LudwigLink April 2013

The endless why

Ludwig postdocs were the kids who wanted to know: why is the sun yellow, will we ever discover aliens, how much does the earth weigh, why can't we eat rocks, or when is the world's birthday? With every answer came more questions.

Science, at its heart, is driven by human curiosity and our ability to dream and imagine. These traits can lead to wonderful discoveries and results. Ludwig scientists have a built-in passion for science. Many of our postdocs will become the next generation of scientific leaders in academia and industry. And they've never stopped asking those pesky questions.

So we've added a new feature to the newsletter called "Ask a scientist." In every issue we'll pose a question and ask several postdocs for an answer. This issue's question is "What do you think has been the biggest achievement of the war on cancer?" Check out their answers on page 6.

No one has a crystal ball that can predict the course of scientific discovery. But we can be sure that today's Ludwig postdocs will play a major role in it.

Rachel Steinhardt,
Director of Communications

INSIDE

TRANSITIONS

Small but mighty

Although it was the smallest Ludwig site, its contributions to cancer research were monumental. Many seminal findings in tumor immunology, the study of the interaction between cancer and the immune system, can trace their origins to Ludwig New York, located at the Memorial-Sloan Ketting Cancer Center (MSKCC). The branch was established and led by Lloyd Old until his death in 2011, and its scientists were committed to developing a continuum between laboratory discovery and clinical application. They pursued targeted approaches to cancer, including tumor antigen-specific cancer vaccines and therapeutic antibodies, to track down and destroy cancer cells without many of the debilitating toxic side effects of chemotherapy and radiation.

Although the New York site's closure at the end of December had been anticipated for some time, senior scientific staff members are not straying far from home. Gerd Ritter has been named developmental research director within Ludwig's technology development team. He is now responsible for moving Ludwig's discoveries forward by assessing promising work in the pipelines of our research teams and collaborators and putting it on the path to development.

Sacha Gnjatic has moved to the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York. And Achim Jungbluth has moved to the Pathology Department within MSKCC.

Ludwig research in New York continues in the form of a new collaborative laboratory at MSKCC headed by Jedd Wolchok. The lab focuses on developing new ways to use the immune system to treat cancer. It is closely aligned with the Ludwig Center at MSKCC and works with that group to monitor immune responses in patients receiving experimental immunotherapy treatments.

New Swiss cancer center

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The AGORA Cancer Center, which is underway in Lausanne, Switzerland, will host integrated research groups, including Ludwig scientists. See story on next page.

TRANSITIONS

Cancer's new toolbox

Ludwig champions close collaborations between clinicians and researchers and is constantly seeking innovative approaches to translate research findings into improved clinical care.

The AGORA Cancer Center, which is underway in Lausanne, Switzerland, is expected to open in early 2016 and will bring together 400 researchers and clinicians under one roof to stimulate collaboration and resource sharing. It will be a key component of a new Swiss Cancer Center. Its ultimate goal is to move viable treatments from the 'bench to the bedside' as soon as they emerge from research.

The new cancer research building will host integrated research groups from Ludwig, University Hospital of Lausanne, University of Lausanne and École Polytechnique Fédérale de Lausanne. The building is one of many significant investments that Lausanne is making in cancer research. This is a major area of emphasis for the University Hospital, the University of Lausanne and École Polytechnique Fédérale de Lausanne.

"Bringing together doctors, researchers and bioengineers under one roof will stimulate collaborative efforts that will lead to major breakthroughs in therapeutic strategies aimed at cancer patients," said George Coukos, who leads the Ludwig Center for Cancer Research of the University of Lausanne.

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Architectural renderings of the interior of the AGORA Cancer Center in Lausanne. The new center will feature open floor plans with collaboration areas and lighting that enhance an aura of sustainability and community. These 'casual meeting places' will intensify interactions, facilitate teamwork, and allow communication to occur more naturally, without visual hindrances.

Did you know...?

International Hug Day was January 21.

No one deserves a hug more than a scientist. Here's just one reason why: Breast cancer is the most common cancer in both developed and developing regions. It's the leading cause of cancer death among women worldwide, with almost half a million deaths annually.

The good news is the five-year survival rate from breast cancer among women age 15 and older is 89 percent in the US, 85 percent in the UK, 82 percent in Switzerland and 80 percent in Spain.

