

# LUDWIG LINK

AUGUST 2020

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# LUDWIG CANCER RESEARCH

# **ON THE COVER**

The cover image of this issue derives from a Zoom "whiteboard" generated during a townhall meeting of the Ludwig New York office. Attendees were asked to paint the word or phrase each associates with the genuine achievement of diversity and inclusiveness. The activity was inspired by discussions following the death of George Floyd, which has provoked sustained protests against systemic racism in the U.S. and a broader social awakening to prejudice in its many forms. The cover incorporates a slice of the result.

# LUDWIG LINK

ludwigcancerresearch.org

AUGUST 2020

# LETTER



Cancer isn't waiting for COVID-19 to go away. Nor are Ludwig scientists. Though lockdowns imposed by the pandemic have disrupted lab operations, Ludwig researchers have been hard at work, analyzing data, preparing papers and planning new experiments. You'll

find here a brief report on the Ludwig Scientific Insights webinars this past quarter, which shared tips and resources on managing through the pandemic.

The research news in this issue includes a brief on a clinical trial launched by Ludwig Johns Hopkins researchers to evaluate a generic blood pressure drug as a preventive intervention for the deadliest consequence of COVID-19, the cytokine storm. Our other features include items on, among other things, a urine test to detect lung cancer and a new CAR-T cell that can be switched on and off on demand.

We also have some sad news in this issue: Ludwig Professor at Stanford Sanjiv Sam Gambhir died in July from a cancer of unknown origin. A physician-scientist and an inspired inventor, Sam was also a beloved colleague, teacher and mentor to many. He will be missed.

Along the usual honors and awards won by Ludwig researchers, you'll learn a little in this issue about the accomplished immunologist Bob Schreiber—a new member of the Ludwig Institute's Scientific Advisory Committee. We also thought we'd ask Ludwig scientists to share their thoughts on how the pandemic is likely to influence their own work and cancer research and care in general. Find out what they said in our special Ask a scientist section.

Happy reading!

Rachel Reinhardt Senior Vice President for Communications

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#### Awards and distinctions



Peter Ratcliffe Ludwig Oxford



Rakesh Jain Ludwig Harvard



Kornelia Polyak Ludwig Harvard



Alan D'Andrea Ludwig Harvard



Myles Brown Ludwig Harvard

# FOR HIGH-IMPACT RESEARCH

Five Ludwig scientists were named Fellows of the Academy of the American Association for Cancer Research (AACR) Class of 2020 in May. The honorees include Ludwig Oxford's Sir Peter Ratcliffe-who was recognized for his landmark discoveries on how cells sense oxygen and respond to its depletion-and four Ludwig Harvard researchers. Rakesh Jain was recognized for his investigations of how the tumor microenvironment fuels tumor progression and confers resistance, and how anti-angiogenic therapy can normalize tumor blood vessels and improve chemo- and immunotherapies; Kornelia Polyak for dissecting the role of intratumoral heterogeneity in breast cancer and cancer metastasis; Alan D'Andrea for his contributions to the field of DNA damage and repair, and for defining how such defects drive Fanconi anemia; and Myles Brown for his discoveries on the role steroid hormones and their cellular receptors play in the initiation and progression of various cancers. Election to the Academy is an honor bestowed by the AACR on those whose scientific contributions have "propelled significant innovation and progress against cancer."

# FOR GENERAL SCIENTIFIC EXCELLENCE

In April, Ludwig Oxford Director Xin Lu was elected to the Fellowship of the Royal Society. Xin was recognized by the Royal Society for her contributions to our understanding of cancer cell biology, particularly her work on the regulation of p53, a tumor suppressor protein whose inactivation or mutation aids the progression of a wide variety of cancers. She is perhaps best known for leading the discovery and functional characterization of the ASPP family of proteins, which control p53 activity. Aside from opening new approaches to selectively killing cancer cells, Xin's continuing exploration of those proteins has exposed their role in other disorders, including sudden cardiac death and brain abnormalities. Xin has directed Ludwig's Oxford Branch since it was established in 2007 and is a Professor in the Nuffield Department of Medicine at the University of Oxford, a Fellow of the Academy of Medical Sciences and the Royal Society of Biology, a Fellow by election of the Royal College of Pathologists and a member of the European Molecular Biology Organization. Founded in 1660, the Royal Society is a storied fellowship of eminent scientists, engineers and technologists in the UK and the Commonwealth whose mission is to "recognize, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity."



