



LUDWIG LINK

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cancer prevention

Joint conference looks
at links between nutrition
and cancer

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Bert Vogelstein

Why scientists should
think like science
fiction writers

LUDWIG
CANCER
RESEARCH

LIFE-CHANGING SCIENCE

LETTER



It is the business of Ludwig scientists to push the boundaries of scientific discovery. Proof that they're succeeding abounds in this issue of Ludwig Link. Read on and you'll learn in these pages how a team of researchers figured out the cellular

malfunctions that underpin "chemo brain"—an enduring mind-fog often caused by chemotherapy—and, possibly, how to treat it. You'll find out how a metabolic enzyme helps melanoma cells dull the fury of the immune response and about the results of an ambitious, multi-institutional study that detailed how mutations in the noncoding parts of the genome (which is to say, 98% of it) that are also accessible to the cell's gene reading machinery drive various cancers. And all that, by the way, is just a slice of the exciting Ludwig research you'll discover here.

We also report (page 16) on a December conference in London, co-sponsored by Ludwig, the Conrad N. Hilton Foundation and Cancer Research UK, that focused on how best to improve the science of dietary cancer prevention.

Our Q&A in this issue (page 18) is with Ludwig Johns Hopkins Co-director Bert Vogelstein, a giant in the field of cancer genomics. Find out, among other things, why he believes scientists should shed their inhibitions and think like science fiction fans.

Speaking of science fiction, we asked some Ludwig researchers to weigh in on how artificial intelligence—a staple of the genre—is likely to alter the world of cancer research and care. They share their thoughts on page 23.

Wishing you all a Happy New Year!

Rachel Reinhardt
Vice President for Communications

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On the cover: From left, Kay-Tee Khaw of the University of Cambridge, Walter Willett of the Harvard T.H. Chan School of Public Health, and Bob Strausberg of the Ludwig Institute at the Cancer Prevention and Nutrition Conference in London (see page 16).



Angelika Amon
Ludwig MIT

FOR PROBING CHROMOSOMAL ABERRATIONS

Angelika Amon of Ludwig MIT is one of five scientists who received a 2019 Breakthrough Prize in Life Sciences, which honors “transformative advances toward understanding living systems and extending human life.” She was recognized for her work on aneuploidy, or the presence of an abnormal number of chromosomes in cells, a phenomenon associated with many advanced cancers. Angelika’s research has explored, among other things, the consequences of aneuploidy on cellular health. She has detailed how extra chromosomes

cause imbalances in gene expression that provoke stress responses, alter metabolism and disrupt genomic stability. In receiving her award, Angelika expressed hope that her work will contribute to our understanding of cancer evolution and expose vulnerabilities in cancer cells that can be exploited for the development of cancer therapies. The award comes with \$3 million and was presented at a ceremony in November hosted at a NASA research center in Silicon Valley, California. Watch a short video of Angelika discussing her work [here](#).



Michelle Monje
Ludwig Stanford

FOR CAPTURING MALIGNANT CROSSTALK

Ludwig Stanford investigator Michelle Monje received a 2018 NIH Director’s Pioneer Award in October. The award “supports individual scientists of exceptional creativity who propose highly innovative and potentially transformative approaches to major challenges in the biomedical or behavioral sciences towards the goal of enhancing human health.” Michelle and her team discovered that a

group of aggressive brain tumors called gliomas grow partly in response to nervous system activity, and that their cancerous cells depend on signals from healthy neurons to progress. The award will enable Michelle and her team to further explore how glioma cells interact with healthy brain cells and identify specific activity that might be therapeutically manipulated to improve treatment outcomes.

FOR FIRING UP COLD TUMORS

Ping-Chih Ho of Ludwig Lausanne was one of two researchers who received the Swiss Bridge Award in October. His research focuses on the interplay of cancer cell and immune cell metabolism, a field known as immunometabolomics. He and his colleagues recently uncovered a cellular mechanism by which melanomas that fail to respond to checkpoint blockade—often called “cold” tumors—may be made susceptible to these immunotherapies. They found that “hot” tumors that elicit robust anti-cancer immune responses tend to express high levels of a metabolic protein named UCP2, while cold ones do not. In mouse studies, inducing UCP2

expression in cold melanoma tumors using an existing diabetes drug and following up with PD1 blockade elicited robust anti-tumor immune responses that extended survival. Ping-Chih and his team are now confirming their results with the aim of evaluating the strategy in clinical trials and devising a test to determine whether tumors will respond to immunotherapy. Swiss Bridge is a private foundation associated with the Swiss Cancer League, the Swiss Cancer Research foundation and the Union for International Cancer Control that supports cancer research in Europe.



Ping-Chih Ho
Ludwig Lausanne

FOR ELUCIDATING IMMUNE CHECKPOINTS

Ludwig Harvard's Arlene Sharpe was elected to the US National Academy of Medicine in October. A renowned immunologist, Arlene was recognized for her landmark contributions to our understanding of the immunoregulatory pathways that modulate T cell activation. She was among the first scientists to discover and unravel the complexities of immune checkpoint pathways, which help prevent potentially deadly autoimmune cascades. These mechanisms are frequently hijacked by tumor cells

to evade T cell attack. Arlene's findings, especially her elucidation of the CTLA-4 and PD-1/PD-L1 pathways, led to the development of checkpoint inhibitors that help unleash the immune attack on tumors and are today revolutionizing cancer care. Election to the Academy, considered among the highest of honors in the fields of health and medicine, recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.



