β -catenin from zipping down to the nucleus, where it can fuel the expression of genes that drive EMT—and metastasis.

Nuclear RaDAR

"This is detailed and creative discovery work," says Lu, who began working on ASPP proteins in 2001. "It has taken us this long to understand how they are regulated in human cancers."

Her persistence is paying off. In a second 2014 study, she and her postdoc Min Lu looked into how ASPP proteins enter the



SEBASTIAN NIJMAN

MOLECULAR TEASER

New tools to probe how drugs perturb the interconnected biochemical and genetic networks within cells hold great promise for cancer drug design.

One of the enduring frustrations physicians encounter in treating cancer patients is how unpredictable treatments can be. In two people with ostensibly the same cancer, the same drug can induce remission in one but have little effect on the other. Some mysterious interplay of the cancer cell's molecular circuitry and the drug's intended target is to blame, of course, but what precisely? And how might that same circuitry be better defined, contextualized and targeted to undo the unique malignancy of each patient's cancer?

Sebastian Nijman, who joined Ludwig Oxford in November 2014, seeks to answer these questions. To that end, he has developed powerful new cell- and silicon-based technologies to investigate how drugs interact not only with one gene, or the protein it encodes, but also with the variegated genetic landscape of malignancies—an endeavor known as pharmacogenomics. He is, in other words, interested in the full suite of knock-on effects induced within the cell by that antagonistic encounter. "Many more tools are now coming online that will allow us to begin to address this problem in a much more systematic manner," he says.

A study Nijman published in early 2015, reporting work he did at the Austrian Academy of Sciences, in Vienna, is a case in point. He and his team identified a group of compounds that kill triple-negative breast cancer (TNBC) cells, a deadly tumor type that does not respond to current treatments.

To do this, they generated cancer cells genetically engineered to be similar to triple-negative cancers, with a similar set of genes turned on and off. They then exposed these cells to a vast library of more than 20,000 compounds, including experimental and approved drugs. About 100 compounds could kill the cancer cells—including one, PKC412, that has already been extensively tested in humans as a potential leukemia drug.

"Many more tools are now coming online that will allow us to begin to address this problem ..."

SEBASTIAN NIJMAN | Ludwig Oxford

Through desktop experimentation and computer modeling, they then asked what made PKC412 so special. What did it hit inside the cancer cells? And how did those interactions play out across the circuitry of malignant cells, according to the team's computer models? Their studies revealed that the drug induced suicide in a subset of TNBC cells, and suppressed tumor growth in animal models. Unexpectedly, the target of PKC412 is a signaling molecule called SYK, which turns on a second signaling protein that drives the growth of that subset of cells.

Nijman is eager to move this work forward at Ludwig Oxford. This goal will certainly be helped along by his additional appointment as director of functional genomics of the Target Discovery Institute in Oxford. This new institute, supported in part by Ludwig, is devoted to finding new drugs and drug targets, and it will provide Nijman with easy access to all sorts of new drug discovery technologies.

Nijman is also eager to establish collaborations with Ludwig colleagues who have expertise in the biology of various cancers, and who can help him test the compounds he identifies in mice and human tissues—and, eventually, in clinical trials.

"All these things together made it irresistible to come to Ludwig," said Nijman. "I see a lot of possibilities." ■

“This is detailed and creative discovery work.”