In the 1950s, it was roughly 60 percent in the US.

And we have scientists to thank for these encouraging statistics. With earlier disease detection, treatment advances including hormones and biological therapies, and continuing clinical trials, the prognosis is good.

Have you hugged a scientist today?

AWARDS

Blue skies

Scientists often cannot predict future applications of their research. But they need to have the freedom to carry out flexible, curiosity-driven research that might lead to outcomes not envisaged at the outset. Encouraging an avenue for 'blue skies' research could have immense influence on future scientific discoveries.

The European Research Council understands the value of blue skies research and awarded George Coukos, who leads the Ludwig Center for Cancer Research of the University of Lausanne, an advanced grant for his work on engineering T cells that target tumor blood vessels. George's work focuses on developing chimeric antigen receptor (CAR) immunotherapies against cancer. In CAR immunotherapy, a patient's T cells are modified so that once the cells are reintroduced into the patient they recognize, bind to and destroy target cancer cells. This work could advance cancer therapy, as genetically modifying T cells to express synthetic CARs is an attractive strategy for producing antitumor effects.

The European Research Council is the first pan-European funding organization for pioneering research. The advanced grants allow the brightest scientists to work on their best ideas without worrying about short-term priorities.

Perfect host

Nuclear medicine uses molecular imaging techniques and radiopharmaceuticals to detect and treat cancer, cardiovascular disease and neurodegenerative diseases. Melbourne, Australia, has been chosen to host the 2018 World Congress of the World Federation of Nuclear Medicine and Biology (WFNMB). With more than 2,500 expected delegates, it will highlight outstanding nuclear medical research, diagnostics and therapeutics in Australia and worldwide. It will also showcase one of Ludwig's areas of expertise in the region.

Additionally, the leadership of the World Federation will reside in Australia from 2014 to 2018, with Ludwig researcher Andrew Scott as president-elect. "This win is a very important step forward for the organization, and will bring nuclear medicine specialists and other medical specialists from all over the world together to collaborate in this specialized field of medicine," Andrew said.

The WFNMB charter includes integrating clinical care and research between developed and developing countries, creating opportunities for shared activities, and performing research on unique disease profiles in the developing world. The WFNMB is the premier body for nuclear medicine worldwide, and has key interactions with all global nuclear medicine societies, as well as with the International Atomic Energy Agency and the World Health Organization.

Kudos to Andrew on a great opportunity to promote and encourage the advancement of nuclear medicine worldwide.

National treasure

Lucy Shapiro, a renowned molecular microbiologist, member of Ludwig's Scientific Advisory Committee and the Virginia and D.K. Ludwig Professor at Stanford University, has been awarded the National Medal of Science, the nation's highest honor bestowed on scientists. She was one of 12 eminent US researchers who received the award from President Obama in a White House ceremony on February 1. The National Medal of Science was established by Congress in 1959 and is administered by the National Science Foundation.

NEWS ROUNDUP

Everything old is new again

A Pap test can save a woman's life. For almost 70 years, it has prevented countless deaths from cervical cancer. Now a team led by Ludwig scientists Bert Vogelstein and Ken Kinzler at Johns Hopkins have developed a test that piggybacks on the widely used Pap test and expands it to look for genetic abnormalities associated with ovarian cancer and cancer of the endometrium, the lining of the uterus.

Bert Vogelstein

In a pilot study, the PapGene test, which relies on genomic sequencing of cancer-specific mutations, accurately detected all 24 (100 percent) endometrial cancers and 9 of 22 (41 percent) ovarian cancers. Endometrial cancers are often detected in the early stages of the disease and can usually be cured when caught early. However, there's no simple screening tool for ovarian cancer, and it is usually diagnosed at an advanced stage, earning it the moniker "the silent killer."

Results of the study were published in the **January 9** issue of *Science Translational Medicine*. It offers hope and great promise in battling the deadliest of all gynecological cancers. The research is part of the Hilton- Ludwig Cancer Prevention Initiative.

Holy inflammation, Batman!

Ludwig researchers led by Matthias Ernst in Melbourne have identified a complex of proteins that promotes growth of some types of colon and gastric cancers associated with chronic inflammation. Known as mammalian target of rapamycin complex 1 or mTorc1, the proteins signal inside cells to promote growth. Medications that block the function of this complex, they have shown, could be developed into a new treatment for these diseases. mTorc1 integrates four major signal inputs: nutrients, growth factors, energy and stress.