Arlene Sharpe
Ludwig Harvard



Ralph Weichselbaum
Ludwig Chicago

FOR MELDING THERAPIES

Ludwig Chicago Co-director Ralph Weichselbaum received the 2018 American Society for Radiation Oncology Gold Medal in October. It is the organization's highest honor, bestowed on members who have made outstanding contributions to radiation oncology. Ralph is best known for his work in partnership with former Ludwig Board member Samuel Hellman in defining an intermediate stage of metastatic disease that they named oligometastasis and that can be cured with radiotherapy

or other localized metastasis-directed therapies. His research today increasingly focuses on combining radiation therapy and immunotherapy to better treat widespread systemic disease and explore how patterns of gene expression in human tumors confer resistance to therapy. The Society noted Ralph's dedication and kindness as a mentor and observed that his insights on the biology of the radiation response and the role of radiation therapy in systemic disease are enabling new approaches to helping patients.

News roundup



Michelle Monje
Ludwig Stanford

FOG SOURCE

More than half of cancer survivors experience "chemo brain", a fogging of the brain that can last long after cancer treatment. A [study](#) led by Michelle Monje of Ludwig Stanford and published in *Cell* in January discovered one of the cellular mechanisms behind this condition. Michelle and her colleagues report that the chemotherapy drug methotrexate affects three major types of brain cells: oligodendrocytes, which produce myelin, the insulation of nerve fibers; astrocytes, which support and help connect neurons and link them to their blood supply; and microglia, the brain's resident immune cells. Examining brain tissue from mouse models and humans, the researchers found that chemotherapy inhibits the ability of precursor cells

to generate new oligodendrocytes important for both homeostasis and neural plasticity, and that this is caused by changes in the brain's environment that are induced by chemotherapy. The chemo drug methotrexate, their studies revealed, persistently activates microglia for at least six months after its administration. That, in turn, causes astrocyte dysfunction. Administering a drug currently in clinical trials that selectively depletes microglia reversed in mice many of the cognitive symptoms of chemo brain as well as the abnormalities observed in astrocytes and myelin. Michelle and her colleagues are now examining the precise signaling circuits between the affected cells that are disrupted by chemotherapy.



Shibin Zhou
Ludwig Johns Hopkins



Bert Vogelstein
Ludwig Johns Hopkins



Verena Staedtke
Ludwig Johns Hopkins

CRISIS RESPONSE

Cytokine release syndrome (CRS) is a life-threatening hyperactivation of the immune system and a complication of several new immunotherapies used to treat cancer. A team led by Ludwig Johns Hopkins' Shibin Zhou, Bert Vogelstein, Verena Staedtke and colleagues [reported](#) in *Nature* in December a novel mechanism by which it occurs. The researchers found that atrial natriuretic peptide (ANP), a hormone secreted by the heart, can protect mice from CRS by reducing the levels of circulating catecholamines—hormones, like adrenaline, produced by the adrenal glands and many immune cells, including myeloid immune cells known as macrophages. Catecholamines, they found, drive immune dysfunction by generating a self-amplifying loop

in these macrophages. Deletion of the enzyme tyrosine hydroxylase, an enzyme necessary for producing catecholamines, inhibited this circuit. Blocking catecholamines with ANP or with the anti-hypertension drug metyrosine, prevented excessive cytokine release induced by infections and reduced mortality in mice. The same drugs could protect mice from the CRS induced by immunotherapies such as tumor-targeting bacteria, T-cell activating therapies and CAR-T cells. Because both ANP and metyrosine are already approved for clinical use for other indications, the study suggests a rapidly implementable approach to controlling CRS without impairing therapeutic responses.

A MALIGNANT DIVERSITY

Epigenetic enzymes chemically tag chromosomes at specific sites to control which genes are available for expression in a given cell, and at what levels. Such epigenetic modifications are central to establishing the molecular identity, or phenotype, of all cells. The KDM5 histone H3 lysine 4 demethylase family of genes express enzymes that perform this important function. They are, however, also associated with drug resistance, including resistance to endocrine therapies in breast cancer. But why, precisely, has long been unclear. A [study](#) led by Ludwig Harvard's Kornelia Polyak and Franziska Michor found that a high level of KDM5B expression increases the phenotypic diversity of breast cancer cells and is associated with worse patient prognoses in estrogen receptor (ER)-positive breast cancer. Conversely, loss or inhibition of KDM5 activity increases sensitivity to anti-estrogens by modulating ER signaling and decreasing the diversity of genes expressed by different tumor cells. The researchers show that resistance to endocrine therapy arises from selection for distinct pre-existing cell populations, while resistance to KDM5 inhibitors is acquired via epigenetic changes that can even revive ER signaling. Their findings, published in December in *Cancer Cell*, underscore the importance of cellular heterogeneity in drug resistance.



◀ Kornelia Polyak
Ludwig Harvard



◀ Franziska Michor
Ludwig Harvard



▶ Michal Bassani-Sternberg
Ludwig Lausanne

DICE AND SPLICE DEBATE

Cells display a large repertoire of small fragments of proteins—peptide antigens—that elicit killer T cell responses against tumors and infectious agents. This presentation is done by a family of proteins called human leukocyte antigens, or HLA. It has been shown that, in some cases, the peptides presented by HLA proteins are cut and rearranged—or spliced—by the proteasome, so that their peptide sequences don't match those of any protein in the body. How commonly this happens remains a subject of some debate and is an important question in immunology, and therefore also in immunotherapy research, particularly for cancer vaccine design. A 2016 paper in *Science* concluded that up to 30% of the peptides presented by HLA class I molecules might be spliced. That finding was confirmed by one study but then contradicted by a couple of others. In a December *Molecular & Cellular Proteomics* [paper](#), researchers led by Ludwig Lausanne's Michal Bassani-Sternberg in collaboration with Markus Müller from the Swiss Institute of Bioinformatics reported that their own analysis of the data used in the original *Science* study suggests only a small percentage—just 2% to 4%—could potentially be considered as spliced peptides.