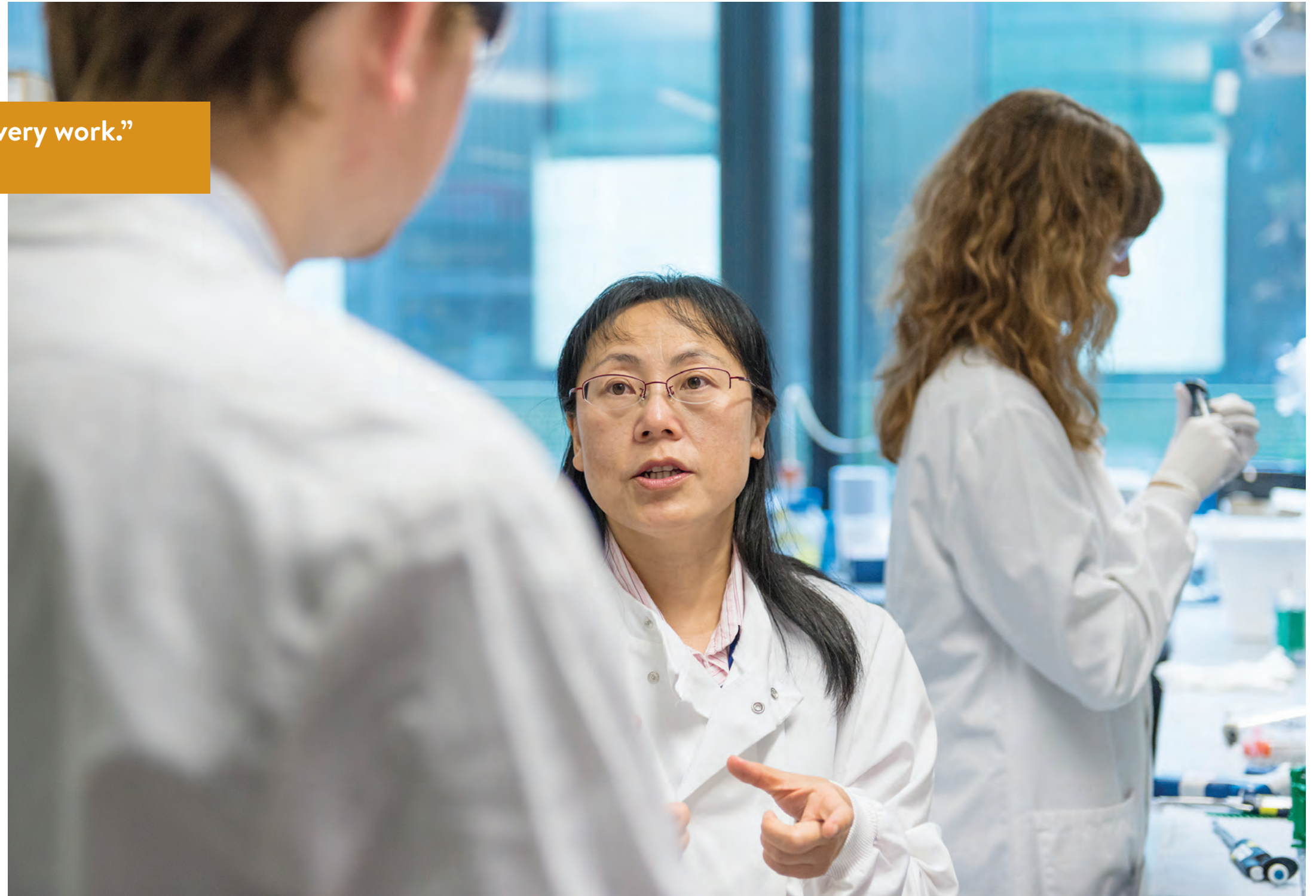
XIN LU | Ludwig Oxford

nucleus. They discovered a hitherto unknown mechanism of nuclear import, which they dubbed the RaDAR pathway. They described the signature amino acid code recognized by the pathway and showed that it is shared by scores of other proteins that shuttle into the nucleus.

Moreover, their identification of the code solves an interesting puzzle in the world of cancer research. It explains why a protein named p16 accumulates at very high levels in the nuclei of cells of people with familial melanoma. The researchers showed that the most frequently occurring familial mutation in p16 confers the RaDAR code on the protein, which contributes to its aberrant accumulation in the nucleus and the loss of a key mechanism of tumor suppression.

The success of these research projects is also strengthening Xin Lu's long-term connections with Chinese researchers. Min Lu's work on iASPP earned him a prestigious “Thousand Talents” grant from the Chinese government. He will be getting over \$1 million in funding to start his own lab in China. “I appreciate what I have learned here at Ludwig Oxford in the past six years,” says Min Lu, who will join the newly established National Centre for Translational Medicine in Shanghai Jiaotong University.

That will doubtless expand Xin Lu's collaborations in China. Meanwhile, she is mulling the use of the RaDAR code to devise novel drugs that might be targeted directly into the nucleus. ■



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Ludwig Brussels researchers are on a quest to expose how a family of signaling molecules influences cancer and its resistance to therapy.

STEFAN CONSTANTINESCU and JEAN-CHRISTOPHE RENAULD

MASTERS OF THE JAKS

NOT MANY RESEARCHERS CAN SAY that their work has contributed directly to major clinical victories. Ludwig Brussels investigator Stefan Constantinescu is one who can.

In 2005, Constantinescu and his colleagues, along with other research groups, uncovered a major molecular driver of myeloproliferative neoplasms—a group of slow-growing but potentially deadly blood cancers. Many of them, they reported, have mutations in a family of cell signaling molecules called Janus kinases (JAKs). The mutant proteins generally prompt the excess proliferation of cells that give rise to the components of blood, such as platelets, red blood cells and certain immune cells. These findings sparked a pharmaceutical race to develop drugs that target JAKs. The drugs have been approved or are being evaluated in clinical trials for the treatment of myeloproliferative disorders and some autoimmune diseases.

Constantinescu, however, stayed out of that race, turning instead to another set of problems. In 2014 and early 2015, he added to his extensive JAK signaling oeuvre with three new studies, milestones on the road to better treatments for blood cancers.

In one study, his team outlined a key driver of chronic myeloproliferative neoplasms and their occasional progression into full-blown acute leukemia. Both conditions involve a persistent activation of the protein STAT5. This regulator of gene expression is normally engaged only as required to transmit JAK signals to the nucleus. In blood cancers, however, the persistent activation of STAT5 results in the expression of an aberrant array of genes.

In many cases, the researchers found, this aberrant expression occurs in cooperation with p53, a protein that is either mutated or improperly activated in most chronic blood cancers that progress to deadly acute leukemia. “We think therapies that target



Stefan Constantinescu

STAT5 could be important for stopping progression to acute leukemia,” says Constantinescu.

His isn't the only Ludwig Brussels lab steeped in JAK studies. On the same floor as Constantinescu's lab, but in a neighboring tower linked by a bridge, Jean-Christophe Renaud is studying the role of wayward JAKs in a distinct but equally linked set of blood cancers known as lymphoid malignancies. These cancers, which include acute lymphoblastic leukemia, Hodgkin's disease and peripheral T cell lymphoma, often carry mutations in the proteins JAK1 and JAK3.

