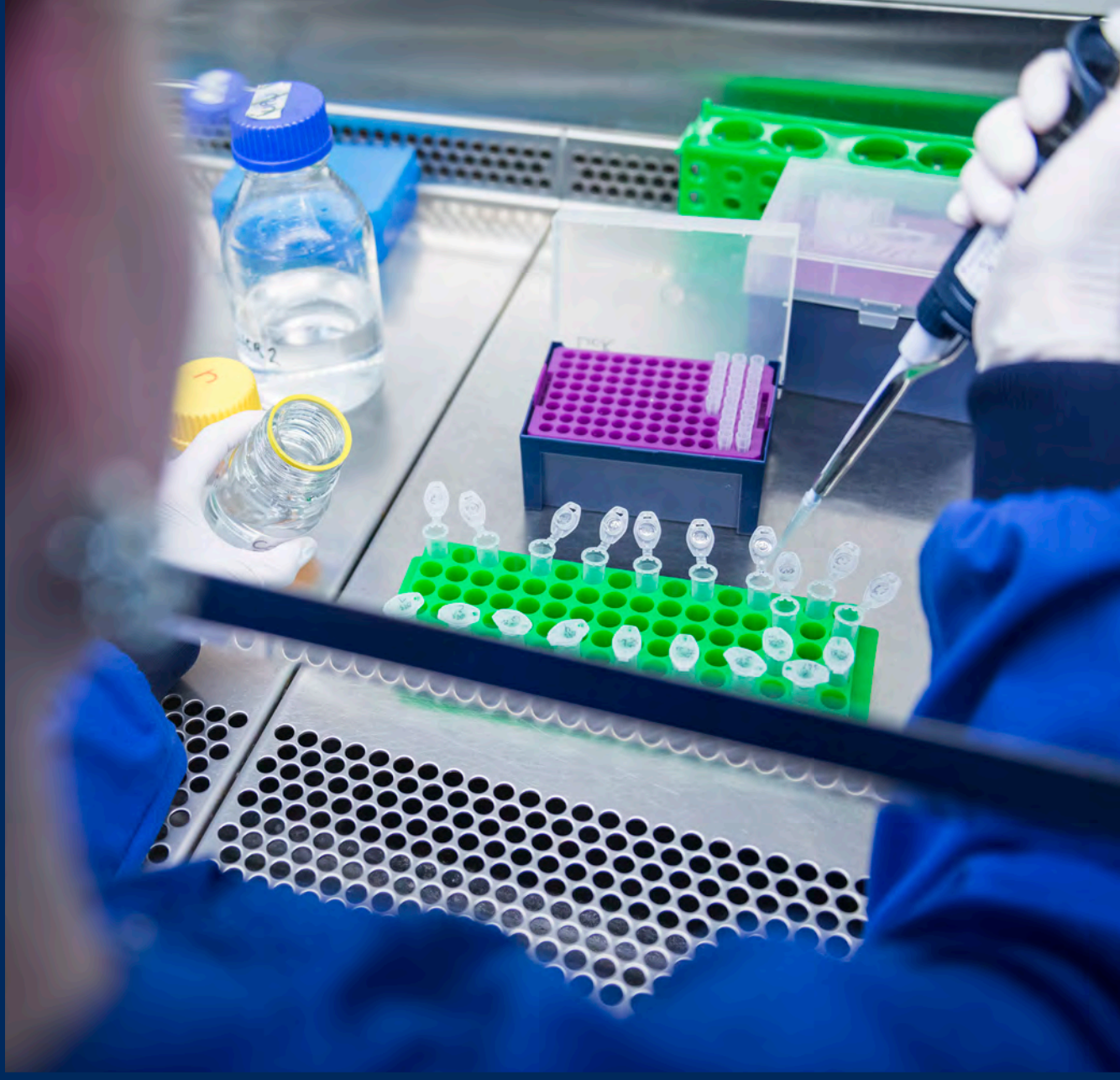


LUDWIG LINK

APRIL 2017

IN THIS ISSUE

LUDWIG CANCER RESEARCH

LIFE-CHANGING SCIENCE

LUDWIG LINK
ludwigcancerresearch.org APRIL 2017

LETTER

This is our first newsletter of the new year and we have a lot of exciting news to share with you. For starters, Ludwig appointed Judge Barbara Jones to our Board of Directors in December, and you can learn a little about her in our feature on page 7. And as you must already know, we also have a new Scientific Director, Chi Van Dang, who will join us starting on July 1. Take a look at our discussion with him starting on page 16. As always, our researchers have been busy collecting accolades and honors for their contributions to cancer research—and publishing new discoveries as briskly as ever.

You'll read in these pages about a novel method to track and monitor T cells in living patients, the immunologic mechanism of an experimental immunotherapy that transforms suppressive immune cells and makes certain resistant tumors susceptible to checkpoint blockade, a new method to capture the full spectrum of small RNAs in a single cell and much, much more. We also have an article on Ludwig Board Member Sam Hellman's new book, a collection of essays that serves as an extended reflection on what he has learned over his five decades as a prominent cancer doctor and researcher.

Big data is a hot topic in science and we love challenging our scientists, so we asked them to weigh in on the question: Does big data equal big gains in cancer research? Read what they said on page 21.

Happy reading!

Sincerely,

Rachel Steinhardt
Vice President for Communications

TABLE OF CONTENTS

On the cover: Oxford Branch.

Stephen Elledge
Ludwig Harvard

Roeland Nusse
Ludwig Stanford

FOR PARADIGMATIC DISCOVERY (TWO "OSCARS")

Ludwig Harvard's Stephen Elledge and Ludwig Stanford's Roeland Nusse were each awarded the Breakthrough Prize in Life Sciences. Stephen was honored for his contributions across multiple fields of biology, including his elucidation of critical mechanisms in cell division, cell aging, cancer and protein breakdown and recycling. One of Stephen's most important discoveries was how cells sense DNA damage and initiate self-repair, a mechanism that safeguards both individual cells and the health of the whole organism. Click here to listen to a brief description of Stephen's work. Roeland was honored for his exploration of the intercellular signaling systems involved in embryonic development, cancer and stem cell biology. He is perhaps best known for the discovery in 1982 of the first Wnt gene and his subsequent illumination of its roles in embryonic development, stem cells, bone growth and cancer progression. Click here for a description of Roeland's work. The Breakthrough Prize recognizes paradigm-shifting discoveries in the life sciences, physics, and mathematics and, since its inception in 2012, has awarded nearly $200 million to researchers. Foundations supported by Google, 23andme, Facebook and DST Global jointly finance the prize.