REGARDING MICROMANAGEMENT

MicroRNAs regulate gene expression and play a critical role in the immune response, cell-cycle control and the stem cell differentiation that constantly replenishes the body's various tissues. They do so by specifically binding and degrading the messenger RNA transcripts that carry the instructions for making proteins. MicroRNA expression or function is impaired in many diseases, including cancer and inflammatory disorders. It has, however, been unclear whether their regulatory activity is determined by the cell type in which they're expressed. In an October [paper](#) in *Nature Immunology*, Ludwig MSK scientists led by Alexander

Rudensky explored how a microRNA named miR-155—which plays an important role in immunity and has been implicated in a variety of cancers—targets mRNAs in the immune system's macrophages, dendritic cells and T and B cells. The team identified many mRNA targets that are differentially bound by miR-155 depending on which cell is expressing them, showing that this microRNA's regulation of gene expression is indeed shaped by cellular context. The study also provides comprehensive maps of miR-155 regulatory networks in immune cells, which should be of considerable use to the biomedical research community.



Alexander Rudensky
Ludwig MSK



Colin Goding
Ludwig Oxford

SIGNALS INTELLIGENCE

Biochemical signaling pathways induce cellular responses to all manner of stimuli by influencing gene expression. They do so through transcription factors (TFs), which can direct the expression of select suites of genes. But how multiple signals are integrated to fine-tune the control of TFs remains an area of intensive research. A team led by Ludwig Oxford's Colin Goding examined how this is accomplished for a master regulator of gene expression—the microphthalmia-associated transcription factor (MITF)—which gives the skin's pigment-making melanocytes their identity and plays a central role in the skin cancer melanoma. They [described](#) in a September issue of the *Proceedings of the National*

Academy of Sciences how signals sent through both the PI3 kinase and WNT pathways and those dispatched via the BRAF/MAP kinase-mediated pathway are integrated to control MITF activity. The addition of a phosphate to MITF due to BRAF/MAPK activation primes MITF for the addition of another one by an enzyme named GSK3, which is inhibited by the PI3 kinase and WNT pathways. The addition of both phosphates—not just one—exposes a hitherto unknown nuclear export code on MITF, causing its expulsion from the nucleus, away from its target genes. The findings have implications for our understanding of melanocyte biology and the development of drugs to treat melanoma.

A VERSATILE STING

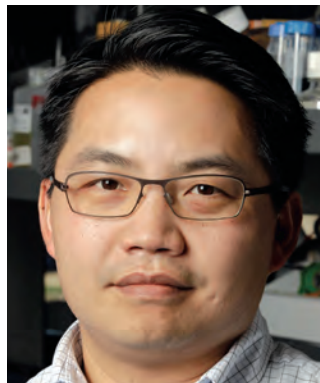
A protein complex known as STING (STimulator of INterferon Genes) is a sensor of DNA fragments that plays an important role in sparking up the innate immune response—the cells and factors that comprise the frontline defenses of the body. STING signaling leads to the production of interferon, which plays a role in activating the innate immune system and, in some instances, T cells that attack infected and cancerous cells. It has long been supposed that the loss of STING in cancer cells promotes tumor growth by compromising anti-tumor immunity—and it certainly seems to do that, especially following radiotherapy, which damages DNA. But in a November [paper](#) in *Cancer Research*, a team led by Ludwig Chicago Co-director Ralph Weichselbaum and Diana Ranoa reported additional roles for STING in cancer. They show that STING also regulates the cell's progression toward division and maintains the integrity of its genome. Its depletion in cancer cells boosted their proliferation and led to the premature activation of cyclin-dependent kinase 1 (CDK1), which pushes cells toward division. The loss of STING prompted the early onset of DNA synthesis and increased chromosome instability, which was exacerbated by ionizing radiation.



◀ Ralph Weichselbaum
Ludwig Chicago



◀ Diana Ranoa
Ludwig Chicago



Howard Chang ▶
Ludwig Stanford

CANCER'S NONCODING GENOME

The DNA within a cell's nucleus is tightly wound around proteins and packaged into a threadlike structure known as chromatin. As a result, only certain stretches of DNA are accessible to the protein machinery that reads genes. Accessible regions vary in different types of cells, which permits that machinery to read unique subsets of genes, creating each cell type. Very little was known, however, about these regions' noncoding sequences—which account for 98% of the genome—or how mutations in these sequences contribute to cancer. A multi-institutional study led by Howard Chang, Virginia and D.K. Ludwig Professor of Cancer Genomics at Stanford University, and Stanford geneticist William Greenleaf surveyed genomes in 410 tumor samples representing 23 types of cancer to produce a sprawling map of noncoding DNA sequences that regulate the expression of specific genes. The researchers show how mutations in sequences thousands of bases away from a gene can create a newly accessible regulatory element that promotes the aberrant expression of that gene. They additionally reported in their October [paper](#) in *Science* the identification of tens of thousands of likely interactions between regulatory elements of DNA and genes known to play an important role in cancer and tumor immune evasion. The findings also shed light on how inherited variations in DNA sequence in noncoding DNA can predispose people to cancer.