Xin Lu Ludwig Oxford



George Demetri 🕨 Ludwig Harvard

# FOR LINKING SCIENCE TO HUMAN BENEFIT

Ludwig Harvard Co-director George Demetri was named the recipient of the 2020 David A. Karnofsky Award in April. He will deliver the Karnofsky Lecture at the virtual ASCO meeting in August 2020. Among the most prestigious honors bestowed by the American Society of Clinical Oncology, the Karnofsky Award recognizes outstanding contributions to cancer research, diagnosis and treatment. George has made major contributions to our understanding and treatment of cancers that arise in the soft tissue and bone, known as sarcomas. His development of selective inhibitors of the mutated KIT oncogene led in 2002 to historic approval of the first targeted therapy, imatinib, for gastrointestinal stromal tumors (GISTs), the most common sarcoma. Imatinib was initially developed to inhibit the fusion oncoprotein, BCR-ABL, in chronic myeloid leukemia; GIST was the second approval. With George's collaboration, the drug has also been approved for DFSP, a different sarcoma driven by a PDGF-gene fusion and other blood cancers. George's subsequent research led to the approval of second and third generation treatments for GISTs, as well as treatments for other sarcomas. His work has influenced the development of drugs for a wide range of malignancies, including the recent inhibitors of oncogenic TRK-fusions in rare subsets of virtually all cancers.

#### Awards and distinctions



Howard Chang Ludwig Stanford

# FOR ILLUMINATING THE DARK GENOME

Ludwig Stanford Professor Howard Chang was elected to the National Academy of Sciences (NAS) and the American Academy of Arts and Sciences (AAAS) in April. Howard's lab has developed powerful new technologies to explore how the large expanses of the genome that encode no proteins-98% of the whole-control the expression of the remaining 2%. Applying these technologies, Howard and his colleagues have made transformative discoveries on how regulatory DNA sequences in these regions influence biological phenomena ranging from embryonic development to aging to the genesis of cancers. Howard has also explored how cells of the body establish and maintain their

positional identity-work that led to his lab's discovery of a sprawling family of genes encoding long noncoding RNAs that regulate gene activity and play critical roles in an array of biological processes, including cancer. Established in 1780, the AAAS honors excellence and seeks "to cultivate every art and science which may tend to advance the interest, honor, dignity, and happiness of a free, independent, and virtuous people." The NAS was established in 1863 and charged with providing independent, objective advice to the nation on matters related to science and technology. Election to the NAS is considered one of the highest honors a scientist can receive.



Jonathan Dudley Ludwig Johns Hopkins

#### FOR A STELLAR START

In May, Ludwig Johns Hopkins researcher Jonathan Dudley was named a winner of this year's prestigious Damon Runyon Physician-Scientist Training Award for his work on a new approach to screening for bladder, endometrial and ovarian cancers. A board-certified pathologist, Jonathan is developing a way to detect cells in urine and pap smears that have abnormal amounts of DNA, or aneuploidy. Aneuploidy is present in over 90% of cancers, but is difficult to detect with traditional liquid biopsy methods in the early stages of tumor growth. Detecting these cancers earlier can improve the odds for a cure. Jonathan also received this year's Benjamin Castleman Award from the United States and Canadian Academy of Pathology at its national conference. The award is given to one pathologist under forty each year for an outstanding paper in the field of human pathology. Jonathan was recognized for work he initiated during his residency and fellowship with Ludwig Stanford investigators Maximilian Diehn and Ash Alizadeh creating a method to detect bladder cancer from cell-free DNA in urine cytology specimens.