Joan Brugge
Ludwig Harvard

FOR SHAPING A FIELD

Ludwig Harvard Co-director Joan Brugge was awarded the American Cancer Society Medal of Honor for Basic Research in January for her landmark identification of the protein encoded by the Src oncogene and her prolific work on how cells regulate the mechanisms that drive cancer. Joan's research focuses on the genetic and non-genetic changes that lead to the development of cancer, and her discoveries have extensively shaped current models of the molecular and cell biology of breast cancer. She continues to push the boundaries of science, establishing the power of 3D culture systems to model cancer progression and test new treatments. The Medal of Honor is awarded to those who have made the "most valuable contributions and impact in saving more lives from cancer through basic research, clinical research, and cancer control."

FOR A STELLAR STUDY

Ludwig Oxford researcher Sarah De Val was awarded the 2017 Werner Risau Early Career Investigator Award in Vascular Biology. Sarah's laboratory explores angiogenesis, tracing the transcriptional pathways that regulate the growth of new blood vessels. Angiogenesis is essential for such healthy processes as healing and embryonic development, but is co-opted by tumors to sustain their growth. Her paper, An Intronic Flk1 Enhancer Directs Arterial-Specific Expression via RBPJ-Mediated Venous Repression, was selected as the most notable paper published in 2016 in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the area of vascular biology. You can download a copy of her paper here. The study identifies a novel mechanism by which arteries and veins acquire their distinct identities during angiogenesis, and exposes a direct link between the Notch and VEGF signaling pathways. The award is named for Dr. Werner Risau, who described concepts central to the study of angiogenesis. Sarah will receive her award from the ATVB Council on May 5 in Minneapolis, Minnesota.

Sarah De Val
Ludwig Oxford

FOR BREAST CANCER STUDIES

Ludwig Chicago Co-director Geoffrey Greene was named a Fellow of the American Association for the Advancement of Science (AAAS) for his contributions to our understanding of steroid hormone action and its role in breast cancer, particularly for the development of estrogen and progesterone receptor antibodies. Geoff has had a profound influence on our understanding of hormone-dependent breast cancer, inspiring new and effective ways to treat and prevent such tumors. He has also led the development of immunoassays for estrogen receptors that are used worldwide to evaluate prognosis and select appropriate therapies for breast cancer patients. AAAS members elect their Fellows for their scientifically or socially distinguished efforts to advance science or its applications. The 391 newly elected Fellows were honored February 18 at the AAAS annual meeting in Boston, Massachusetts.

Geoffrey Greene
Ludwig Chicago

FOR EXPOSING SUPPRESSION

Ludwig MSK's Alexander (Sasha) Rudensky was one of the recipients of the SEK 6 million (US $671,000) 2017 Crafoord Prize in Polyarthritis awarded by the Royal Swedish Academy of Sciences for his discoveries relating to regulatory T cells (Tregs), which restrain certain immune responses. In 2003, building on work done by his Crafoord Prize co-recipients, Shimon Sakaguchi of Osaka University in Japan and Fred Ramsdell from the Parker Institute for Cancer Immunotherapy in California, Sasha knocked out the FOXP3 gene in mice. This disrupted the generation of Treg cells, inducing severe autoimmunity. The work established FoxP3 as the key regulator of Treg identity and complemented similar findings made by the Sakaguchi and Ramsdell laboratories around the same time. The discoveries spawned a new subfield of immunologic research, and numerous clinical trials targeting Treg cell activity are today being conducted around the world to address ailments ranging from autoimmune and infectious diseases to cancer. The award ceremony will be held at the Royal Swedish Academy of Sciences on May 18, in the presence of H.R.H. Crown Princess Victoria. Click here for the video press release from the Royal Swedish Academy of Sciences.

Alexander (Sasha) Rudensky
Ludwig MSK

FOR CHARTING CANCER'S COURSE

Ludwig Johns Hopkins Co-director Bert Vogelstein was awarded the first 2016 Bob Pinedo Cancer Care Award by The Royal Dutch Academy of Arts and Sciences (KNAW) in December for his contributions to elucidating the genetic mechanisms of cancer progression. The biennial award is given to outstanding cancer researchers or caregivers. Bert described how a series of DNA mutations, adding up silently over decades, turn cells cancerous. He and his collaborators were the first to explain the precise genetic process by which a common human malignancy, colorectal cancer, originates in healthy tissues. His methodical, incisive studies done in collaboration with Co-director Kenneth Kinzler laid the foundations for a host of new anti-cancer therapies, diagnostics and preventative strategies. The award is named after the Dutch oncologist and researcher Bob Pinedo, an early pioneer of translational research who, over four decades, played a major role in advancing immunotherapy and our understanding of angiogenesis.

Bert Vogelstein
Ludwig Johns Hopkins

OUR NEW BOARD MEMBER

Barbara Jones joined the Ludwig Board of Directors in December. A former judge who served for 16 years in the US District Court for the Southern District of New York, Barbara is currently partner at Bracewell, in Houston, Texas, specializing in white-collar defense, corporate compliance and internal investigations. Prior to her nomination to the bench, Barbara was the first woman to head a US Department of Justice strike force office as the chief of the Manhattan Organized Crime Strike Force. During her judicial service, she presided over a range of high-profile cases, including the trial of Bernard Ebbers, the former CEO of WorldCom. The case was among the largest accounting fraud prosecutions in US history. She also adjudicated a challenge to a section of the "Defense of Marriage Act" (DOMA), ruling in 2012 that it violated the US constitution's guarantee of equal protection under the law. Her decision was upheld by the Supreme Court. In November, Barbara was presented with the prestigious Emory Buckner Award for Outstanding Public Service by the Federal Bar Council in New York City. A graduate of Temple University School of Law, Barbara has also served as an adjunct assistant professor at Fordham Law School and New York University School of Law.