Renaud and his team published a study in 2014 that is likely to have significant implications not only in his field, but also for therapeutic JAK inhibition in myeloproliferative neoplasms and for models of cancer drug resistance in general. Their studies revealed that cells treated over a long term with JAK inhibitors can acquire

mutations in two different JAKs. This occurs via a sort of ping-pong mechanism, in which cells mutated in one type of JAK respond to treatment by mutating another JAK family member. Further, the two mutations cooperate in their transforming effects. This cooperation, they showed, not only significantly boosts STAT activation within cells but also confers on them resistance to JAK inhibition. The findings provide a framework for developing new treatments.

Reaching out

Renaud and Constantinescu make full use of opportunities and resources available through Ludwig's global network. They work closely with a protein biochemistry lab at the Brussels branch and are collaborating with the Small Molecule Discovery group at Ludwig San Diego.

“The long-term support we have received has been critical to developing the experimental model we use today to conduct our studies,” says Renaud. “Access to the larger Ludwig



Jean-Christophe Renaud

community has been very helpful to our studies as well.”

Constantinescu, for example, recently collaborated in a study led by Ludwig Stanford's Christopher Garcia to specifically inhibit a commonly mutated version of JAK2 using antibody-based agents called diabodies. They showed that these diabodies could from outside the cell gently manipulate the receptor to which the mutant JAK2 is attached in such a way as to turn off its aberrant signaling.

The Brussels researchers have also branched out into studies of the signaling molecule interleukin-22 with Ludwig investigator Matthias Ernst in Australia. Interleukin-22 operates through JAKs and prompts inflammation and cancer in the colon.

“These are projects that pharmaceutical firms find too risky,” says Constantinescu. “With its continuous support, Ludwig is helping us solve complicated problems.” ■

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Studies of how tumor cells prepare to migrate suggest new ways to thwart the spread of cancer.

CARL-HENRIK HELDIN

STUDENT OF METASTASIS

EVERY YEAR, CARL-HENRIK HELDIN convenes a summit that also serves as a homecoming of sorts. The gathering typically includes dozens of researchers from around the world who once worked at Ludwig Uppsala, and his current colleagues at the branch, where Heldin is the director. At the meetings, which are held alternately in Uppsala and in Leiden, The Netherlands, the researchers grill each other, examine their own assumptions, get a sneak peek at new data and make sure they're staying current on their shared scientific obsessions.

Heldin's knack for staying connected serves him well in other ways. Until 2014, he was vice president of the European Research Council, which provides generous funds to gifted researchers in Europe, and he was appointed chairman of the board of the Nobel Foundation in 2013. This outreach supports his driving interest: the study and conquest of cancer. "Our colleagues motivate us to go one step further," he says.

Last year, Heldin and his colleagues took a big step forward in an area of enduring interest to the Uppsala summiteers: transforming growth factor β (TGF- β), a molecular switch that appears to be a key driver of metastasis. In two studies published in 2014, the team showed how TGF- β induces the reengineering of a cancer cell. Their research suggests that γ -secretase inhibitors, a class of drugs being tested as a treatment for Alzheimer's disease, may also thwart metastasis.

Breaking out

Any settled cell that hopes to become metastatic must first bust out of its comfort zone, cutting connections to neighboring cells, pulling out molecular pegs, loosening up its form and preparing to go mobile. The process that makes all this possible is called the epithelial-mesenchymal transition, and it can be triggered when TGF- β binds to receptors on the surface of the cell, firing up a vast network of signaling circuits within.



“The process is extremely multifactorial,” says Heldin. “We have been gradually teasing out one component after another.”

In one of the 2014 studies, Heldin collaborated with Maréne Landström, a former Ludwig Uppsala researcher who is now a professor of pathology at Umeå University in Sweden. The pair and their colleagues had previously shown that, in some cells, TGF- β prompts cleavage of a TGF- β receptor, generating a small receptor fragment that migrates to the cell’s nucleus. Once in the nucleus, that fragment helps turn on genes that promote cell invasion.

Heldin, Landström and their colleagues showed how an enzyme called γ -secretase snips the receptor, generating the protein fragment implicated in metastasis. γ -secretase also operates in a separate process to promote Alzheimer’s disease, and the drugs that shut it down have been extensively tested in human studies. The researchers found that these drugs prevented cancer cell invasion in a petri dish and inhibited tumor growth in mice implanted with prostate cancer cells. They are now testing whether inhibition of this pathway can also quell other types of tumors.

In his second major study of 2014, Heldin collaborated with current Ludwig Uppsala investigator Aristidis Moustakas to show how a nuclear protein called high mobility group A2 (HMGA2) can carry out the instructions transmitted by TGF- β . They find that HMGA2 helps turn off a key gene involved in gluing neighboring cells together. With that gene shut down, cells become invasive.

Bringing it all back home

Heldin and his colleagues are now planning to build a complete map of the genes that are turned on or off as cells prepare for metastasis and undergo epithelial-mesenchymal transition, a project that could generate new research trajectories and expose new drug targets. They are also

“We create a good milieu for young scientists. We give them the opportunity to develop and then to fly.”

CARL-HENRIK HELDIN
Ludwig Uppsala

working to identify compounds that can stop cancer by inhibiting TGF- β signaling and metastasis.

Heldin says support from Ludwig has helped him to nurture and develop the next generation of researchers. “We create a good milieu for young scientists,” he says. “We give them the opportunity to develop and then to fly.” Luckily for Ludwig and for cancer research, many of them like to come back home every once in a while. ■

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New possibilities for killing cancer cells emerge from studies of how chromosomes are parceled out during cell division.