# In memoriam SANJIV SAM GAMBHIR 1962-2020

Sanjiv Sam Gambhir, Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research at Stanford University, died July 18th from a cancer of unknown origin. He was 57. A renowned scientist and physician, and a beloved mentor and colleague, Sam was considered among the founders of modern molecular imaging and a pioneer of its application to the early detection of cancer. He was Chair of the Department of Radiology and Director of the Molecular Imaging Program and of the Precision Health and Integrated Diagnostics Center at Stanford. He was also co-founder and director of the Canary Center at Stanford for Cancer Early Detection. Finishing college at the age of 19, Sam, an immigrant from India, enrolled in an MD/PhD program at the University of California, Los Angeles, where he developed a lifelong fascination with applying math and physics to visualize molecular processes in the living body. Early in his career, Sam was instrumental to bringing PET scans to the clinic, writing many of the decision algorithms that enabled its use for cancer diagnostics. Sam sought with great urgency-and remarkable success-to pioneer new methods of molecular imaging for the early detection of cancer and better monitoring of therapy. Among his most notable recent inventions is one that permits the visual tracking of immune cells activated in patients to monitor the therapeutic efficacy of immunotherapies. Technologies developed in Sam's lab formed the basis of three biotechnology





companies and will, in time, help save the lives of countless cancer patients. An author of hundreds of scientific papers and scores of patents, Sam was elected to the National Academy of Medicine in 2008, the American Association for the Advancement of Science in 2014, and the National Academy of Inventors in 2016. You can learn more about Sam's life, inventions (see page 13) and intellectual passions in a profile we prepared of him for our annual 2018 Research Highlights report. Ludwig's statement upon his death is available here.

Ludwig CEO Ed McDermott (third from left) with Ludwig Stanford Professors Irv Weissman, Lucy Shapiro, Howard Chang, the late Sam Gambhir and Peter Kim

# MANAGING THE NEW NORMAL

The Ludwig Scientific Insights webinar series turned its focus this past quarter on the universally relevant issue of managing through the COVID-19 pandemic and dealing with its disruption of scientific research. The first webinar, broadcast June 10th, began with a highly interactive presentation by Chad Owen, an expert in virtual team facilitation who has worked with Sundance Film Festival, Nike and Google, among other organizations. His presentation included a survey (and quick demonstrations) of the most effective tools and technologies out there for remote teamwork, and recommendations on best practices for the conduct of virtual meetings. The tools and platforms he covered can be accessed here. In the second half of the webinar, Chad interviewed Ludwig Oxford's Chunxiao Song and Ludwig Stanford investigator Ravi Majeti about their experience and insights on managing remote teams during the lockdown, offering his own thoughts on the successes and challenges they identified.

The second webinar, held on June 23rd, was a panel discussion on the future of cancer research in the "new normal" and how best to resume research while ensuring the safety of research staff and patients. Panelists included Ludwig Harvard Co-director George Demetri and investigator Peter Sorger, Ludwig Lausanne Member Johanna Joyce and Ludwig MSK Member Jedd Wolchok. The discussion was moderated by Ludwig's Senior Vice President for Communications Rachel Reinhardt. The panelists discussed how they've adapted to the lockdowns imposed by the pandemic and what they've learned from the experience, including best practices for conducting cancer research in the current environment. They also spoke about their experiences returning, or their plans to return, safely to the lab.

A recording of the June 10th webinar is available here, and the June 23rd webinar can be accessed here.



Chunxiao Song Ludwig Oxford



Ravi Majeti Ludwig Stanford



George Demetri Ludwig Harvard



Peter Sorger Ludwig Harvard



Johanna Joyce Ludwig Lausanne



Jedd Wolchok Ludwig MSK

#### People on the move

#### News roundup

# A NEW SCIENTIFIC ADVISOR

Robert Schreiber, the Andrew M. and Jane M. Bursky Distinguished Professor of Pathology and Immunology at Washington University School of Medicine, has joined Ludwig's Scientific Advisory Committee. He is also the Interim Director of the Division of Immunobiology, Director of the Washington University Bursky Center for Human Immunology and Immunotherapy Programs and Co-Leader of the Tumor Immunology Program at Washington University's Siteman Comprehensive Cancer Center. A pioneer of modern tumor immunology, Bob demonstrated early in his career that the immune-stimulating factor IFN-y activates macrophages to target cancer cells and microbes. Working with the late Lloyd Old, Ludwig's former scientific director and CEO, Bob discovered that the disruption of IFN-y signals helps cancer cells evade immune clearance. The pair went on to formulate and experimentally validate the concept of "cancer immunoediting," the process by which the immune surveillance of tumors drives their evolution into forms that evade immune detection and attack. Bob continues to make notable contributions to our understanding of basic tumor immunology while also developing novel approaches to personalized cancer immunotherapy. An author of more than 300 peer reviewed papers, Bob is a member of the American Academy of Arts and Sciences and the National Academy of Sciences, and a Fellow of the American Association for Cancer Research.