Barbara Jones
Ludwig Board of Directors

Rickard Sandberg
Ludwig Stockholm

SMALL MATTER OF IDENTITY

Small RNAs, which are known to regulate gene expression, are a hot topic of biological research. But it isn't clear what specific roles these molecules play in different types of cells or diseases. To begin addressing this challenge, Ludwig Stockholm's Rickard Sandberg and his team developed a new method that relies on the global capture of RNAs expressed in a single cell and applied it to characterize short, non-coding RNA sequences in individual embryonic cells. As described in December in *Nature Biotechnology*, the researchers used two types of embryonic stem cells intended to mimic the early embryo before and after it has attached to the uterine lining. They detected numerous small RNAs in both cell states and detailed how large numbers of one type, known as microRNAs, are expressed differently in each. They also analyzed small RNA expression in brain cancer cells. The researchers propose that miRNAs could be useful markers for distinct cell types and states.

A HELPFUL REVERSION

Genetic reprogramming in the laboratory can turn many types of mature cells into induced pluripotent stem cells (iPS), which can generate a broad variety of cell types. Even though the technology has been around for 10 years, no one had accomplished this feat with a human leukemia cell. Until now. Ludwig Stanford scientists Ravi Majeti, Mark Chao, and their colleagues reported in a March paper in *Cell Stem Cell* how they went about it and what they learned. They found that when they grew the leukemia iPS cells into other kinds of tissues, like heart cells or neurons, the cells looked and behaved as they should. But when they grew them back to be blood cells, they became cancerous. Since leukemia cell populations contain a number of subclones that have different genetic mutations, this approach might be used to create and study the leukemia generated by each subclone in a patient's cancer and so refine the selection of drug therapies.

Ravi Majeti
Ludwig Stanford

Mark Chao
Ludwig Stanford

A TAB ON T CELLS

Sanjiv (Sam) Gambhir
Ludwig Stanford

Tracking cancer immunotherapy just got a lot easier. Using genetically engineered T cells (CAR-T cells) to seek out and destroy tumor cells, Ludwig Stanford Professor Sanjiv (Sam) Gambhir and his team have developed a technology that reveals the movements of immune cells in living patients. In a paper published in January in *Science Translational Medicine*, the researchers demonstrated the first visualization of human immune cells as they hunt down brain tumor cells. Their technique can track the location, numbers and viability of the introduced T cells, and gives physicians a quick and frequently repeatable way to assess immune responses to immunotherapeutic treatment. The researchers first engineered T cells to better recognize patients' cancer cells. Later, they added a "reporter gene" to the T cells encoding a protein that can be detected with a positron emission tomography scan. Although the work was done in patients with brain cancer, the groundbreaking technique can be adapted to track immune cells targeting any kind of tumor. Click here to see a brain scan of a glioma patient before and after T cell immunotherapy.

MENA AS MARKER

A team led by Ludwig MIT scientist Frank Gertler has identified a biomarker that could reveal whether patients with the aggressive, triple-negative form of breast cancer are likely to be helped by the drug Taxol. The findings published in January in *Molecular Cancer Therapeutics* may also offer doctors a new way to choose drugs for this type of breast cancer, which lacks all three key molecular markers: estrogen receptor, progesterone receptor and Her2. The potentially new biomarker, a protein called Mena, has previously been shown to aid the spread of cancer cells. The researchers showed that triple-negative breast cancer cells with higher levels of Mena were the most resistant to Taxol. Treatment with this drug increases the expression of ERK1, a protein that at high levels allows cells to become resistant to the drug. The researchers found that combining Taxol with an ERK inhibitor increased cancer cell death when compared to Taxol treatment alone. Clinical trials testing this combination are already underway, and looking at Mena expression in tumors could reveal which patients are most likely to benefit from such treatment. The researchers will next evaluate whether their findings hold in patient-derived tumors.

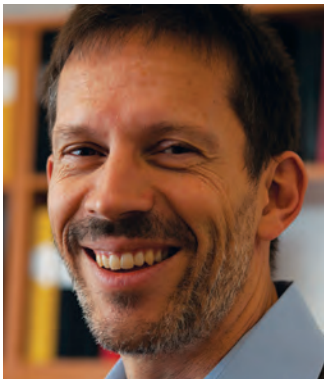
Frank Gertler
Ludwig MIT

Don Cleveland
Ludwig San Diego

HUMPTY DUMPTY CHROMOSOME

A team of researchers led by Ludwig San Diego's Don Cleveland has detailed how one type of error during cell division can give rise to dramatically rearranged chromosomes in a process that leads to shattering of one chromosome into dozens to hundreds of pieces that are subsequently re-stitched together in random order. This process is called chromothripsis, Greek for "chromosome shattering", and occurs frequently in bone, blood, and brain cancers but its underlying mechanisms had not been identified. In their study published in the January issue of *Nature Cell Biology*, the researchers report that the process begins in mitosis when a single chromosome is erroneously left behind from the other chromosomes and forms its own nucleus, called a micronucleus. Led by postdoctoral fellow Peter Ly, the team developed a method to divert the Y chromosome into a micronucleus to trigger its chromothripsis. In their step-by-step analysis of what happens next, they demonstrate that the solo chromosome shatters into more than 50 pieces that are then stitched together in random order by a process known as non-homologous end joining. They show that over the next three cycles of cell division, this creates an extensively mutated chromosome.

THE RIGHT NERVE



Thomas Perlmann
Ludwig Stockholm

Rickard Sandberg
Ludwig Stockholm

The first transplantation of stem cells in patients with Parkinson's disease (PD) is almost within reach. PD is a neurodegenerative brain disorder affecting nerve cells in the brain that produce dopamine. In two studies published in January in *Cell Stem Cell*, Ludwig Stockholm scientists and colleagues at Lund University presented results that could significantly improve currently experimental cell therapies for PD. The first, led by Ludwig Stockholm Director Thomas Perlmann and including Rickard Sandberg, also a member of Ludwig Stockholm, addresses the identity of cells that give rise to dopaminergic neurons. Applying single-cell RNA sequencing technology developed in Sandberg's lab, the researchers pinpointed the origins of dopamine-producing cells in the mouse embryonic brain. They found that during their early development, dopamine cells are very closely related to a type of cell that develops into STN cells, which don't degenerate during Parkinson's disease.