ARSHAD DESAI

THE CHROMOSOME MONITOR

ARSHAD DESAI'S LAB AT LUDWIG San Diego looks like a congress of microscopes. Small desktop types perch on benches. Larger, more elaborate contraptions, gussied up to peer more deeply into cells, crowd the side rooms, jostling for space beside computer displays, high-resolution cameras and elaborate stages for manipulating samples.

Desai and his team spend a good part of their days bent over these devices, probing a process fundamental to life: the parceling out of chromosomes during cell division. After chromosomes have duplicated, the two sister chromosomes remain together until they are yanked apart by the mitotic spindle, which places one sister into each of two daughter cells. This process, which ensures that each of our cells contains a single intact copy of our genome, often goes awry in tumors, resulting in cells with odd numbers of aberrant chromosomes—some missing, some broken, others just as dangerously duplicated.

Last year, Desai and his team helped uncover a molecular mechanism that controls when the sister chromosomes separate, and another that ensures that each new chromosome can attach to the spindle. Their findings could guide the design of new cancer-fighting compounds that selectively target such processes.

MAD connections

Not surprisingly, one of Desai's most memorable scientific moments in 2014 occurred as he peered down a microscope.

He and his colleagues had been studying a complex of two proteins, MAD-1 and MAD-2. These checkpoint proteins monitor chromosomes, ensuring that they're properly lined up, with the two matching sisters connected to the spindle in a way that allows for one to be pulled into each of the two daughter cells. "MAD-1 and MAD-2 send out a signal that stops the entire cell from dividing until each pair of chromosomes is properly connected," says Desai.

Researchers can visualize proteins by tagging them with fluorescent molecular probes that light up under the right conditions. This technique has shown that MAD-1 and MAD-2 coat the structures that attach chromosomes to the spindle before cell division. But it has been less clear how they get there. MAD-1, it was known, attaches to MAD-2, but how does the MAD-1–MAD-2 complex then attach to the chromosome?

To find out, graduate student Mark Moyle had made precise mutations to a chief suspect in the scheme, a protein named BUB-1. When Moyle called Desai over to his microscope, Desai knew they'd found the answer. Where they should have seen MAD-1, they did not. "Normally you see this bright strip of protein enriched on the chromosome, and now it was completely gone," says Desai.

With the attachment site on BUB-1 gone, MAD-1 disappeared from the chromosome. "That was the 'aha' moment," says Desai, "the cleanest moment in this project." MAD-1 was tacked onto the chromosome by a tethering protein, and that protein had to be BUB-1. "This connection is controlled by proteins that are targets in clinical therapies under development," says Desai. By better understanding how all these proteins interact, researchers could develop drugs that disable a key mechanism in the molecular engines of cancer.

Desai carried out this research in a small worm, *Caenorhabditis elegans*. At barely a millimeter long, the worm is a lot easier to work with than mice or human cells. And when it comes to fundamental processes, such as cell division, humans are not much different from worms—there is evidence that BUB-1 operates similarly in people. Proteins Desai has helped identify as actors in cell division in worms and yeast are now seen as promising targets for cancer therapies.

"My whole career I have worked on these fundamental mechanisms," says Desai. "But,



"People are always running into each other. It drives people to do interesting stuff."

ARSHAD DESAI | Ludwig San Diego

at the same time, we want to be able to connect this understanding to cancer."

The long view

Desai's lab has a deliberately open floor plan, and his team shares space with those of other Ludwig researchers, including his wife and frequent collaborator, Karen Oegema. "People are always running into each other," says Desai. "It drives people to do interesting stuff."

Some of it involves other Ludwig researchers in San Diego as well, such as the head of Ludwig's Small Molecule Discovery program, Andrew Shiau, who is working with Desai to develop compounds that target chromosome segregation. The idea is that such agents would disproportionately cripple rapidly dividing cancer cells, mangling their

chromosomes enough to kill them or prompt their self-destruction.

Desai is also taking aim at other proteins, such as the components of the centromere, a protein complex that forms the foundation for assembling the structures that allow the spindle to grab onto the sister chromosomes and parcel them out to the two daughter cells. In February 2015, Desai's lab published a study in yeast that clarifies the important role of the centromere protein CENP-A. The team showed how a small region of CENP-A stabilizes the centromere, allowing it to form on the same part of the chromosome generation after generation to ensure proper chromosome inheritance and secure the integrity of the genome.

Desai is currently testing compounds that target chromosome segregation to see if they might stop the deadly proliferation of cancer cells. Meanwhile, he continues to squint through his many lenses for the next fundamental insight into a defining process of life. ■

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A powerful new gene editing technology sets the stage for the massive acceleration of basic and applied cancer research.

TYLER JACKS

SPEEDY MODELER

IT'S ALREADY SOMETHING OF A machine for scientific discovery. But now Tyler Jacks' laboratory at Ludwig MIT is stepping up production.

The laboratory is renowned for its mice, which Jacks and his team engineer to carry mutant versions of genes involved in cancer. Their engineered mice have provided great insight into how cancer develops and spreads, but generating such models is painstaking work that can take years. In 2014, however, they showed that things don't have to be that way. Jacks and his colleagues applied an emerging gene editing technology dubbed CRISPR/Cas9 to rapidly alter cancer genes in adult mice and study the consequences.

"This technology is huge," says Jacks. "It has overtaken my laboratory in a remarkably short period of time." Mouse models that once took years to make, he notes, are now being turned out within months.