Robert Schreiber Ludwig Scientific Advisory Committee



Johanna Joyce **b** Ludwig Lausanne

# DIVERSE LANDSCAPES

In a Cell paper published online in May, Ludwig Lausanne's Johanna Joyce and her team reported a sweeping comparative analysis of the distinct immune landscapes of tumors that arise in the brain, or gliomas, and those that metastasize to the organ from the lungs, breast and skin. They surveyed the numbers and preferential locations of 14 different types of immune cells in the tumor microenvironment (TME) of 100 samples obtained from patients. They also profiled a spectrum of proteins, including cytokines and growth factors, in the samples and the global gene expression patterns of individual immune cells. These diverse analyses were then integrated to comprehensively map the immune landscape of each tumor type and capture key differences in the functional states of their resident and recruited immune cells. Their study identified the types of immune cells that predominantly sculpt the brain TME and showed that the composition of the immune landscapes and the functional states of their constituent cells are shaped by the interplay of the brain's unique biology and the innate characteristics of each type of tumor. These richly detailed findings are likely to be an invaluable resource for the development of highly personalized immunotherapies at Ludwig Lausanne and beyond.



Nickolas Papadopoulos Ludwig Johns Hopkins



Bert Vogelstein Ludwig Johns Hopkins



Ken Kinzler Ludwig Johns Hopkins

# TOWARD EARLY DETECTION

Researchers led by Ludwig Johns Hopkins investigator Nickolas Papadopoulos and Co-directors Bert Vogelstein and Ken Kinzler reported in an April paper published online in Science the results of a pioneering study evaluating the feasibility of a liquid biopsy combined with standard screening to detect multiple cancers in the general population. The study enrolled more than 9,900 women who had no evidence or history of cancer and gave them a blood test developed at Ludwig Johns Hopkins named CancerSEEK to look for undiagnosed cancers. Collaborators in the study included Thrive Earlier Detection, a company co-founded by the Ludwig Johns Hopkins team, and

researchers at the Geisinger Health System. The liquid biopsy more than doubled the number of cancers detected when added to traditional screening, identifying 26 previously undetected malignancies, of which 65% hadn't spread far. Adding standard screening to the blood test improved the sensitivity of detecting breast, colon and lung tumors from 47% to 71%. The blood test also detected seven cancers for which screening tests do not exist, such as thyroid, kidney and ovarian cancers, with a sensitivity of 31%. Most identified cancers were localized by diagnostic PET-CT scanning, and twelve could be surgically removed with intent to cure.

# AN OUNCE OF PREVENTION

In a letter published in the Journal of Clinical Investigation in April, a team of researchers led by Chetan Bettegowda and Maximilian Konig from Ludwig Johns Hopkins presented a rationale for a trial employing a hypertension drug named prazosin to prevent cytokine storm syndrome-a leading cause of COVID-19 mortality. Induced by a cascading immune response that causes runaway, systemic inflammation, the cytokine storm is the main reason COVID-19 patients wind up in the ICU on ventilators with acute respiratory distress (ARD). In 2018, Ludwig Johns Hopkins researchers led by Bert Vogelstein, Verena Staedtke and Shibin Zhou had detailed in Nature the molecular mechanisms, mediated by immune cells, that precipitate cytokine storms. That study showed that hypertension drugs known as alpha-1 adrenergic receptor antagonists (alphablockers) could impede self-amplifying cycles of cytokine release in mice. In a recent analysis on arXiv, an extended team including Susan Athey and Joshua Vogelstein retrospectively examined clinical data on 13,125 men who had ARD from multiple causes and had been taking alpha-blockers for other reasons and compared their outcomes to men who hadn't. They found patients who had ARD and were taking alphablockers had a 35% lower risk of requiring ventilation and 56% lower risk of dying while on ventilators. In May, the researchers received approval from the U.S. Food and Drug Administration for a clinical trial led by Chetan to test the alpha-blocker prazosin as an early, preventive intervention against cytokine storms in hospitalized patients with COVID-19. With case numbers rising, the team is currently focused on extending clinical trials to non-hospitalized COVID-19 patients in the earliest disease stages to prevent hospital admission.