SOURCING THE MISFITS

Barrett's esophagus, often found in the lower esophagus adjacent to the stomach, is a precancerous condition frequently associated with chronic acid reflux disease. The normal esophagus is lined with squamous epithelium but in Barrett's esophagus this is replaced by a tissue type known as columnar epithelium, which lines most of the rest of the digestive tract. Furthermore, Barrett's esophagus contains a weird assortment of other types of cells, many of which are ordinarily found in the stomach or intestine. Untangling the cellular origins of these abnormal cells—whether they travel in from elsewhere or arise within the esophagus itself—has proved difficult and there are currently five competing theories. Four of these are supported by mouse models but the other theory is based solely on pathological evidence. To determine which might apply in humans, a team of researchers led by Ludwig Oxford Director Xin Lu performed single-cell RNA sequencing on multiple patient biopsies from Barrett's esophagus and normal esophagi. Their [results](#), published in October in *Nature Communications*, support the pathologists' theory. They indicate that abnormal cells in Barrett's esophagus share gene expression profiles with gland cells in the walls of the esophagus but not with intestinal or gastric cells, suggesting they arise from within the organ and are not gastrointestinal immigrants. The study also identified two markers, SPINK4 and ITLN1, found in precursors of goblet cells of Barrett's esophagus and the colon that might prove useful in identifying the precancerous tissue.



◀ Xin Lu
Ludwig Oxford



Benjamin Izar ▶
Ludwig Harvard



Aviv Regev ▶
Ludwig MIT

PROGRAMS OF RESISTANCE

Benjamin Izar and Aviv Regev, researchers at Ludwig Harvard and Ludwig MIT, are taking on melanoma one cell at a time. In a [study](#) reported in *Cell* in November, they and their colleagues explored why immune checkpoint inhibitors produce durable responses in some melanoma patients but not others. Profiling the genes expressed in thousands of individual melanoma cells obtained from patients who responded to immunotherapy and others who resisted it, they identified a gene expression program that predicts resistance to checkpoint blockade. The program captures mechanisms by which cancer cells may exclude T cells out of the tumor or directly evade immunity, and thereby reduce the potential activity of immune checkpoint inhibitors. The researchers show that detection of this program predicted clinical responses to anti-PD-1 therapy in an independent cohort of melanoma patients. Analysis of a second patient cohort treated with anti-PD-1 antibodies revealed that the program was ramped up upon exposure to immunotherapy. The researchers report that CDK4/6 inhibitors, an existing class of cancer drugs, could partially repress the immune resistance program—a possibility that could be relatively quickly examined in clinical trials, since the required drugs are already available.

QUALITY CONTROL

When healthy cells divide, they bequeath an equal complement of normal chromosomes to each of their daughter cells—a capability often compromised in cancer. To prevent errors in this process, dividing cells assemble a mitotic checkpoint complex (MCC) that acts as a “wait for me” signal that blocks later steps in cell division until every chromosome has been successfully positioned for delivery to each daughter cell. To prevent a premature mitotic exit before the chromosomes have the chance to generate this signal, MCC is also produced at low levels before the mitotic process begins. In an October [paper](#) in *Nature Communications*, a team led by Ludwig San Diego’s Don Cleveland reported that the enzyme TRIP13—a tumor suppressor that is, paradoxically, also overexpressed in many cancers—is required for both the assembly of MCC and its disassembly prior to appropriate mitotic exit. They also showed that an alternative, functionally distinct enzyme, APC15, can separately cause the disassembly of MCC to permit mitotic exit, and that the two enzymes normally act synergistically to that end. When both approaches to MCC disassembly are hindered, cells become completely incapable of exiting mitosis, even when the assembly of the MCC is disrupted. This discovery enables development of a therapeutic strategy to inhibit cancer cell growth by simultaneously blocking both pathways of MCC inactivation.



◀ Don Cleveland
Ludwig San Diego



Stephen Elledge ▶
Ludwig Harvard



Sida Liao ▶
Ludwig Harvard

BETS OFF AGAIN

Fewer than 100 people are diagnosed with NUT midline carcinoma in the US every year, but it is aggressive, with a median survival time of less than 7 months from diagnosis. Patients can be treated with bromodomain and extraterminal domain (BET) inhibitors, which are currently in clinical trials, but cancer cells usually evolve to resist the therapy in a variety of ways. Interested in these mechanisms of resistance, Ludwig Harvard investigators Stephen Elledge, Sida Liao and their colleagues used gene editing tools to study several driver genes that the lab had identified in NUT midline carcinoma. They determined that some six classes of genes and signaling pathways play a role in resistance to BET inhibitors. Notably, it turned out that pathways targeted by another class of drugs—CDK4/6 inhibitors—are involved in resistance. Combining pre-clinical versions of the two drugs—BET inhibitors and CDK4/6 inhibitors—halted tumor growth in animal models. The study suggests a new approach to treating not only NUT midline carcinoma but perhaps other cancers responsive to BET inhibitors. It also vets a powerful method to expose the causes of drug resistance in cancer. The [results](#) were published in September in *Genes & Development*.



Suzana Kahn
Ludwig Stanford



Siddhartha Mitra
Ludwig Stanford



Samuel Cheshier
Ludwig Stanford

ONE SWITCH OPERATION

Medulloblastoma is the most common malignant brain tumor of childhood, accounting for approximately 20% of all such tumors. The current treatment consists of surgery, followed by radiation and high doses of chemotherapy, a grueling regimen that can result in lasting cognitive and physical disabilities. In a [study](#) reported in *Nature Communications* in October, Ludwig Stanford researchers Suzana Kahn, Siddhartha Mitra and Samuel Cheshier found that NOTCH1, a cell surface protein, regulates both the growth of the primary Group 3 medulloblastoma tumor and its metastasis. The researchers also identified the signaling circuit through

which NOTCH1 exerts its effects in the cancer, showing that its activation makes the cancer cells—particularly malignant stem cells—less likely to stick to their spot and more inclined to migrate to the spine. In mouse models implanted with human medulloblastoma tumors, the team could slow the metastasis of the tumor and extend the lives of the animals using an antibody that binds NOTCH1 and blocks its signaling. The researchers are currently developing a clinical trial to test anti-NOTCH1 therapy for medulloblastoma, a treatment they hope will result in fewer side effects and better outcomes.