The second paper, in which Perlmann is a co-author, examined whether the information obtained in the first could be used to improve experimental stem cell therapies for Parkinson's. The authors describe how they applied RNA sequencing to analyze global gene expression in more than 30 batches of neural grafts prepared from human embryonic stem cells. They found that the molecular markers currently used to capture progenitors of dopaminergic neurons generate subpar grafts because they capture neurons that make STN cells as well. The researchers then applied the markers identified in the first study, and showed that this generates a far superior graft of dopaminergic neurons. Their method is ready for immediate use in clinical trials evaluating cell therapy for Parkinson's disease.

OLD STORY, NEW INSIGHT

How cancer cells pull up stakes to metastasize has been a subject of exhaustive study in recent years. But few researchers have examined why they do so. Now a study led by Ludwig Oxford's Colin Goding and published in *Genes & Development* in January offers an answer to this enduring question. The researchers identify a cellular response conserved through eons of evolution that underlies the spread of the aggressive skin cancer melanoma. The researchers show that when deprived of a key nutrient, melanoma cells switch on an innate stress-response mechanism that also sparks up a program to go mobile and seek food. They do this by switching off a key controller of protein synthesis named eIF2B that enables cells to conserve resources under starvation conditions. But the same switch also turns on a gene named ATF4 that orchestrates the cell's responses to stress. The researchers show that inflammatory signals, which fuel metastasis, activate the same stress-response mechanism in melanoma cells. The cancer cells, it appears, have hijacked the starvation mechanism to create a universal response to "get out of here" signals to escape challenging environments. The findings also reveal clues on why some melanoma patients respond relatively poorly to both a key targeted therapy and an immunotherapy known as PD-1 blockade, and suggest novel strategies for treating this form of skin cancer.

Colin Goding
Ludwig Oxford

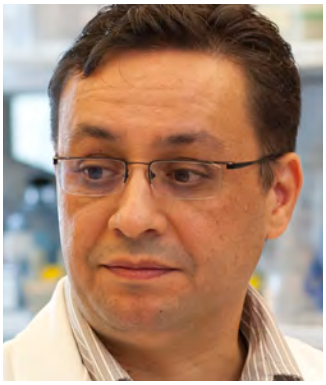
Sanjiv (Sam) Gambhir
Ludwig Stanford

CHEAPER, QUICKER, SAFER BIOPSY

A new test developed by Ludwig Stanford Professor Sanjiv (Sam) Gambhir and colleagues requires just half a teaspoon of blood and allows doctors to see how well cancer patients are responding to treatment. If it passes muster in larger studies, its cost could be as little as US $30. The test provides results in less than five hours. This is all good news because lung cancer is the most common cancer in the world, with 58% of cases in less developed countries. Sam and his team described in December in the *Proceedings of the National Academy of Sciences* how they isolated rare circulating tumor cells (CTCs) from the blood of cancer patients and read a handful of genes in each. The researchers used antibodies specific to CTCs to mark the cells. The antibodies were then labeled in turn with magnetic nanoparticles, which permitted the researchers to isolate the CTCs using a device one of the researchers developed known as the magnetic sifter, or MagSifter. Their liquid biopsy could aid the study of tumor evolution and transform cancer research and care, helping doctors select better targeted therapies as evolving tumors become resistant to initial treatments. It could also reduce the need for surgical lung biopsies, which are expensive, invasive and risky.

SUPPRESSING SUPPRESSION

A team of researchers led by Taha Merghoub and Jedd Wolchok of Ludwig MSK published a paper in *Nature* in November showing that an experimental drug currently in clinical trials can boost the effects of immunotherapy. The drug in question works by targeting cells often found in tumors that suppress immune responses. Using mouse models of melanoma, the researchers applied a growth factor to boost the number of these immune-suppressive tumor-associated myeloid cells (TMACs) in tumors and demonstrated that this made them resistant to the checkpoint blockade immunotherapy known as PD-1 inhibition. Further, tumors initially sensitive to PD-1 blockade became resistant when researchers artificially boosted their TMAC populations. Taha, Jedd and their team then showed that the candidate drug IPI-549, which inhibits the activity of an enzyme called PI3Kγ, turns suppressive TMACs into an immune-activating variety. Tumors rich in TMACs became highly susceptible to the immunotherapy following IPI-549 treatment in multiple cancer types. The findings, which can be immediately tested in human trials, will allow doctors to inform studies testing these drugs and could help them better tailor treatment for cancer patients.



Taha Merghoub
Ludwig MSK

Jedd Wolchok
Ludwig MSK

Alexander (Sasha) Rudensky
Ludwig MSK

TREG TELL

Tumors use multiple mechanisms to evade potentially lethal immune responses. One of their favorites is the hijacking of regulatory T cells (Treg cells), which are often elevated in tumors and serve to suppress antitumor immunity. A study led by Ludwig MSK Director Alexander (Sasha) Rudensky and published November in *Immunity* sheds light on how cancers use Treg cells to orchestrate their defense and describes how those that infiltrate tumors differ from their counterparts in the rest of the body. Sasha and his team looked at Treg cells from over 100 human breast tumors. They report that, compared to normal tissue and peripheral blood, breast tumors possess a relatively large number of Treg cells, and the most aggressive ones have the largest numbers of the cells. These Treg cells are also distinguishable from others by their expression of a cell-surface receptor named CCR8, which is important for effector T cell trafficking to inflamed sites and is associated with many autoimmune and chronic inflammatory conditions. This suggests CCR8 targeting could offer a more selective strategy to deplete the cells and enhance immunotherapies for breast and other types of cancer.