Chetan Bettegowda Ludwig Johns Hopkins



Bert Vogelstein Ludwig Johns Hopkins



Shibin Zhou Ludwig Johns Hopkins



Maximilian Konig Ludwig Johns Hopkins



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Verena Staedtke Ludwig Johns Hopkins

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Sangeeta Bhatia Ludwig MIT

## A NIP IN THE BUD

Lung cancers are far more curable when they're caught early. In an April paper in Science Translational Medicine, Ludwig MIT's Sangeeta Bhatia and her team describe a simple urine test that captures lung cancer in its earliest stages in mice, and does so accurately. The test relies on nanoparticles developed in Sangeeta's lab that are coated with short protein fragments, or peptides, which are specifically cut by protease enzymes associated with various tumors. This releases biomarkers that can be easily detected in urine. Sangeeta and her colleagues identified proteases preferentially expressed by

lung cancer cells and created a panel of 14 nanoparticles coated with their target peptides. They then inserted the sensors into the airways of mouse models engineered to spontaneously develop one of two different types of lung tumors. Their urine test accurately detected tumors in one of the mouse models as early as 7.5 weeks after the onset of tumor growth, when the tumors were only about 2.8 cubic millimeters in size. In the other mouse model, tumors could be detected at 5 weeks. The sensors detected cancer at least as well or better than CT scans. Click here to watch a video on this new technology.



Crystal Mackall Ludwig Stanford

# A CAR-T FULL OF PROMISE

Atypical teratoid/rhabdoid tumors (ATRT) are rare and aggressive tumors of the brain and spinal cord found in fewer than 10% of children with brain tumors, and most often seen in toddlers. Median survival for this cancer, even with treatment, is only about 17 months. In a Nature Medicine paper published in April, Ludwig Stanford's Crystal Mackall and colleagues reported their development of a chimeric antigen receptor T (CAR-T) cell therapy to treat ATRT that virtually eliminated the tumors in mice. The CAR-T cells were engineered to target a surface protein on ATRT cells known

as B7-H3, which Crystal and her team found is abundantly expressed by this cancer and drives its growth. Infusing the CAR-T cells into the cerebrospinal fluid that bathes the brain of mice was safer and more effective than administering the cells into a blood vessel. The approach curtailed dangerous brain inflammation because it required about 10 times fewer CAR-T cells than intravenous injection. The researchers plan to conduct clinical trials of the CAR-T cells beginning next year, first in adult patients with the brain cancer glioblastoma and-if all goes well-later in kids with ATRT.

# **VERY SMART TOILET**

We already have smart watches-why not a smart toilet? A team led by Sam Gambhir-the Virginia and D.K. Ludwig Professor for Clinical Investigation at Stanford University, who died from cancer July 18-came up with an answer. Sam and his colleagues designed a smart toilet that uses cameras, motion and pressure sensors and dipstick tests to detect a range of disease markers in stool and urine, including those of some diseases, such as irritable bowel syndrome or urologic cancers. Stool and urine are recorded on video and computationally analyzed by algorithms that can identify abnormal consistencies

and flows. The dipstick tests, meanwhile, currently detect and analyze ten biomarkers. A flush lever equipped with a fingerprint reader and the photographic identification of unique "anal prints" link results to individual users. All data is stored in a cloud-based system for doctors-or an artificial intelligence-to examine later. So far, the toilet has been tested on 21 participants, and a survey of 300 prospective participants found that at least 52% were at least somewhat comfortable with using such a smart toilet. The technology was first described in Nature Biomedical Engineering in April, and has garnered much media attention.