Benjamin Schuster-Böckler
Ludwig Oxford



Skirmantas Kriaucionis
Ludwig Oxford

SIGNATURE ANALYSIS

DNA contains a sequence of four bases (A, T, C and G) that encode genes. These bases can mutate in several different ways—for example, C can mutate to A, or A to G—introducing potential errors to gene and regulatory sequences that can, in turn, cause cancer and other disorders. Some mutations occur through errors made during normal replication of DNA. Other mutations are the result of mutagens like UV light and chemical carcinogens. Many of these processes favor distinct combinations of bases in the genome, resulting in so-called “mutational signatures”. In a September [paper](#) in *Genome Biology*, a team led by Ludwig Oxford’s Benjamin Schuster-Böckler

and Skirmantas Kriaucionis reported its analysis of mutational signatures—from 3,056 patients in 19 types of cancer—with regard to the timing and asymmetry of DNA replication. They found that DNA replication influences the distribution of nearly all mutational signatures across the genome, regardless of whether they’re the product of carcinogens or not. The analysis also reveals novel aspects of the mechanisms underlying certain cancer types. They discovered evidence, for example, that oxidative damage to the pool of bases that are incorporated into the replicating DNA strand plays a key role in the development of esophageal cancer.



Irv Weissman
Ludwig Stanford



Ravi Majeti
Ludwig Stanford

STIMULUS PACKAGE

A novel immunotherapy targeting the CD47 receptor, a “don’t eat me” signal that cancer cells exploit to escape ingestion by the immune system’s macrophages, appears safe for use in patients with the blood cancer non-Hodgkin’s lymphoma (NHL), according to the results of a phase-1b multicenter clinical trial sponsored by Forty Seven Inc., a biotech startup that licensed the program originally led by Ludwig Stanford’s Irv Weissman and Ravi Majeti, who co-founded Forty Seven Inc. and serve on its Board of Directors. NHL originates in the lymphoid system and is the [seventh](#) most common cause of cancer-related deaths in the US. The therapy evaluated in the trial combined an experimental antibody, Hu5F9-G4, that was developed by Irv and Ravi and a commercially available anti-cancer antibody called rituximab. Patients enrolled in the trial had one of two types of NHL: diffuse large B-cell lymphoma—the most common type of NHL—and follicular lymphoma, a slow-growing cancer. All patients were in relapse and 21/22 were refractory to rituximab prior to entry into the study. Half of the 22 people enrolled in the trial had a positive response to the therapy, and about one-third went into complete remission. The [results](#) were published in November in *The New England Journal of Medicine*.



REIMAGINING DIETARY CANCER PREVENTION

It may not be the best thing for business, but doctors have long recommended prevention over cure, certainly when it comes to cancer. With good reason. Some 40% of cancer diagnoses and roughly half of cancer-related deaths in the US are thought to stem from preventable factors like tobacco and alcohol use, physical inactivity, obesity and poor diet. Policies to discourage smoking have had considerable impact on cancer in the western world, and people generally know that exercising, shedding pounds and cutting back on alcohol can reduce the odds of illness. But how exactly these wholesome habits

deter cancer remains largely unclear. Doctors, at any rate, have very little to offer by way of specific, consistent, scientifically validated advice to dispense on diet and cancer prevention—what works, what doesn't, and for whom in each case.

With a shared interest in these questions, Cancer Research UK (CRUK), Ludwig Cancer Research and the Conrad N. Hilton Foundation—with which Ludwig launched a program in dietary cancer prevention in 2015—convened a Cancer Prevention and Nutrition Conference in London in early December. The meeting

focused on the best approaches to identifying causal links between diet and cancer prevention, with an eye to providing precise and actionable information to medical professionals and policymakers.

“This very interactive meeting brought together distinguished scientists in epidemiology, cancer biology, and public health to discuss limitations in our understanding of how nutritional choices can be better utilized to prevent the development and progression of deadly cancers. Our goal is to further enable a vigorous collaborative research environment

Special event

to achieve impactful scientific advances to keep people healthy,” said Bob Strausberg, Ludwig deputy scientific director.

“It is rare to bring together such a diverse grouping of scientists with shared interests in the nutrition space and that provides an exciting opportunity to spark new conversations, broaden collaborative networks and, we hope, catalyze thinking in this area. Prevention forms one of the four pillars of our Research Strategy at CRUK, and we are keen to encourage proposals in this space. We are delighted to be partnering with our colleagues at Ludwig Cancer Research and the Conrad N. Hilton Foundation to enable this,” said Fiona Reddington, head of population, prevention and behavioral research funding at CRUK.

Sequential sessions of the conference covered what we’ve learned from ongoing epidemiological studies; the linking of laboratory, epidemiological and clinical studies to pin down mechanisms and causal links; the interplay of diet and human development; the genome, diet and cancer; preventing cancer recurrence; and the food environment of the real world in which dietary cancer prevention and associated policies would play out. Speakers in each of these sessions presented studies or overviews of



“Our goal is to further enable a vigorous collaborative research environment to achieve impactful scientific advances to keep people healthy.”