FIREs WITHIN

In a resting cell, chromosomes are not arranged like the neatly structured baguettes we see in textbook snapshots but are unwound and pooled into what look like distinct yet relatively shapeless masses. This does not mean, however, that they lack structure and researchers have in recent years begun to unspool the secrets of their physical organization. This architecture, which determines which parts of the chromosome are open for business, and which are bundled away in a latent state, ultimately controls the expression of genes that give each cell type its identity and function. An analysis of genome-wide chromosome interactions led by Ludwig San Diego's Bing Ren and published in *Cell Reports* in November describes a novel element of this subtle architecture. The researchers report in their paper a structural element they call frequently interacting regions (FIREs), which display markedly high levels of interaction with nearby sequences of a given chromosome. The researchers' examination of chromosomal organization in 21 primary tissues and cell types revealed that FIREs contain a high frequency of DNA sequences known as super-enhancers, which dramatically boost gene expression. FIREs are also associated with genes characteristically expressed in or unique to a given type of cell. Their formation, the researchers show, is partially dependent on proteins known as CTCF and the cohesin complex, both of which modulate enhancer/promoter interactions in mammalian cells.

Bing Ren
Ludwig San Diego

LINKING SIGNALS

Angiogenesis, the generation of new blood vessels, depends on precise patterns of gene expression in particular subtypes of endothelial cells. But it has not been clear how inducers of angiogenesis, such as vascular endothelial growth factor A (VEGFA), control gene expression. A team of Ludwig Oxford scientists led by Sarah De Val identified MEF2 transcription factors—gene activators central to the control of cell differentiation and organ formation—as crucial regulators of sprouting angiogenesis, in which new blood vessels form from existing ones. Driven in response to insufficient supplies of nutrients and oxygen, among other things, this type of blood vessel growth is a hallmark of tumor progression. In an October paper in *Genes & Development*, Sarah and colleagues demonstrate MEF2 transcription factors are central effectors of VEGFA signaling in sprouting angiogenesis and show how they trigger relevant signaling circuits. They detail how MEF2 activation ramps up the production of many other genes involved in blood vessel growth. Most notably, it boosts the expression of Dll4, a critical regulator of sprouting angiogenesis involved in the Notch signaling pathway, which is also essential to the process.

Sarah De Val
Ludwig Oxford

Hiro Nakauchi
Ludwig Stanford

LIVING CHIMERA

A team led by Ludwig Stanford investigator Hiro Nakauchi has developed a novel approach to creating chimeras—single animals with cells of two species—overcoming cellular compatibility issues that have long troubled their construction. The new approach works by inhibiting programmed death in more advanced types of stem cells, typical when they're combined with the embryonic stem cells of another animal in the earliest stages of development. The new capability could be of significant use to researchers working in developmental biology and regenerative medicine. In a paper in *Cell Stem Cell* published in November, the researchers showed that the artificial expression of the BCL2 gene, which determines whether a cell lives or dies, helps foreign tissue injected into early embryos in the blastocyst stage to survive and to form chimeras. The researchers also show how to select transplanted cells to generate either whole chimeric animals or animals with alien tissue in a defined area. The findings have far-reaching medical implications, including enabling the growth of a patient's own tissues or organs in animals. Some 120,000 people in the US are waiting for lifesaving transplants, and every day two dozen die before they get them. Chimeric animals might shorten waits on the "transplant list" by providing patient-specific organs.

A WORTHY READ

Ludwig Board Member Sam Hellman can't remember a time when he didn't want to become a doctor. That's worked out pretty well for both the man and his chosen field of research. Patients worldwide have benefitted from his many contributions to cancer care, research and medical instruction. A prolific writer, Sam's published writings over 50 years cover the history, principles and best practices of cancer care. Now they've been compiled into a book titled *Learning While Caring: Reflections on a Half-Century of Cancer Practice, Research, Education and Ethics*, published in January 2017 by Oxford University Press. Sam argues that "medicine is a learned profession, but perhaps more important, it is a learning profession," and doctors need to continue their professional education while practicing medicine. The book has five sections—medical ethics and learning, academic medicine, research, perceptions of cancer, and heroes—with each section organized chronologically. He shares some thoughts on societal issues as well: *Medical science is general, but patient care is individual. The strict application of market principles to medicine is not in the best interest of patients, health care professionals or society at large.* Click here for a description of the book and its table of contents.

Sam Hellman
Ludwig Board
of Directors

T CELL STIMULUS

Immune checkpoint agonists are a new class of immunotherapies that boost the immune system's attack on cancer. Ludwig's agonist antibodies to checkpoint receptors GITR and OX40, discovered in a collaboration with Agenus, are currently being evaluated in clinical trials and were presented at the AACR Annual Meeting in April 2017. Agenus and its development partner Incyte previously announced that the first patients had been dosed in separate phase I/II clinical trials of the anti-GITR agonist antibody INCAGN1876 and the anti-OX40 agonist antibody INCAGN1949. The antibodies stimulate activated T cells and promote the killing of cancer cells. The phase I studies are evaluating the safety and tolerability of INCAGN1876 and INCAGN1949 in patients with advanced or metastatic solid tumors and examining the pharmacologically active and maximum tolerated dose. The phase II part of the studies will evaluate the recommended dose of INCAGN1876 and INCAGN1949 against multiple tumor types. In addition, preclinical studies of a third Ludwig antibody discovered in the Agenus collaboration, the anti-CTLA-4 antagonist AGEN1884, were presented at the AACR Annual meeting. AGEN1884 is being developed by Agenus and is in a phase I clinical trial to evaluate its safety and tolerability in patients with advanced solid tumors. Finally, results from preclinical studies evaluating the combination of AGEN1884 and Ludwig's anti-PD1 antibody AGEN2034—which also stems from the Agenus collaboration—and their combined effect on primary human T cell responses were presented at the AACR Meeting.

HEADY PROMISE

Data from a phase II clinical trial managed by Ludwig that is testing durvalumab in patients with glioblastoma mutiforme (GBM)—the most aggressive form of adult brain cancer—were reported by David Reardon of Dana-Farber Cancer Institute at the 21st Society for Neuro-Oncology Annual Scientific Meeting in November. David reported that the trial showed that durvalumab was well tolerated and generated durable responses in patients with recurrent GBM, who had not previously received bevacizumab (anti-VEGF). Durvalumab is an investigational human monoclonal antibody against the programmed cell death ligand 1 (PD-L1) protein. Signals from PD-L1 help tumors avoid detection by the immune system. Durvalumab blocks these signals, countering the tumor's immune-evading tactics. Currently, GBM patients have an average life expectancy of just 15 months and it is anticipated that adding a promising immunotherapy to the treatment regimen could help turn this around. This study is an international collaboration between the Cancer Research Institute in New York, Ludwig Cancer Research and MedImmune, partly supported by the Cure Brain Cancer Foundation. The trial is being conducted in the US and Australia.