Sam Ghambir (1962–2020) Ludwig Stanford

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# **HELPFUL BUGS**

A study led by Ludwig MSK Director Alexander Rudensky and published in Nature reported in April that isoDCA, a metabolite of bile acids made by friendly, commensal bacteria in the intestines, boosts the local generation of regulatory T cells-immune cells that suppress autoimmune reactions and inflammation. Such locally generated, or "peripheral", regulatory T cells (Tregs) help dampen chronic intestinal inflammation, a major driver of colorectal cancers. Alexander and his team screened a spectrum of bile acids produced by bacterial metabolism for such effects in co-cultures of Treg precursors and dendritic cells which, among other things, help direct the

generation of Tregs. They showed that isoDCA, which is relatively abundant in the human intestine, opposes the signals issued by a bile acid sensor in dendritic cells, the farnesoid X receptor (FXR). This pushes dendritic cells into an antiinflammatory state in which they drive the generation of peripheral Tregs. Alexander and his team also showed that mice colonized with bacteria engineered to make isoDCA had many more peripheral Tregs in their intestines than those colonized with the same bacteria tweaked to lack this capability. The discovery has implications for efforts to prevent colon cancer through dietary intervention.



Alexander Rudensky Ludwig MSK

# SECONDHAND SENSITIVITY

Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer. While KRAS mutations are common in NSCLCs, it has so far proved difficult to devise drugs that target this driver of cancer growth. In an April paper in Cancer Cell, Ludwig Harvard investigator Karen Cichowski and colleagues reported that many KRAS-mutant NSCLC tumors might be responsive to a combination of therapies that target other proteins in their constituent cells. They found that about half such lung tumors express high levels of a protein named HOXC10 due to other, so far unappreciated, gene defects. Their studies demonstrated that those defects, in PRC2 genes, conferred sensitivity to MEK and BET inhibitors in mice bearing HOXC10 over-expressing KRAS-mutant tumors. Karen and her team showed that these drugs exert their effects by inhibiting DNA replication and triggering cell death in the tumors. Aside from defining a potentially novel approach to treating many KRAS driven lung tumors, the study identifies a biomarker that might be used to stratify patients eligible for BET/MEK-targeting therapy.



Karen Cichowski Ludwig Harvard



Maximilian Diehn 🕨 Ludwig Stanford



Ash Alizadeh 🕨 Ludwig Stanford

# EARLY WARNING SYSTEM

Non-small cell lung cancers (NSCLCs), the leading cause of cancer death worldwide, can be cured if they're caught before they spread to other organs and promptly treated. Trouble is the current gold standard of screening, the CT scan, generates many false positives. Further, most high-risk people currently do not receive the scans for a variety of reasons, including reluctance to get them done and access difficulties. To address these challenges, a team led by Ludwig Stanford researchers Maximilian Diehn and Ash Alizadeh developed a blood test that detects NSCLC by analyzing extremely rare bits of DNA shed into the blood by tumors. Max, Ash and their colleagues devised a method to differentiate genuine NSCLC-related mutations in such circulating tumor DNA (ctDNA) from mutations found in the far larger pool of circulating DNA that does not come from cancer cells. Integrating that capability with other molecular features of ctDNA, the researchers developed a machine learning-based approach named Lung-CLiP (for lung cancer likelihood in plasma) that they showed can detect between 40% and 70% of early stage NSCLCs. Although CT scans are more sensitive, Lung-CliP generates fewer false positives. Given its ease of use, Lung-CliP could be combined with CT scans to detect thousands of additional early-stage NSCLCs each year-providing, of course, it passes muster in large scale clinical trials. The method was detailed in a March paper in Nature.

# A LONG READ

The optimization of short-read sequencing-in which DNA strands about 300 bases in length are sequenced and then computationally reassembled-has made DNA sequencing much cheaper and revolutionized genomic profiling. But the computational assembly of short sequences into the full sequence can sometimes prove difficult, especially when those strands encode repeating sequences of bases. Similar challenges have complicated the sequencing of chemical, or epigenetic, modifications to DNA that play a critical role in an array of biological processes, especially cancer. In 2019, Ludwig Oxford's Chunxiao Song's and Benjamin Schuster-Böckler's groups published the TAPS (Tet-assisted pyridine borane sequencing) method for the detection of the epigenetic modifications 5-methylcytosine and 5-hydroxymethylcytosine. The new method, now at the heart of a recentlylaunched startup named Base Genomics, is gentler, cheaper and far more efficient than the prevalent standard for such sequencing. This permits its use in sequencing epigenetic marks on even vanishingly tiny samples, potentially including circulating tumor DNA. In a new paper published in Genome Biology in March, Chunxiao and his colleagues describe their adaptation of TAPS for long-read sequencing applications and demonstrate its use on embryonic stem cells and the hepatitis B virus.