Bob Strausberg
Ludwig Institute

their research. The presentations and panel discussions were followed on the second day by a summary of each of the sessions and an open-floor discussion in which the audience got to share their suggestions, insights and concerns about the best way forward.

Attendees left the conference with a lot to think about and Ludwig and CRUK are considering options on how best to share its proceedings and recommendations with policymakers and the broader research community.

Next up: A joint meeting CRUK and Ludwig are planning for next year—on exercise and cancer prevention.

BERT VOGELSTEIN

LUDWIG JOHNS HOPKINS CO-DIRECTOR

A pioneer of cancer genetics and champion of translational research



Why don't we all have cancer?

If we live long enough, we all will. It's just a question of stochasticity. No single factor causes cancer—it's a complex group of diseases with many possible origins. The first two that were recognized are heredity and environmental exposures such as cigarette smoke or radiation. These factors result in the mutations that drive the disease. Obesity has a very strong correlation with the development of cancer but the mechanisms are unknown. A third factor, one that actually causes most of the mutations in many cancers, is random errors during normal cell division. Every time a cell divides, approximately five new mutations occur. Most of those mutations are harmless but, occasionally, one will occur in a driver gene—a gene that can contribute to the development of cancer. It's inexorable in the sense that our cells are dividing throughout our life so they are always making more mutations, no matter what we are exposed to, or how we live. For children, the incidence of cancer is fortunately very low, but it increases dramatically as we get older. If we live to an age of 300 years, most of us would have at least one cancer. So we're all, in a sense, ticking time bombs.

You've been quoted as saying, "You should think like a science fiction writer." What did you mean by this?

Science is about reality and understanding

the universe we live in. If you ask a scientist to predict the future, they usually will not get it right. Scientists, including me, are very tethered to reality—what can be done now. We look at what seems feasible in the near future based on the technology that we know and understand. Science fiction writers, on the other hand, are not tethered to reality and are not limited to what we can do now but focus on what the future might be like. Young people who are in the formative years of their science careers can and should think like science fiction writers. I would counsel them not to think about what can be done now or the next month or even the next year or two. But to think about what might be possible several decades from now. It requires a good amount of judgment and wisdom to choose projects like this that are viable, but that's where the real advances come from. Occasionally scientists make discoveries that were totally unanticipated and not even on the radar of most other scientists—those are the kinds of things that are worth working towards.

Why do you think early detection will change the tide of cancer research?

Early detection is a type of prevention. Primary prevention is preventing the disease from ever occurring—and in our case preventing cancers from ever occurring. Secondary prevention does not entail preventing their occurrence but rather detecting them and treating them early enough so that intervention is possible—while they are still curable. Now that we understand so much about the genetic basis of cancer, I'm optimistic

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Young people who are in the formative years of their science careers can and should think like science fiction writers. I would counsel them not to think about what can be done now or the next month or even the next year or two. But to think about what might be possible several decades from now.

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we'll make progress in early detection in the years to come. But I also think that we, as a community of those interested in cancer, need to readjust our efforts and spend more of our resources and intellectual energy on prevention and early detection.

Do you think these concepts of early detection and prevention are underappreciated by the pharmaceutical industry?

Yes. Right now, we spend an inordinate amount of our efforts developing drugs to fight metastatic disease. Such efforts are certainly critically important—because we will never prevent all cancers—but I'd like to see 40% to 50% of our efforts directed to early detection and prevention. Think



about it—if cancers are detected earlier, then whatever drugs the pharmaceutical industry produces will work better on those cancers detected earlier than on those detected much later. And the duration of treatment will be longer. All societies are generally more reactive rather than proactive and our focus has been on curing cancers. There are a lot of reasons why. It's much more dramatic to put a patient with an advanced cancer into remission than it is to prevent a cancer from ever occurring. And there are more economic incentives for developing new therapeutics than there are for developing new tests for earlier detection or new ways of prevention. The sooner we

come to the realization that prevention is at least, if not more, important than therapy for reducing cancer morbidity and mortality, the sooner more advances in this area will occur.

There's a famous story that during your internship you encountered a family with a four-year-old daughter who you diagnosed with leukemia. Why did that particular girl drive you to focus your research career on cancer?

That little girl was one of the first patients assigned to me when I was doing my internship in pediatrics. I remember very clearly when she came into the clinic on a late Friday afternoon. We did the usual

diagnostic studies and it was obvious that she had leukemia from her blood smear. Her father was a mathematician and about my age. He asked me, “Why did this happen to my beautiful little girl?” I had no answer. Not only that, what he really wanted to know was, did he or his wife do anything that caused his little girl to have this horrible disease? I could not answer his question at all. At that moment, it seemed to me that answering this question would be a valuable thing to spend my life on. This was in 1974 and we knew nothing about cancer. It was like some strange beast that came from outer space and attacked people. We had no idea what the molecular underpinnings of it were. If we were to ever be able to prevent or treat cases like this in the future, so that little girls like his wouldn’t die from the disease or perhaps not even get it, then we needed to understand the disease.

Your scientific discoveries are legendary. Your group was the first to discover that P53 was a tumor suppressor. Your group found that mutations in APC underlie most colorectal cancers, created the concept of transcriptomes, invented digital PCR that enabled liquid biopsies and many, many other things. What is your secret to accomplishing so much?