CHI VAN DANG

LUDWIG'S NEW SCIENTIFIC DIRECTOR

Chi Van Dang
Ludwig Scientific Director

Chi Van Dang, a renowned cancer biologist and hematologist-oncologist, was appointed Scientific Director of the Ludwig Institute for Cancer Research in December. He joins Ludwig from the University of Pennsylvania's Abramson Cancer Center, which he has directed since 2011. At Penn, Chi launched a series of multidisciplinary, disease-specific Translational Centers of Excellence designed to accelerate the development of new solutions in cancer care. He is best known for research that established the first link between the cancer gene Myc—among the most frequently deregulated genes in cancers—and the aberrant metabolism of cancer cells. His studies, which explored how cancer cells alter the metabolic processing of a key sugar, explained a hallmark of cancer known as the "Warburg effect" and revived a long latent subfield of cancer biology. Therapies based on this work are today in various stages of clinical development.

Chi earned a PhD in chemistry from Georgetown University, an MD from Johns Hopkins University and then completed a fellowship at the University of California, San Francisco. He then returned to Hopkins as a researcher and instructor, rising to become Vice Dean for Research and Director of the Hopkins Institute for Cell Engineering before joining the Abramson Cancer Center. He was recently appointed to the Blue Ribbon panel to provide strategic guidance to former US Vice President Joe Biden's Cancer Moonshot initiative. Chi is a member of the National Academy of Medicine, a Fellow of the American Academy of Arts and Sciences and currently chairs the National Cancer Institute's Board of Scientific Advisors.

Q&A

Could you tell us a little about your early life, your family, when you got here and where you studied?
I was born in Saigon, one of 10 children and the son of Vietnam's first neurosurgeon and dean of the University of Saigon's School of Medicine. I was very privileged and fortunate to have a nurturing, loving and academically enthused family. When I was 12, the Vietnam War was intensifying and my parents sent my brother Chuc and me to live with an American family in Flint, Michigan, with whom they had forged a deep friendship. In our new home in America, we developed many strong relationships that have lasted to the present. We were reunited with our family in 1975, when my remaining family members, after having endured the refugee camps, immigrated to the US and settled in California. I attended the University of Michigan for my undergraduate degree, Georgetown University for a doctoral degree in chemistry, and Johns Hopkins School of Medicine for my medical degree. After my internship and residency in medicine at Johns Hopkins Hospital, I completed a fellowship in hematology-oncology at the Cancer Research Institute of the University of California at San Francisco. In 1987, I was appointed assistant professor of medicine at Johns Hopkins, where I remained until joining Penn.

Chi, far left, with his parents and nine siblings in Vietnam.

You initially got a Ph.D. in chemistry. What prompted you to switch to medicine?
A medical degree was always my goal, but I was considered stateless since I carried a passport from the Republic of South Vietnam, which ceased to exist as of April 1975 at the time when I applied to medical school. Despite my undergraduate record (highest honors), none were willing to admit me except Georgetown University, contingent on a combined chemistry-medical graduate training.

Did your depth of knowledge in chemistry give you any special insight into the research you subsequently began in the biomedical sciences?
Definitely. Chemistry provides the basic principles for biochemistry and biology

Click here to watch a video conversation with Chi Van Dang. Enter the password *LudwigSD2017*

Chi, second from left, with his brother Chuc and the family they lived with in Flint, Mich.

and is an invaluable science that plays a critical role in the drug development process. It has helped me a lot in terms of the kind of work we've been doing over the past couple of decades, focusing not only on what happens in cancer biology but also understanding the mechanisms that contribute to disease. Chemistry explains how the world around us works, which is a philosophy that has always driven my own research—to understand how things work not just what they look like.

What leadership advice would you would give to the next generation?
My philosophy is that when you're good to people, you're paid back much more than what you put in. It really comes down to the old adage—you reap what you sow—your deeds, good or bad, will repay you in kind. Trust builds respect and loyalty and is essential in every organization. You shouldn't trust people blindly, but I believe it's always better to give people the benefit of the doubt.

Can you name a person who has had a significant impact on you as a leader?
I have had many mentors and teachers and learned from each one of them starting with my high school biology teacher and on to my thesis advisor at the University of Michigan, who taught me a lot about how to think about science. I would have to single out Edward Miller, who was the former dean at the Johns Hopkins Medical School under whom I served as Vice Dean for Research. Ed definitely had a pivotal influence on my thinking and my managerial style. He was by far one of the smartest people I have ever dealt with and his people skills were unparalleled. He was an effective leader, in that he recognized that people are the single most important part of the equation in the success of an organization. He had a big heart and truly cared about people as individuals.

How do you foster an environment that encourages scientists to think big?
Part of my job at Ludwig will be to deploy resources, which is an important component of getting people to think big. I often find that junior faculty members don't want to take a risk on something that might not yield positive results because it might hinder their career advancement so I would encourage them to spend 70-80 percent of their time on things they're comfortable with and sure of. The other 20-30 percent should be spent on taking some risks. It might not yield much but it's an opportunity to think big, which could