Chunxiao Song Ludwig Oxford



Benjamin Schuster-Böckler Ludwig Oxford



Ralph Weichselbaum 🕨 Ludwig Chicago

# **BUGS STING CANCER**

Commensal gut bacteria help regulate the immune system and can, in that capacity, significantly influence patient responses to cancer immunotherapy. In a March paper in the Journal of Experimental Medicine, a research team led by Ludwig Chicago's Ralph Weichselbaum and Yang-Xin Fu of the University of Texas Southwestern Medical Center reported that they can aid immunotherapy more directly as well. The researchers found that one denizen of the gut, Bifidobacterium, also preferentially accumulates in tumors, where it can stimulate responses to anti-CD47 immunotherapy (an experimental therapy first developed by Ludwig Stanford's Irv Weissman and his colleagues). The bacteria, it turns out, work this wonder through dendritic cells, sentinels of the immune system that help activate antitumor immune responses. Ralph, Yang-Xin and colleagues show that their intratumoral presence boosts the signaling of a protein in dendritic cells named STING, which activates immunestimulating factors known as interferons. Systemic administration of Bifidobacteria to mice led to their preferential accumulation in tumors, where they stimulated responses to subsequent anti-CD47 immunotherapy. Their removal with antibiotics eliminated the effect. The finding could have significant implications for broadening the efficacy of anti-CD47 immunotherapy, which is now being evaluated in clinical trials as a treatment for multiple tumor types.

# **TRAITOROUS TARGETS**

The cores of tumors are often acidic and starved of oxygen and vital nutrients. This forces resident cells to adapt their metabolism to survive. Ludwig Lausanne's Ping-Chih Ho and colleagues reported in a February paper in Nature *Immunology* a novel mechanism by which regulatory T cells (Tregs), which suppress immune responses and autoimmunity, adapt their metabolism to deal with the acidity. The mechanism, Ping-Chih and his team found, is exclusively engaged by Tregs that reside in tumors and could be selectively disrupted in a mouse model to boost immunotherapy without inducing autoimmune side effects. They discovered that intratumoral Tregs

express high levels of genes involved in lipid uptake and metabolism-particularly CD36, a receptor involved in lipid import. CD36 deficiency induced in intratumoral Tregs a form of cell suicide known as apoptosis, driven by a decline in their mitochondria, the power generators of cells. Likewise, treating mice bearing melanoma tumors with an antibody to CD36 resulted in the decimation of intratumoral Tregs (though not other Tregs) and boosted the effects of anti-PD-1 immunotherapy, which stimulates a T cell attack on cancer cells. Ping-Chih's lab is now working to translate these findings into a potential cancer therapy.



Ping-Chih Ho Ludwig Lausanne

# **INNATE POTENTIAL**

Only about 20% of all cancers respond to checkpoint blockade, which unleashes an attack on tumors by T cells of the immune system. Researchers are therefore targeting a variety of other immune cells that might be additionally harnessed to eliminate tumors. In a February paper in Nature, a team led by Ludwig MSK's Taha Merghoub and pancreatic cancer physician-scientist Vinod Balachandran reported one such candidate: the innate lymphoid cell (ILC), which helps regulate inflammation and immunity in tissues where it resides. Taha and colleagues noticed that a subtype of these cells, ILC2s, were present in relatively large numbers in pancreatic

ductal adenocarcinomas (PDACs) and that patients with more of these cells in their tumors tend to live longer. The researchers then demonstrated in mouse models of PDAC that an immune factor named II -33 boosted the ILC2 attack on tumors. But it also prompted them to express higher levels of PD-1, a protein that acts like a brake on the activation of T cells and other immune cells. Taha, Vinod and their team showed that combining IL-33 and anti-PD-1 immunotherapy dramatically boosted tumor rejection in the mice-identifying a potential combination immunotherapy for a cancer that has stubbornly resisted all forms of treatment.