Part of my secret is not thinking I’ve accomplished so much. Which drives me to accomplish more. If I were satisfied with what I’ve accomplished, I probably would have accomplished less. But I’m still not satisfied because I look at the hospital right across the street from our research building and it’s still filled

up with cancer patients, so I couldn’t have done that much. If I had, then that building would be devoted to patients with a different disease. The second thing is that my group, and particularly the trainees, has always been made up of careful, creative scientists who work extremely hard. The third thing is that I’ve always had a sign up on my wall that reads IT’S AMAZING HOW MUCH A PERSON CAN ACCOMPLISH IF HE OR SHE DOESN’T CARE WHO GETS THE CREDIT. Neither my research partner Ken (Kinzler) nor I really care about the credit. Not that credit is bad, but it’s less important than trying to do something important. Our end goal is not just publishing papers and making important discoveries. It’s about emptying out that hospital across the street. We’re continually trying to do new things that get us closer to that goal.

What is some advice you give to young scientists who want to join your lab?

Don’t do evolutionary research; try for revolutionary research that opens up new vistas. Evolutionary research is simply the very next obvious step. The vast majority of research today is evolutionary and that’s because it’s easier and because of all the pressures to get grants and publish. When I speak to incoming graduate students, one of the things I tell them is that you’re in graduate school because you want to set the world on fire. If you don’t want to set the world on fire, then go do something else, something easier, with less risk, that is more certain. As a

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The sooner we come to the realization that prevention is at least, if not more, important than therapy for reducing cancer morbidity and mortality, the sooner more advances in this area will occur.

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... now that we understand so much about the genetic basis of cancer, I'm optimistic we'll make continued progress in the years to come. There is a still huge amount to learn but we know enough so that we can begin to think about how to prevent it better and how to treat it better.

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scientist, you have the opportunity “to go where no one has ever gone before”.

Are you generally optimistic about the future of cancer biology—that we will be able to prevent life-threatening cancers?

Yes. Medicine shows that once you understand the disease, you'll be able to do something about it. A deeper understanding about the genetic faults fueling tumors can lead to ways to detect them earlier. And spotting a cancer at an earlier stage means that treatment is more likely to be effective. Now it won't come next year or maybe not even in the next decade but now that we

understand so much about the genetic basis of cancer, I'm optimistic we'll make continued progress in the years to come. There is a still huge amount to learn but we know enough so that we can begin to think about how to prevent it better and how to treat it better. So, in the long run, I am extremely optimistic.

If you were to change anything about your career, what would that be?

As you reach your 60s, you realize that you're mortal and you don't have an infinite amount of time left to reach your goals. Your time is limited. In terms of what I would have done differently—I would have focused more on what I consider the most important things I could accomplish. Some of the things we've done were important and they were successful to the extent that they were published in *Nature* or *Science*, but they weren't necessarily the best way to spend my time. It can be very hard to focus on the one thing you can accomplish over the next decade or two. So often, you're like that kid in the candy shop surrounded by so many wonderful flavors to choose from that it's easier to say that one looks good, let me try that one today. The next day, you're tempted to try a different one. I know I've engaged in some areas of research that were productive by metrics of publication but they probably distracted me from reaching my main goals, which are basically in prevention and developing novel therapeutics based on the genetic alterations in cancers. Now that I am getting older, virtually all my efforts are devoted to those goals.

How will artificial intelligence revolutionize cancer research and care?



AI has already revolutionized many everyday activities and has similar potential for the medical and scientific fields. However, AI is not true intelligence and its successes will only be as good as the supplied data and questions addressed with it. As scientists equipped with any new tool, we will be faced with defining the true opportunities and avoiding the follies.

KEN KINZLER
Ludwig Johns Hopkins



It is true that machine-learning algorithms have improved recently. But what makes it powerful this time around is that there is a great deal of data to “train” the models. The bottleneck now will be institutional barriers—we will need creative approaches to incentivize aggregation of data from multiple institutions.

PETER J. PARK
Ludwig Harvard



With the recent advances in multidimensional techniques to interrogate tumors and the concurrent AI breakthroughs, the question is no longer whether AI will be a key component of cancer research and care, but when. I am convinced this transition has already started. In Lausanne, we are actively designing AI strategies bringing together molecular and clinical data to guide personalized therapies.

OLIVIER MICHIELIN
Ludwig Lausanne



AI is a powerful tool that is extremely proficient at discovering patterns. This will greatly assist in prognosis and treatment options by increasing automation, prognosis accuracy, and discovering complicated patterns across research disciplines as more high quality and reproducible data becomes available.

NATHAN T. JOHNSON
Ludwig Harvard

Required reading

Ludwig Chicago

Cancer Research
2018 November 27
[Epub ahead of print]
STING promotes homeostasis via regulation of cell proliferation and chromosomal stability.

Ranoa DRE, Widau RC, Mallon S, Parekh AD, Nicolae CM, Huang X, Bolt MJ, Arina A, Parry R, Kron SJ, Moldovan GL, Khodarev NN, Weichselbaum RR.

Ludwig Harvard

Cancer Cell 2018
December 10
KDM5 histone demethylase activity links cellular transcriptomic heterogeneity to therapeutic resistance.

Hinohara K, Wu HJ, Vigneau S, McDonald TO, Igarashi KJ, Yamamoto KN, Madsen T, Fassl A, Egri SB, Papanastasiou M, Ding L, Peluffo G, Cohen O, Kales SC, Lal-Nag M, Rai G, Maloney DJ, Jadhav A, Simeonov A, Wagle N, Brown M, Meissner A, Sicinski P, Jaffe JD, Jeselsohn R, Gimelbrant AA, Michor F, Polyak K.

Genes & Development 2018
September 1

Genetic modifiers of the BRD4-NUT dependency of NUT midline carcinoma uncovers a synergism between BETis and CDK4/6is.