Although mTorc1 has been implicated previously in the development of other cancers, this is the first time it has been shown to promote the growth of colon and gastric cancers associated with inflammation.

"We were excited to discover that the growth of these cancers in laboratory models could be prevented by treatment with mTorc1 inhibitors that are already in clinical trials for other types of cancer," Matthias said. "In the future, we hope that this finding might lead to better treatment options for colon and gastric cancers that are associated with inflammation."

Their findings were published in the **February** issue of the *Journal of Clinical Investigation.*

Opposites attract

Epigenetic markers on an individual's DNA may explain why some people become more susceptible to disease as they age. With new tools and techniques to study the epigenetic marker 5-hydroxymethylcytosine (5hmC), scientists are shedding new light on just what the heck it does. In the **December 21** issue of *Cell*, Ludwig researcher Skirmantas Kriaucionis in Oxford and Nathaniel Heintz at Rockefeller University showed that 5hmC and another epigenetic marker, 5-methylcytosine (5mC), have opposite effects on gene expression. As a global depletion of 5hmC takes place in a broad range of tumor cells, these findings could be valuable in cancer research.

Each type of cell selectively expresses a unique suite of genes and silences those irrelevant to its function. Scientists have long known that such gene silencing can occur by the chemical modification of cytosine—one of the four bases of DNA that write the genetic code—to create 5mC.

Appropriate placement of this marker is essential to many normal biological processes, including embryonic development. Conversely, its faulty distribution contributes to the evolution of a broad range of cancers.

But 5mC is not the only epigenetic marker on the genomic block. 5hmC

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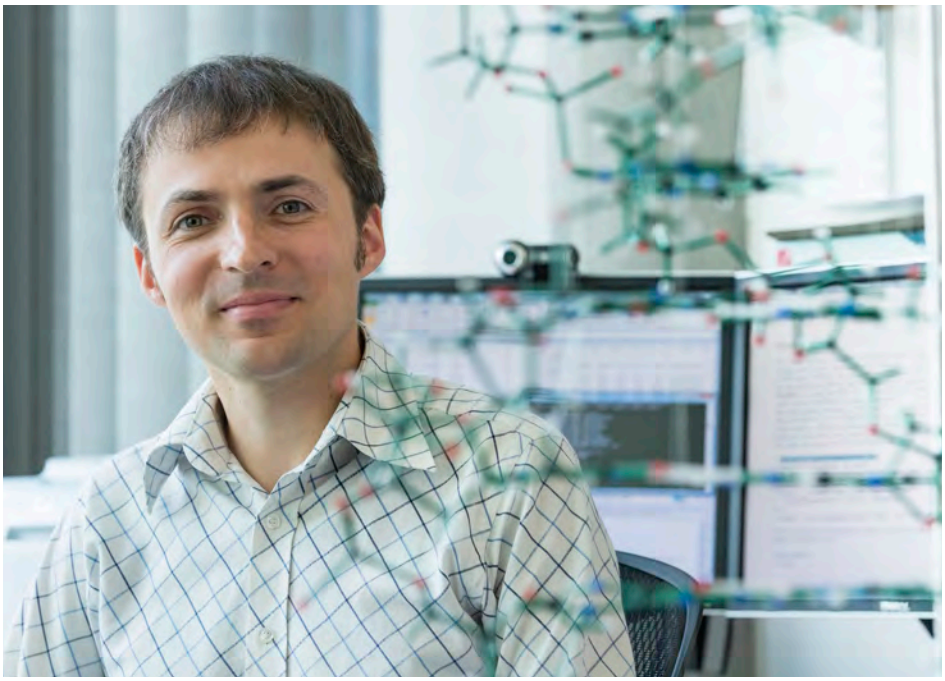


Skirmantas Kriaucionis

seems to play a similarly vital role in the selective expression of the genome, and changes in its distribution occur in a broad range of tumor cells. Skirmantas's lab is now assessing the role of 5hmC in the development of different types of blood cells, with the aim of deciphering how its loss contributes to the generation of blood cancers.

The gist of it

A gastrointestinal stromal tumor (GIST) is a rare type of tumor that usually affects the stomach or small intestine. Although there are no known causes of GIST, 95 percent of people with this condition have a type of GIST that originates when a protein called KIT becomes abnormal. In roughly three-quarters of GIST cases, mutations in KIT are present that drive the proliferation of these tumors.