Traditional methods of engineering mice involve generating changes to DNA in embryos and breeding the mice for a few generations. By contrast, the new CRISPR/Cas9 technology is direct and efficient, and can be used on adult mice with relative ease. Cas9 is a DNA-snipping enzyme from bacteria. It is directed to specific sequences in the DNA by small, complementary RNA molecules. The RNA shows where to cut and the enzyme snips the DNA. In addition to knocking out genes, the technology can be adapted to replace or add genes, or to change them subtly.

The technique was first used to engineer mammalian genes barely two years ago. Since then, laboratories across the world have quickly adapted it to their particular investigations. Jacks was eager to put it to the test in cancer research.

Snipping genes

His first task was to test whether CRISPR/Cas9 worked just as well as traditional methods for making modified mice.

To examine this, his team knocked out two familiar genes in the liver. CRISPR/Cas9 mice lacking these genes resembled the corresponding mouse models they had made using traditional techniques.

The researchers next used CRISPR/Cas9 to generate mice with novel combinations of altered genes in the lung to recapitulate lung cancer. To do so, they injected the lungs of mice with viruses that produced Cas9 and RNA guides corresponding to the genes they wished to perturb.

Jacks and his colleagues knocked out three genes—NKX2-a, PTEN and APC—that act as tumor suppressors in mice that had already been engineered to express a cancer gene called KRAS. The study accurately reproduced the effects of the first two mutations, and showed for the first time that APC might play a role in lung cancer as well.

Jacks and his colleagues showed that they could also use CRISPR/Cas9 to knock out more than one gene simultaneously. And they could generate mice with genes altered to gain functions similar to those seen in human cancers.

Fast forward

The technique is unleashing a flurry of new projects in the Jacks lab. “Until now, the field has been kind of stuck,” says Jacks, who is gearing up to test panels of genes implicated in human cancers by generating mice with the same defects seen in human tumors. “Now we can get through lists of genes of interest much more rapidly and cost effectively than we ever could have before.” Such an approach has the potential to lead to subtler biological insights and significantly improve the identification of new drug targets.

Jacks and his colleagues are also now mutating various genes thought to be involved in metastasis, a focus of Ludwig MIT. “We have an extremely cohesive group of

“When things happen this quickly and this effectively, it kind of takes your breath away.”

TYLER JACKS
Ludwig MIT

Ludwig investigators here,” says Jacks. “We all are sharing ideas, strategies and reagents.” Jacks will soon pass along some new CRISPR/Cas9 mice to his Ludwig colleagues so they can take a close look at how tumors spread and establish themselves at new sites in the mouse body.

“I am used to things taking their time and having to slog through it,” says Jacks.

“But when things happen this quickly and this effectively, it kind of takes your breath away.”

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MOVING
DISCOVERIES



An analysis of genome expression in melanoma tumors exposes precise signatures that predict response to a groundbreaking immunotherapy.

JEDD WOLCHOK

CANCER'S GRAPHOLOGIST

WHEN IPILIMUMAB HIT THE CLINIC IN 2011, it was widely regarded a game changer. It gave years of life to many patients with metastatic melanoma, which has historically been a swiftly lethal cancer in its latter stages. Tumors disappeared entirely in some patients.

Jedd Wolchok of Ludwig MSK, who conducted pivotal clinical trials of the antibody drug before its approval by the US Food and Drug Administration, has since participated in many studies of its effects in combination with existing and experimental therapies. And with good reason. For all their promise, ipilimumab and other “checkpoint inhibitors,” when given individually, still help only about 20–40% of melanoma patients.

In 2014, Wolchok finally figured out why.

A study led by Wolchok and his MSK colleague Timothy Chan uncovered a precise set of genetic signatures borne by

tumors that are susceptible to ipilimumab treatment. Their results, published in the *New England Journal of Medicine*, could help improve outcomes for metastatic melanoma by allowing doctors to screen patients likely to respond to ipilimumab and devise other treatment strategies for those less likely to do so.

Proffered targets

Cancer cells generate countless mutations across their genomes as they multiply. Those mutations are often expressed as subtle changes in the chains of amino acids that make protein molecules. Like all cells, cancer cells chop up and hold out tiny bits of such proteins—each about nine amino acids in length—for the immune system to assess.

The trick is to get immune cells to “see” those mutated bits and respond to the danger they betray. Checkpoint inhibitors accomplish the latter by blocking a molecule named CTLA-4, which is found on killer T cells and functions as a brake on their

DMITRIY ZAMARIN

CANCER'S WHITE-HAT HACKER

An engineered bird virus delivered together with an immunotherapy in mouse models crashes tumor defenses

Dmitriy Zamarin brought useful expertise with him when he joined the Ludwig MSK in 2012. A clinical oncologist and research virologist, Zamarin has long explored the use of viruses to destroy tumors. Oncolytic virotherapy, as the strategy is known, has fascinated researchers since at least the 1950s and is today enjoying something of a renaissance in academic and industry labs.

Zamarin is especially interested in using the Newcastle disease virus—which primarily afflicts birds but also has a taste for cancer cells—in combination with immunotherapy to treat cancers. In 2014, he passed a major milestone en route to that goal. In a study he led with Ludwig's Jedd Wolchok and James Allison of the MD Anderson Cancer Center in Houston, Zamarin showed that the combination can have a potent effect on tumors in mice.