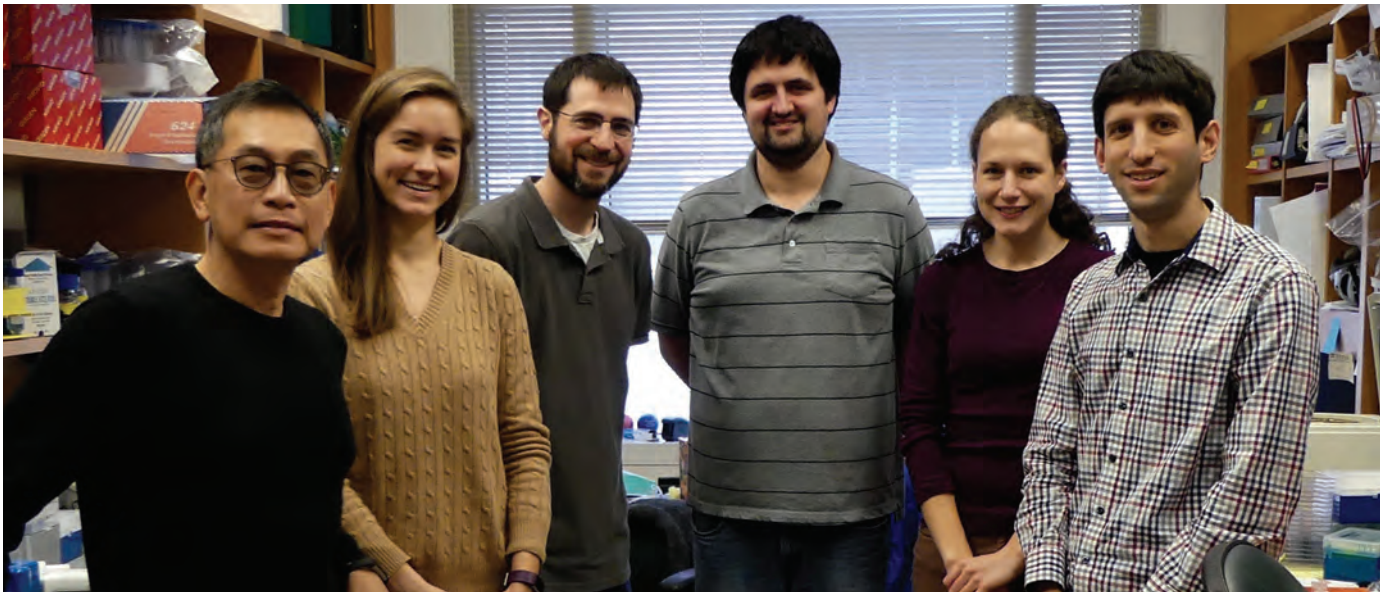
ultimately lead to challenging and maybe even changing accepted paradigms. I would also suggest to senior scientists who are established and world famous to take risks. They've reached the pinnacle of their academic careers and are now in a unique position to take risks, think big and make breakthroughs. They can be bold and step out of the box to ask new questions and find new answers that can help change the world, and perhaps make the world a better place. Teamwork is another way to think big because a lot of breakthroughs require teams rather than individuals. Today, with the advances in technology and explosion of information, it would be tough for a single person to contribute all the necessary expertise to solve increasingly complex problems.

What excites you most about the future trajectory of your research?
Finding drugs that are disadvantageous to the cancer cell but at the same time advantageous for the immune cell. To do this we really need to better understand how metabolic pathways are regulated in immune cells, how specific metabolic programs alter immune function and how immunity may in turn influence metabolism. This would be the Holy Grail and one that requires a lot of basic and animal work to develop into models. Over the past 10 years, I have consulted with a number of pharmaceutical companies that are currently developing drugs that could selectively disrupt key metabolic pathways for cancer cell survival and growth. I'm really excited about launching my Ludwig activities in July, as we have some new ideas for drug development that could have significant therapeutic potential.

Are there any natural connections between your studies and Ludwig research?
Definitely. We will be undertaking local CRISPR/Cas 9 screening and harnessing its power for use across the drug discovery platform to identify new targets and hopefully, down the line, new drugs. We'll need to prove them in biological models once we've validated them, and that will probably take a couple of years. The Small Molecule Discovery group at the San Diego Branch will be instrumental in this area, as it is quite adept at creating small molecules that could act like drugs and assessing whether they might be worth turning into treatments. Our work also intersects with immunity and anti-cancer immunology, so this is a natural connection to the work at Oxford and Lausanne. If we get really lucky we'll find new drugs that will hopefully end up in some clinical trial in Lausanne, among other places.

What were the biggest challenges you faced when creating the Translational Centers of Excellence at Penn?
The recognition that no single organization can excel in all areas. We had experts from across the Penn community who came together to identify and decide which projects to support that would ultimately become flagship programs. It was a very rigorous application process—every application had to be competitive and underwent an outside peer review. Only four centers were approved on the first round. As I transition out, my

> "My philosophy is that when you're good to people, you're paid back much more than what you put in. It really comes down to the old adage—you reap what you sow—your deeds, good or bad, will repay you in kind."



Chi in his lab at the University of Pennsylvania's Abramson Cancer Center.

recommendation is to continue to define the areas of strength and invest in them but without ignoring opportunities in areas where Penn might need to strengthen, and to find ways to initiate efforts to both build and leverage those shortcomings to achieve greater success.

Is the approach you took there transferrable to Ludwig?

Ludwig is different because it's comprised of an international network of scientists with specific areas of expertise. Within this framework, you can draw on each group's expertise to forge collaborations aimed at solving specific challenges and ultimately translating them into therapies. My goal would be to grow through connectivity by focusing on each site's strengths and capabilities and connecting investigators at different sites through their complementary strengths.

In your opinion, are there best practices for advancing promising discoveries into the translational pipeline?

I have used the Stand Up To Cancer (SUTC) research model for the translational opportunities here at Penn. I was part of one of the initial teams to go after pancreatic cancer and saw first-hand how a multi-disciplinary, multi-institutional, team-oriented approach accelerated the pace of groundbreaking translational research by identifying and pursuing ideas that other agencies probably wouldn't support. We addressed bold questions—not all of which panned out. Ultimately a series of clinical trials to test different therapies resulted in expedited FDA approval of a combination of Abraxane and Gemcitabine, which led to a new standard of care for pancreatic cancer patients.

What do you want most to be remembered for?

I wish to be remembered first and foremost as a teacher and compassionate healer. In addition to any contributions I've made to science, I'd like to be remembered for my deeds.

Does big data equal big gains in cancer research? Why or why not?

Big data no doubt advances cancer research, but it can also have limitations. For example, next-generation sequencing identifies amplifications, but cannot spatially resolve chromosomal or extra-chromosomal regions. Our recent work harnessed the power of DNA sequencing, integrated with cytogenetics, to discover oncogenes reside on extra-chromosomal DNA, which promote tumor evolution. Big data will continue to accelerate research as novel findings are experimentally validated.

KRISTEN M. TURNER
Ludwig San Diego

While I'm convinced that big data, like single-cell cancer-omics, will contribute enormously to the field, strong interdisciplinary research teams are equally important. The analytical skills of computational cancer biologists must be combined with the insights and intuitions of their experimental colleagues to direct the right questions and guide data mining.