Liao S, Maertens O, Cichowski K, Elledge SJ.

Cell 2018 November 1

A cancer cell program promotes T cell exclusion and resistance to checkpoint blockade.

Jerby-Arnon L, Shah P, Cuoco MS, Rodman C, Su MJ, Melms JC, Leeson R, Kanodia A, Mei S, Lin JR, Wang S, Rabasha B, Liu D, Zhang G, Margolais C, Ashenberg O, Ott PA, Buchbinder EI, Haq R, Hodi FS, Boland GM, Sullivan RJ, Frederick DT, Miao B, Moll T, Flaherty KT, Herlyn M, Jenkins RW, Thummalapalli R, Kowalczyk MS, Cañadas I, Schilling B, Cartwright ANR, Luoma AM, Malu S, Hwu P, Bernatchez C, Forget MA, Barbie DA, Shalek AK, Tirosh I, Sorger PK, Wucherpennig K, Van Allen EM, Schadendorf D, Johnson BE, Rotem A, Rozenblatt-Rosen O, Garraway LA, Yoon CH, Izar B, Regev A.

Ludwig Johns Hopkins

Nature 2018 December
Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome.

Staedtke V, Bai RY, Kim K, Darvas M, Davila ML, Riggins GJ, Rothman PB, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S.

Ludwig Lausanne

Molecular & Cellular Proteomics 2018 December 1
Estimating the contribution of proteasomal spliced peptides to the HLA-I ligandome.

Mylonas R, Beer I, Iseli C, Chong C, Pak HS, Gfeller D, Coukos G, Xenarios I, Müller M, Bassani-Sternberg M.

Journal of Experimental Medicine 2018 November 5
Multiple roles of lymphatic vessels in peripheral lymph node development.

Bovay E, Sabine A, Prat-Luri B, Kim S, Son K, Willrodt AH, Olsson C, Halin C, Kiefer F, Betsholtz C, Jeon NL, Luther SA, Petrova TV.

Ludwig MIT

Cell 2018 November 1
A cancer cell program promotes T cell exclusion and resistance to checkpoint blockade.

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Ludwig MSK

Nature Immunology 2018
October
The effect of cellular context on miR-155-mediated gene regulation in four major immune cell types.

Hsin JP, Lu Y, Loeb GB, Leslie CS, Rudensky AY.

Ludwig Oxford

Nature Communications 2018
October 15
Single cell RNA-seq reveals profound transcriptional similarity between Barrett's oesophagus and oesophageal submucosal glands.

Owen RP, White MJ, Severson DT, Braden B, Bailey A, Goldin R, Wang LM, Ruiz-Puig C, Maynard ND, Green A, Piazza P, Buck D, Middleton MR, Ponting CP, Schuster-Böckler B, Lu X.

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BRAF/MAPK and GSK3 signaling converges to control MITF nuclear export.

Ngeow KC, Friedrichsen HJ, Li L, Zeng Z, Andrews S, Volpon L, Brunsdon H, Berridge G, Picaud S, Fischer R, Lisle R, Knapp S, Filippakopoulos P, Knowles H, Steingrimsdottir E, Borden KLB, Patton EE, Goding CR.

Genome Biology

2018
September 10
Mutational signature distribution varies with DNA replication timing and strand asymmetry.

Tomkova M, Tomek J, Kriaucionis S, Schuster-Böckler B.

Ludwig San Diego

Nature Communications 2018
October 19
TRIP13 and APC15 drive mitotic exit by turnover of interphase- and unattached kinetochore-produced MCC.

Kim DH, Han JS, Ly P, Ye Q, McMahon MA, Myung K, Corbett KD, Cleveland DW.

Ludwig Stanford

Cell 2019 January 10
Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment.

Gibson EM, Nagaraja S, Ocampo A, Tam LT, Wood LS, Pallegar PN, Greene JJ, Geraghty AC, Goldstein AK, Ni L, Woo PJ, Barres BA, Liddelow S, Vogel H, Monje M.

Required reading

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Medicine 2018 November 1**
**CD47 blockade by Hu5F9-G4
and Rituximab in non-Hodgkin's
lymphoma.**

Advani R, Flinn I, Popplewell L,
Forero A, Bartlett NL, Ghosh N,
Kline J, Roschewski M, LaCasce
A, Collins GP, Tran T, Lynn J, Chen
JY, Volkmer JP, Agoram B, Huang J,
Majeti R, Weissman IL, Takimoto CH,
Chao MP, Smith SM.

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**The chromatin accessibility
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cancers.**

Corces MR, Granja JM, Shams
S, Louie BH, Seoane JA, Zhou W,
Silva TC, Groeneveld C, Wong CK,
Cho SW, Satpathy AT, Mumbach
MR, Hoadley KA, Robertson AG,
Sheffield NC, Felau I, Castro MAA,
Berman BP, Staudt LM, Zenklusen
JC, Laird PW, Curtis C; Cancer
Genome Atlas Analysis Network,
Greenleaf WJ, Chang HY.

**Nature Communications 2018
October 8**

**Notch1 regulates the initiation
of metastasis and self-renewal
of Group 3 medulloblastoma.**

Kahn SA, Wang X, Nitta RT,
Gholamin S, Theruvath J, Hutter
G, Azad TD, Wadi L, Bolin S,
Ramaswamy V, Esparza R, Liu KW,
Edwards M, Swartling FJ, Sahoo D,
Li G, Wechsler-Reya RJ, Reimand
J, Cho YJ, Taylor MD, Weissman IL,
Mitra SS, Cheshier SH.

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