This condition is called KIT-positive (KIT+) GIST. Normally, KIT signals cells in the body to grow and divide only when new cells are needed. In KIT+ GIST, KIT becomes abnormal because of a mutation, and the signal to the cells does not turn off. KIT sends out a constant signal that tells cells to keep growing and dividing, resulting in uncontrolled cell growth that leads to tumor formation.

Irving Weissman

In a study published online **February 4** in *Proceedings of the National Academy of Sciences*, Ludwig scientists at Stanford led by Irving Weissman showed that the anti-KIT monoclonal antibody SR1 can significantly inhibit stromal tumor GIST cell growth. It could become an alternative or supplementary therapy for patients who develop resistance to imatinib (Gleevec), a drug approved by the US Food and Drug Administration. The drug works by inhibiting, or turning off, the signal from the KIT protein, so that most of the cancer cells stop growing.

SR1 treatment may also prove useful in other KIT+ tumors, such as in breast cancer, melanoma and neuroblastoma, a malignant tumor that develops from nerve tissue.

Stefan Constantinescu

Turning it on

Thrombopoietin promotes the growth and proliferation of platelet cells, which are involved in blood clotting, and the thrombopoietin receptor is important in blood formation. Thrombopoietin signaling may also help renew stem cells within the bone marrow that have the potential to develop into red blood cells, white blood cells, and platelets.

In a paper published **January 28** in *Proceedings of the National Academy of Sciences*, a team led by Ludwig researcher Stefan Constantinescu in Brussels and colleagues showed how a mutation that alters a single amino acid in the thrombopoietin receptor turns it on permanently. They explained how this leads to the blood malignancies essential thrombocythemia and primary myelofibrosis, related diseases in which abnormal blood cells and fibers, respectively, build up inside the bone marrow.

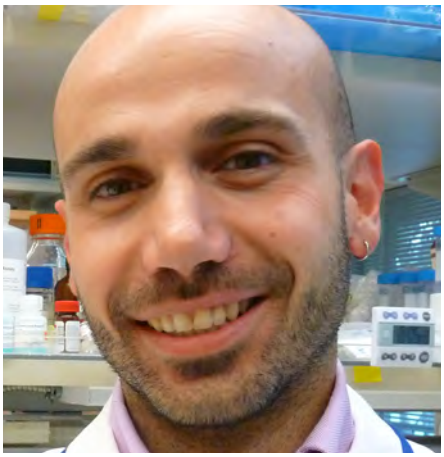
This finding is significant for both the basic science of signal transduction and applied cancer research. The amino acid in question, tryptophan, is found at similar points in other cell surface receptors, and molecular biologists had presumed that it marks the point at which the receptor emerges from the membrane into the cell's cytoplasm. In contrast, this study showed that it prevents close pairing of upstream membrane domains and receptor activation. Stefan and his colleagues have begun bioinformatics studies to test this new hypothesis—and determine whether similar mutations on other receptors are also associated with cancer.

Ask a scientist

What do you think has been the biggest achievement of the war on cancer?

As a medical oncologist, I'm impressed by how the FDA approval of ipilimumab has changed the landscape in the 'war on cancer': transforming the standard of care for melanoma and acting as a catalyst for the broader development and clinical testing of immunotherapies in melanoma and beyond.

—Maggie Callahan,
Ludwig New York



A cancer diagnosis is no longer a death sentence. Early detection and advances in tumor biology and genetics shifted it from being an enigmatic killer to a familiar enemy. Moving forward, we need to diversify research and treatment strategy to fully unmask this heterogeneous and devious disease.

—Ciro Zanca,
Ludwig San Diego

We are just beginning to understand how complex cancer really is, with genetic heterogeneity found within single tumor biopsies. The dawn of inexpensive and fast whole-genome sequencing will enable individualized diagnosis and treatment, providing the unique opportunity to unify all aspects of cancer research into comprehensive cancer systems biology.

—Rasmus Freter,
Ludwig Oxford

COMPANY NEWS

Grand alliance

Tumors have an uncanny ability to evade immune responses.