SANTIAGO J. CARMONA
Ludwig Lausanne

Big data does not automatically result in major breakthroughs. That said, the combination of many large data sets has the power to reveal the interplay between genomics, epigenomics, transcriptomics and clinical features. In this way, big data helps to separate spurious events from disease-relevant changes, providing big gains for cancer research.

MARKÉTA TOMKOVÁ
Ludwig Oxford

Required reading

Ludwig Johns Hopkins

Proceedings of the National Academy of Sciences USA 2016 December 13
Evaluating the evaluation of cancer driver genes.

Tokheim CJ, Papadopoulos N, Kinzler KW, Vogelstein B, Karchin R.

Ludwig MIT

Molecular Cancer Therapeutics 2016 November 3 [Epub ahead of print]
Mena confers resistance to Paclitaxel in triple-negative breast cancer.

Oudin MJ, Barbier L, Schäfer C, Kosciuk T, Miller MA, Han S, Jonas O, Lauffenburger DA, Gertler FB.

Ludwig MSK

Immunity 2016 November 15
Regulatory T cells exhibit distinct features in human breast cancer.

Plitas G, Konopacki C, Wu K, Bos PD, Morrow M, Putintseva EV, Chudakov DM, Rudensky AY.

Nature 2016 November 9 [Epub ahead of print]
Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells.

De Henau O, Rausch M, Winkler D, Campesato LF, Liu C, Cymerman DH, Budhu S, Ghosh A, Pink M, Tchaicha J, Douglas M, Tibbitts T, Sharma S, Proctor J, Kosmider N, White K, Stern H, Soglia J, Adams J, Palombella VJ, McGovern K, Kutok JL, Wolchok JD, Merghoub T.

Ludwig Oxford

Genes & Development 2017 January 17 [Epub ahead of print]
Translation reprogramming is an evolutionarily conserved driver of phenotypic plasticity and therapeutic resistance in melanoma.

Falletta P, Sanchez-Del-Campo L, Chauhan J, Effern M, Kenyon A, Kershaw CJ, Siddaway R, Lisle R, Freter R, Daniels MJ, Lu X, Tüting T, Middleton M, Buffa FM, Willis AE, Pavitt G, Ronai ZA, Sauka-Spengler T, Hölzel M, Goding CR.

Genes & Development 2016 October 15
MEF2 transcription factors are key regulators of sprouting angiogenesis

Sacilotto N, Chouliaras KM, Nikitenko LL, Lu YW, Fritzsche M, Wallace MD1, Nornes S, García-Moreno F, Payne S, Bridges E, Liu K, Biggs D, Ratnayaka I, Herbert SP, Molnár Z, Harris AL, Davies B, Bond GL, Bou-Gharios G, Schwarz JJ, De Val S.

Ludwig San Diego

Nature Cell Biology 2017 January
Selective Y centromere inactivation triggers chromosome shattering in micronuclei and repair by non-homologous end joining.

Ly P, Teitz LS, Kim DH, Shoshani O, Skaletsky H, Fachinetti D, Page DC, Cleveland DW.

Cell Reports 2016 November 15
A compendium of chromatin contact maps reveals spatially active regions in the human genome.

Schmitt AD, Hu M, Jung I, Xu Z, Qiu Y, Tan CL, Li Y, Lin S, Lin Y, Barr CL, Ren B.

Ludwig Stanford

Cell Stem Cell 2017 March 2
Human AML-iPSCs reacquire leukemic properties after differentiation and model clonal variation of disease.

Chao MP, Gentles AJ, Chatterjee S, Lan F, Reinisch A, Corces MR, Xavy S, Shen J, Haag D, Chanda S, Sinha R, Morganti RM, Nishimura T, Ameen M, Wu H, Wernig M, Wu JC, Majeti R.

Science Translational Medicine 2017 January 18
Reporter gene imaging of targeted T cell immunotherapy in recurrent glioma.

Keu KV, Witney TH, Yaghoubi S, Rosenberg J, Kurien A, Magnusson R, Williams J, Habte F, Wagner JR, Forman S, Brown C, Allen-Auerbach M, Czernin J, Tang W, Jensen MC, Badie B, Gambhir SS.

Proceedings of the National Academy of Sciences USA 2016 December 27
Molecular profiling of single circulating tumor cells from lung cancer patients.

Park SM, Wong DJ, Ooi CC, Kurtz DM, Vermesh O, Aalipour A, Suh S, Pian KL, Chabon JJ9, Lee SH, Jamali M, Say C, Carter JN, Lee LP, Kuschner WG, Schwartz EJ, Shrager JB, Neal JW, Wakelee HA, Diehn M, Nair VS, Wang SX, Gambhir SS.

Cell Stem Cell 2016 November 3
Inhibition of apoptosis overcomes stage-related compatibility barriers to chimera formation in mouse embryos.

Masaki H, Kato-Itoh M, Takahashi Y, Umino A, Sato H, Ito K, Yanagida A, Nishimura T, Yamaguchi T, Hirabayashi M, Era T, Loh KM, Wu SM, Weissman IL, Nakauchi H.

Ludwig Stockholm

Cell Stem Cell 2017 January 5
Single-cell analysis reveals a close relationship between differentiating dopamine and subthalamic nucleus neuronal lineages.

Kee N, Volakakis N, Kirkeby A, Dahl L, Storvall H, Nolbrant S, Lahti L, Björklund ÅK, Gillberg L, Joodmardi E, Sandberg R, Parmar M, Perlmann T.

Cell Stem Cell 2017 January 5
Predictive markers guide differentiation to improve graft outcome in clinical translation of hESC-based therapy for Parkinson's Disease.

Kirkeby A, Nolbrant S, Tiklova K, Heuer A, Kee N, Cardoso T, Ottosson DR2, Lelos MJ, Rifes P, Dunnett SB, Grealish S, Perlmann T, Parmar M.

Nature Biotechnology 2016 December
Single-cell sequencing of the small-RNA transcriptome.

Faridani OR, Abdullayev I, Hagemann-Jensen M, Schell JP, Lanner F, Sandberg R.

LUDWIGCANCERRESEARCH.ORG