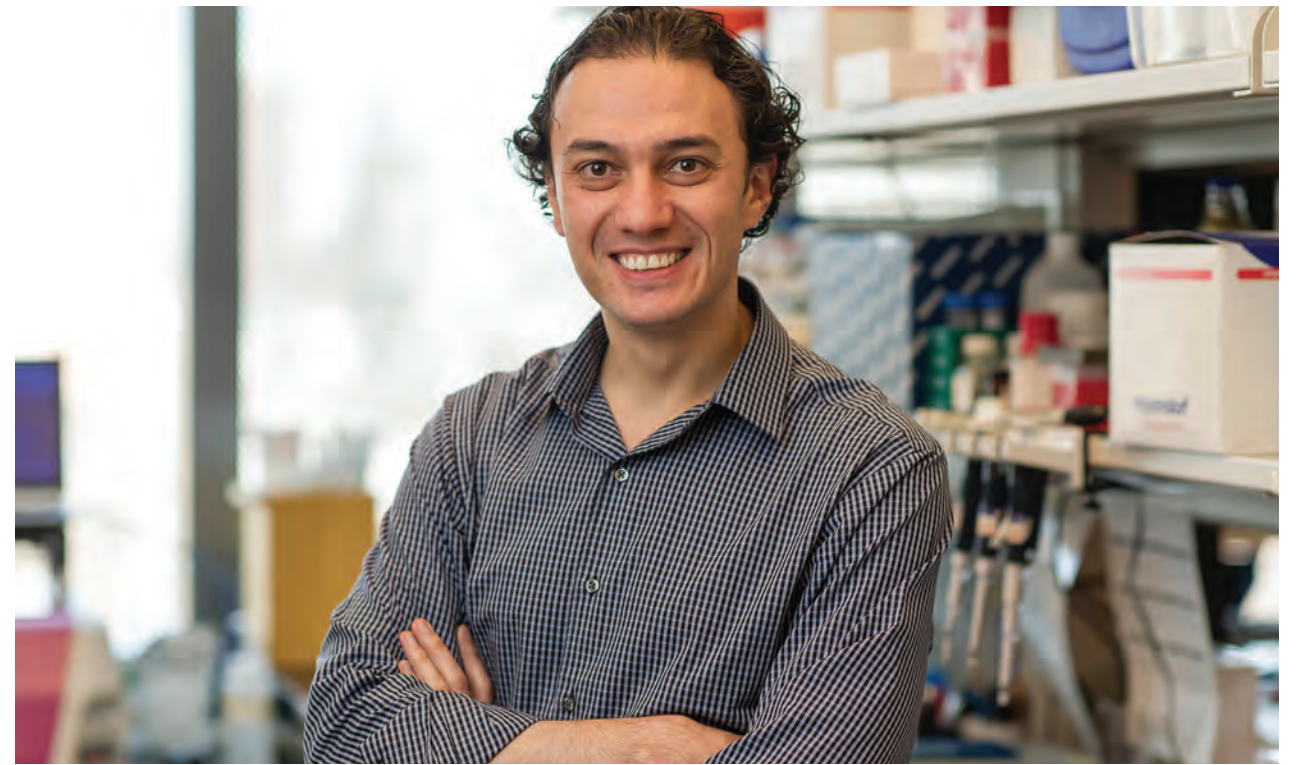
Oncolytic viruses multiply so furiously in cancer cells

that they pop the cells open from the inside. In doing so, they can also revive immune responses against tumors. Yet the approach has not worked very well so far in people, in part because the immune system often clears the virus before it has a chance to reach its target, and in part because tumors suppress immune responses in a variety of ways.

To circumvent these problems, Zamarin and his colleagues transplanted one melanoma tumor on each flank of a mouse, and then directly injected one of them with the Newcastle disease virus. This ensured that the virus would get into cancer cells before the immune cells could clear it. As the team expected, the injected tumors shrank dramatically.

"The surprise," says Zamarin, "came when we looked at the tumor on the other side."

Those tumors, though intact, were now being invaded by



immune cells. When these mice were given a dose of anti-CTLA-4 antibody (a mouse version of a human drug called ipilimumab), which boosts killer T cells of the immune system, both tumors were destroyed. Better yet, the effect was durable—newly transplanted tumors could not gain a foothold in treated mice. It was also inducible against

prostate and colon tumors, which are typically resistant to immunotherapy.

Zamarin is now working with his colleagues to prepare the virus for human studies. "We hope that our findings can be translated into a therapy that will benefit our patients," says Zamarin. "That's the ultimate goal of the work we do here." ■

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activation. With the brakes lifted, immune cells that see the mutated proteins held out by cancer cells proliferate and attack them. But for that to happen, they first have to see the danger.

To explore this phenomenon, Wolchok drew on a unique Ludwig resource. Ludwig MSK has for years saved blood and biopsy tissue from cancer patients treated in

its clinical trials. "This is an international repository of biospecimens that was started by Ludwig's former scientific director, the late Lloyd Old," says Wolchok. "It was established to help answer unforeseeable scientific questions that might arise in the future."

Wolchok had one of those questions. So he and his colleagues accessed samples from

25 patients treated with checkpoint inhibitors. They then compared all of the genes within the tumors and found that, as they expected, tumors with more mutations were more susceptible to CTLA-4 blockade.

But there was more to it than that. A sophisticated computational analysis of the tumor genomes revealed that, within

the bits of proteins presented by cancer cells, there is a defined set of core peptide sequences—each four amino acids long—that are unequivocally associated with response to treatment.