But Ludwig is fighting back on several fronts. In January, the Ludwig Institute and 4-Antibody, a Swiss antibody technology company, signed a multitarget research and clinical development collaboration with Recepta Biopharma, a company founded by Ludwig and a group of Brazilian investors. Recepta is the leading developer in Brazil of therapeutic antibodies, which can block the growth of a tumor and/or recruit the body's immune system to attack it. The new deal extends a collaboration between Ludwig and 4-Antibody that began in 2011, and expands Recepta's antibody pipeline.

The research and clinical development partnership will focus on generating and developing three antibody therapeutics that target regulatory checkpoints of the immune system. These checkpoints act as on- or off-switches for the T cells of the immune system, and are important in anticancer therapy. The only FDA-approved immune checkpoint antibody to date is ipilimumab (Yervoy); it is currently the highest grossing melanoma drug in the US and the five major European Union markets.

4-Antibody will generate panels of fully human therapeutic antibodies against these targets. The Institute has developed a novel assay platform that it will use to select candidate antibodies for further evaluation. The parties anticipate that the first candidate will enter clinical trials in early 2015.

"We have seen tremendous progress in the development of treatments that harness the power of the immune system to better detect and treat cancer. This expanded collaboration will provide Ludwig scientists with access to important clinical agents and enable us to identify and evaluate new combinations of treatments to facilitate the development of the next generation of more potent immunotherapy drugs," said Jonathan Skipper, head of Ludwig's technology development program.

Once these antibodies have been validated, the Institute will use them in clinical trials that Recepta will conduct in Brazil.

Q&A WITH ANDY SHIAU AND TIM GAHMAN

Three years ago, biochemist Andy Shiau (program director) and chemist Tim Gahman (director of medicinal chemistry) came to Ludwig to help our scientists perform cutting-edge research and take their ideas from concept to clinical testing. We recently had a chance to sit down with our San Diego-based 'drug hunters' and learn more about their unique group.

Andy Shiau

Tim Gahman

What are small molecules?

Small molecules are chemical compounds. They can be substances you find in nature or things chemists make in the lab. Table sugar is a small molecule. Vitamin C is a small molecule. So are drugs, including pain relievers like aspirin and antibiotics such as penicillin. Right now, small molecules make up about 90 percent of the drug market.

Why was the Small Molecule Discovery Program started?

Targeted small molecule therapies hold great promise for the battle against cancer. They block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression. In fact, today there are several small molecules that are targeted cancer therapies, for example Gleevec, which is approved to treat gastrointestinal stromal tumor, a rare cancer of the gastrointestinal tract.

The small molecule lab provides the Ludwig community around the world access to small molecule tools for research and helps them move basic scientific findings from the lab to a clinical setting.

How do you go about creating a small molecule?

Making any kind of drug is a technically exacting process. And making small molecule drugs is no exception. Once we've identified a target, we create molecules from scratch by using sophisticated computer modeling. At other times we apply a process called high-throughput screening, which can be used to quickly conduct millions of chemical tests on cells or proteins. Both of these approaches help us to determine what type of molecule controls the activity of a specific protein that tells cancer cells to grow and multiply out of control. We're looking to slow or block these types of biochemical signals and cause cancer cells, but not normal ones, to die.

The results of these experiments provide starting points for understanding the interaction or role of a particular biochemical process in biology, an important early step in drug development. The chemical hits we get from our initial screening or design process are then optimized, or altered to make them more effective and safer. For example, we can modify a compound to make it less likely to interact with certain pathways in the body and reduce the potential for side effects, such as toxicity to a healthy organ.

We test hundreds or even thousands of compounds against a target to identify any

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that might be promising. And based on the results, we might select several lead compounds for further study. We've used these types of approaches to identify inhibitors of many proteins, such as enzymes and receptors that Ludwig scientists are interested in.

Can you give us an example?

We are working with Karen Oegema's and Arshad Desai's labs to use our polo-like kinase 4 (PLK4) inhibitors to figure out how normal and cancer cells divide. This is a pretty basic concept that we still have a lot to learn about. PLK4 is an important cell cycle regulator that's involved in the regulation of centrosome duplication. Centrosomes help regulate the cell's progression through the cell cycle. Errors in the centrosome duplication cycle may be an important cause of aneuploidy, a chromosome problem caused by an extra or missing chromosome, which may contribute to cancer formation.

We've screened multiple small molecules against PLK4 and identified one that potently and specifically inhibits the enzyme in both biochemical and cellular assays. If we find differences between the dependence of normal and cancer cells on PLK4 and centrosomes, we can use this information to make a totally new class of drugs targeting tumors in which PLK4 regulation is disrupted. Small molecules that target PLK4 could hold great promise as anticancer drugs.

What excites you about your work?

The incredible wealth of knowledge that has been generated with the sequencing of the human genome has really revolutionized the discovery and development of small molecule cancer drugs over the last decade. We're moving from a one-size-fits-all approach that emphasized chemotherapy to a personalized medicine strategy that focuses on the discovery and development of molecularly targeted drugs that exploit the vulnerabilities of cancer cells. Because of its vision and resources, Ludwig is uniquely positioned to help in this transition.

Working with the small-molecule team

Paul Mischel of Ludwig San Diego talks about his collaboration with the small-molecule development team.

Working with the group, we're able to use small molecules to better understand the biology of our targets and to then develop drugs that could potentially have a major impact in the care of patients. For example, we've identified a novel mechanism by which brain cancer cells regulate cholesterol levels and might turn out to be a powerful therapeutically targetable opportunity. The group has been developing and refining compounds that target this mechanism, causing tumor cells to die in well-controlled pre-clinical models. These results are very exciting and may lead to a clinical trial. Without their expertise, we wouldn't have been able to do it because in the traditional academic model, we'd be compelled to try and convince a pharmaceutical company that the target is of interest.

Why is it important that Ludwig undertakes drug discovery research?

Biological systems are very complicated, so it's virtually impossible to foresee what projects will ultimately pay off. This makes it very expensive and risky. Many people think discovering and making drugs is like manufacturing cars or electronics. It's a lot less predictable than that. Maybe one out of a thousand or even ten thousand projects will lead to a drug. So, the drug industry is more like Hollywood—it's very hit driven. Pharmaceutical companies are reluctant to undertake early-stage research, and it's getting harder to fund biotech startups as venture capitalists realize how much work and time goes into developing a drug. That's why Ludwig is important. It's willing to invest in research today to develop the drugs of tomorrow.

What is the biggest challenge the group faces?

Our biggest challenge is that we're starting at the very beginning of the drug discovery process. We're talking to people about ideas. We're talking about results of an experiment that researchers have seen for the very first time. But we're in the

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ideal place to take this approach because we have great colleagues who do fantastic science, the support of Ludwig, and a mission to deliver therapeutics.

What gets you up in the morning?

Finding a small molecule drug that will drive cancer cells to suicide. Walking the halls and interacting with some of the world's leading scientists. Working in an environment where people are constantly looking for answers and challenging themselves to do incredibly novel things.

Kick-starting the body's own tumor-destroying systems to trigger cell death in cancerous but not healthy tissue is a project we're working on with Benoît Van den Eynde. Understanding cholesterol metabolism in brain tumors and uncovering new biology are part of an exciting collaboration with Paul Mischel.

Bottom line: Driving the science forward gets us up in the morning.

And figuring out how to do that keeps us awake at night.

Working with the small-molecule team

Benoît Van den Eynde of Ludwig Brussels talks about his collaboration with the small-molecule development team.

Immunotherapy – boosting the body's natural immune system to fight cancerous tumors – is the next frontier in life-extending cancer treatment. We've identified two targets whose inhibition with a drug could enhance the ability of the immune system to reject cancer cells. We've chosen to push the development of these drugs through the creation of a start-up company, iTeos Therapeutics. Andy and Tim have been involved in this project from the very beginning, by accelerating the medicinal chemistry programs, helping to vet medicinal staff candidates and selecting the most efficient subcontractors for chemical synthesis. They're also providing ongoing guidance during the development program, and directly participating in the research effort through the development of a new assay to screen for compounds inhibiting one of our targets. Their input has been invaluable.

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Kinde I, Bettegowda C, Wang Y, Wu J, Agrawal N, Shih IeM, Kurman R, Dao F, Levine DA, Giuntoli R, Roden R, Eshleman JR, Carvalho JP, Marie SK, Papadopoulos N, Kinzler KW, Vogelstein B, Diaz LA Jr.

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Huber F, Lang HP, Backmann N, Rimoldi D,* Gerber Ch.*
**These authors contributed equally to this work*

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