To test the prognostic power of these genetic signatures, the team sequenced the expressed genes of tumors from 39 other melanoma patients treated with CTLA-4

blockade. They found that all those in this set who had responded to the therapy had at least one and typically several more of the core sequences they had identified. Nonresponders did not. Importantly, their results also show that the mutant DNA sequences in those core peptides can occur anywhere in the genome—not just within ‘driver’ genes that are already known to contribute to the growth of cancer.

Bigger benefits

The researchers hope this work will lead to the development of tests to screen patients before they are treated with checkpoint inhibitors. This would save precious time and money—and certainly save lives. “What do you do for those patients who do not have favorable mutations?” says Wolchok. “How do you get the immune system to notice and attack the tumor?”

Wolchok, Chan and their colleagues did notice that some of the core sequences that excite an immune attack in response to ipilimumab closely resemble those borne by known viruses and bacteria. This opens up some tantalizing opportunities for combination therapies using ipilimumab with, say, existing vaccines or even engineered bacteria and viruses (see sidebar). It also suggests that tumors with more mutations, such as those that stem from tobacco use, are likely to be more vulnerable to checkpoint blockade.

Wolchok and Chan note that the vision and long term-funding offered by Ludwig permitted the open-ended storage of tumor samples—and it paid off. “This is a very valuable resource for researchers at Ludwig and the larger biomedical research community,” says Wolchok. “It was indispensable to this study.” ■



“What do you do for those patients who do not have favorable mutations? How do you get the immune system to notice and attack the tumor?”

JEDD WOLCHOK
Ludwig MSK

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A new class of drugs used to treat autoimmune diseases and a blood cancer may also stymie colon cancer.

MATTHIAS ERNST

DRUG REPURPOSER

IT'S A GOOD THING WHEN A CLASS OF drugs for one disease can be used to treat another. Such repurposing can hasten a new therapy's journey to the clinic, since it has already passed tests of its stability and safety.

Inhibitors of the family of signaling proteins named Janus kinases (JAKs) are a case in point. Approved by the US and other drug agencies for the treatment of a form of leukemia and for autoimmune diseases, this class of drugs is now also being tested in people diagnosed with lymphoma and other advanced malignancies. Ludwig Melbourne's Matthias Ernst hopes to add another cancer to his team's therapeutic portfolio. In 2014, he and his colleagues showed that JAK inhibitors shrink colon tumors in mice. If these findings hold true, the researchers could quickly begin testing their effects in patients.

In that regard, it certainly helps that Ernst is the inaugural scientific director of the Olivia Newton-John Cancer Research Institute (ONJCRI) in Melbourne. The ONJCRI,

which opened its doors last year and is the successor to the Ludwig Melbourne-Austin Branch, is functionally integrated with the Olivia Newton-John Cancer and Wellness Centre, which is one of Melbourne's three major cancer hospitals and runs more than 60 clinical trials per year. "We are all in the same building, with hospital beds for cancer patients on one side and basic research done on the other," says Ernst. The ONJCRI will focus much of its effort on basic and early translational research, though its clinician-scientists will also be running many phase 1 and 2 clinical trials through the Olivia Newton-John Cancer and Wellness Centre. "This is what everybody talks about when they think about comprehensive cancer centers," Ernst says.

Busting bowel cancer

Ernst's studies exploiting JAK inhibitors stem from a combination of long-standing interests, including cellular mediators called cytokines and their involvement in bowel, or colorectal, cancer, the second-

leading cause of cancer-related deaths in most industrialized countries. Researchers have identified some of the key molecular drivers of this disease. For instance, about 80% of colon cancers involve mutations in a tumor suppressor gene called adenomatous polyposis coli (APC). These mutations drive uncontrolled cell division and tumor growth.

Unfortunately, this knowledge has not yet led to the development of clinically approved drugs that target tumors with APC mutations. One reason for this is that experimental drugs that interfere with the signaling pathway that involves APC can stop tumor growth, but they can also damage normal colon tissue. This is because they stop the ordered cell division that keeps the self-renewing organ healthy and prevents conditions like colitis.

JAK inhibitors may offer a route around this problem: Ernst showed in 2013 that their targets are important for the growth of colitis-associated colon cancers. In their new study, Ernst and his colleagues demonstrated in mice that JAK inhibitors could also stop much more common forms of sporadic colon cancer that arise from APC mutations. Better yet, they could do so without damaging the healthy parts of the intestines.

Ernst's team is conducting further tests in mouse models and following up on preliminary studies suggesting that the drugs may be useful in other cancers, such as those of the lung. JAKs are activated in response to inflammation, which is a hallmark of the cellular environment of many tumor types.

Forging partnerships

Ernst's studies leverage a network of academic and pharmaceutical partners, including the Melbourne-based biopharmaceutical company CSL. He is working with CSL on a parallel approach to treating bowel cancer. This approach targets interleukin-11, a secreted molecule

“This is what everybody talks about when they think about comprehensive cancer centers.”

MATTHIAS ERNST
Ludwig Melbourne

for intercellular communication that sends its signal into target cells through the JAK pathway. In previous studies, Ernst has shown that antagonists of the interleukin-11 receptor, which have been developed by CSL, can foil bowel cancer in mice.

Ernst has also helped build productive partnerships between some of the institutions that support research at the ONJCRI, which include Ludwig, La Trobe University, the State Government of Victoria and the National Health and Medical Research Council of Australia. “This is a very exciting environment,” he says. “It is well suited to where my research is going.”

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How an old hunch spawned a Ludwig spin-off dedicated to undoing the defenses that shield tumors from the immune system.

BENOÎT VAN DEN EYNDE and ITEOS THERAPEUTICS

BOOSTERS OF ANTITUMOR IMMUNITY

WHEN BENOÎT VAN DEN EYNDE ASKED Michel Detheux in 2010 if he would like to start a new biotechnology company, Detheux did not hesitate. “It took me three seconds to decide,” he recalls.

Van den Eynde, director of Ludwig Brussels, was eager to develop drugs against two immunotherapy targets he had identified, indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). Compounds that blocked these enzymes could fend off cancer in mice, but Van den Eynde was a long way from turning them into testable drugs. The new company would provide the framework for that effort and help him secure the funding to make it happen.

“The proposal involved a partner I could trust, excellent scientists, and people who shared my vision for a drug discovery company,” recalls Detheux, a biochemist with extensive experience working in biotechnology companies.

Neither partner has been disappointed. In August 2011, the researchers cofounded Brussels-based iTeos Therapeutics, and by April 2012 they had won major backing from Ludwig and other investors. In December 2014, with Detheux as its chief executive officer, the biotechnology company forged a multiyear, multimillion-Euro partnership with the pharmaceutical giant Pfizer. Detheux and Van den Eynde’s path to this agreement showcases Ludwig’s dedication to moving basic findings to the clinic through partnerships—a process buoyed by the extensive scientific and technological know-how of its network of scientists.

Pfizer will soon initiate clinical trials of drugs targeting IDO and TDO. As part of the deal, iTeos received an upfront payment of €24 million, some of which will go toward the discovery of new drug targets. It’s not a bad outcome for a project that began as a hunch.

Embryonic idea

“I sometimes have ideas that are a bit



Jonathan Skipper

Sustained support

Van den Eynde had a few false starts, including unsuccessful attempts to identify a competitive anti-IDO drug. But along the way he identified a second drug target, TDO, which has the same function as IDO and is similarly exploited by tumors. And in the summer of 2011, iTeos got its big break—a €6 million award to fund IDO and TDO drug discovery programs from the Walloon Regional Government in Belgium. But the award came with a stipulation: iTeos had to raise €3 million from other sources by the end of the year.

iTeos approached Jonathan Skipper, executive director of technology development at Ludwig, starting an intense series of discussions. The scientific solidity and clinical potential of Van den Eynde's discovery were immediately apparent to Skipper, but he also knew the tough and costly business of drug development. "It was clear they needed substantial investment if they were going to be successful," recalled Skipper, who started a discussion within Ludwig that culminated in an investment of €1.5 million in the project. Ludwig's vote of confidence convinced other private and angel investors in Belgium to provide another €1.5 million to the fledgling company.

iTeos was ready to roll.

Researchers across Ludwig supported the project over the next two years. Chemists in San Diego, for instance, advised iTeos on where to outsource tasks such as drug synthesis. Colleagues like Gerd Ritter of Ludwig New York provided invaluable advice on the preclinical development of the compounds.

After about two years, the company emerged with a pair of promising drug candidates. In mice, the compounds synergized with other immunotherapies such as cancer vaccines and immune checkpoint

crazy," admits Van den Eynde. One of them popped up in 1998, when he read a study on how the placenta protects the fetus from immune attack. The researchers reported that the organ produces an enzyme named IDO, which participates in the degradation of tryptophan, an amino acid especially important to immune cells.

A tumor looks like a foreign body to the immune system, mused Van den Eynde. Perhaps tumors also use the same defense mechanism. It was a shot in the dark, but he asked a research technician in his lab to begin looking into that possibility in his down time. "I didn't believe it would be the case," says Van den Eynde.

Much to his surprise, however, the technician found that IDO was present in a large variety of human tumors. IDO-blocking compounds, it turned out, could dissolve the immune shield around tumors and expose them to devastating attack.

Van den Eynde's journey had just begun with this discovery. "Between fundamental research and a drug candidate there is a huge amount of applied research," says Detheux.



Benoît Van den Eynde

drugs like ipilimumab, shrinking tumors more powerfully than either treatment could alone. Van den Eynde and Detheux were finally ready to find a partner who could take them into clinical development.

Partnering up

"We spoke with more than 40 venture capital groups and 28 pharmaceutical companies," recalls Detheux. In December 2014, they sealed the deal with Pfizer. "The company has access to our programs, but in a setting where it will be collaborative," says Van den Eynde, who now regularly meets with Pfizer to help chart the project's course.

Pfizer also brings to the table a pipeline of immunotherapy drugs, opening a world of possibility. "The scope of different combinations of IDO and TDO with immunotherapies that can be tested before going into clinical trials is very large," says Detheux, who anticipates that clinical trials will begin soon. iTeos will also collaborate with Pfizer on a program to identify new

immunotherapy drug targets, which will then be developed by the two companies either together or alone.

Though he continues to work with iTeos as head of its scientific advisory committee and as a board member, Van den Eynde is back to focusing primarily on his own research into how tumors evade the immune system. "I like being back in my lab, exploring new ideas," he says.

So 2014 was a very eventful year for iTeos and its founders. But one moment in particular stands out for Van den Eynde. After signing off on their agreement, iTeos and Pfizer organized a kickoff meeting in San Diego last December. "There was Michel, and me, and several other scientists, and more than 30 people from Pfizer involved in our programs," recalls Van den Eynde. "It hit me then—the research I did ten years ago in Brussels had given rise to a major worldwide pharmaceutical program. That was very gratifying." ■

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