Taha Merghoub Ludwig MSK

# CALCULATED ODDS

Tweaking the harsh conditions and dysfunctions of the tumor microenvironment (TME) to improve and broaden the efficacy of existing immunotherapies is a subject of feverish research these days. Ludwig Harvard researcher Rakesh Jain has, for example, demonstrated that drugs that normalize the dysfunctional blood vessels or alter the noncancerous supportive tissuethe stroma-of the TME can improve responses to both chemotherapy and immunotherapy. In February, a team led by Rakesh and a colleague at the University of Cyprus reported in the Proceedings of the National Academy of Sciences a mathematical model that predicts how such interventions might affect treatment outcomes. The model, uniquely, captures complex interactions between cancer cells, blood vessels, molecular factors and immune and other noncancerous cells in the TME and predicts whether and how various drug interventions might influence immunotherapy. Its predictions fared well when compared to results of experimental studies. It also made some helpful suggestions. The model predicts, for example, that for certain tumors, lowdose antiangiogenic drugs to normalize blood vessels improve checkpoint blockade immunotherapy when the two drugs are given sequentially. Other tumor types, meanwhile, are likely to be more responsive when their stromata are normalized by treatment with blood pressure drugs.



Rakesh Jain Ludwig Harvard



Sandro Santagata 🕨 Ludwig Harvard

# **FOCI FOR RESEARCH**

Ceaseless proliferation can be quite stressful for cells. It can, for one thing, cause a dysfunction in the production, proper folding, management and degradation of proteins that's collectively referred to as proteotoxic stress. Cancer cells cope with such stress by permanently activating a master regulator of gene expression, heat-shock factor 1 (HSF1), which controls the production of stress-response proteins known as chaperones. HSF1 accumulates in foci known as "stress bodies" within the nucleus of stressed out cancer cells and their presence has been taken to be a proxy for the activation of chaperones. In a February paper in Nature Cell Biology, researchers at Ludwig Harvard led by Sandro Santagata explored what differentiates HSF1 disposition in tumor cells that survive proteotoxic stress from those that do not. Using an integrated suite of imaging technologies, Sandro and his colleagues discovered that the dissolution of foci rather than their formation is what promotes HSF1 activity and tumor cell survival. During prolonged stress, the foci transform into gels, immobilizing HSF1 and reducing chaperone expression, which leads to cell death. The researchers suggest the dynamic balance of HSF1-bearing foci in different states determines the fate of a cell during proteotoxic stress.

# **KILL SWITCH**

A team led by Ludwig Lausanne's Director George Coukos and Melita Irving, together with their colleague Bruno Correia of the École Polytechnique Fédérale de Lausanne, reported the design of a novel chimeric antigen receptor (STOP-CAR) in the February issue of Nature *Biotechnology*. The STOP-CAR system can be switched on and off on demand to prevent dangerous runaway immune responses and CAR-T cell exhaustion. By structure-based computational design, the researchers devised a strong interface between two human proteins: one natural, and the other a rationally modified scaffold to which it binds. This interface can, however, be dissociated by a specific small molecule. The proteins were then incorporated into a novel chimeric antigen receptor (CAR) design that placed the tumor-antigen binding part of the CAR on one chain and the T-cell signaling part—which functionally activates the CAR-T cell-on a second chain. Due to the interface, the two chains spontaneously associate and can activate their host CAR-T cells in response to antigen. But the activation can be switched off by the small disruptive molecule-and restored upon its removal. The system highlights the potential of structure-based design to add a layer of control to cellular immunotherapies. The researchers are now adapting their STOP-CAR for clinical use.



George Coukos Ludwig Lausanne



Melita Irving Ludwig Lausanne



Aaron Newman 🕨 Ludwig Stanford

# **TELLTALE NUMBER**

Not all cancer cells are created equal. Only a relatively rare subset of tumor cells typically drive malignancies and seed metastases. To truly snuff out a cancer, then, drugs must target such stem-like cells. In a January paper in Science, Ludwig Stanford investigators led by Aaron Newman reported an elegant way to identify stem cells in healthy tissues and their counterparts in tumors. They first confirmed that the number of genes expressed by a cell reliably correlates with the developmental state of that cell: the more genes expressed, the less differentiated and more stem-like that cell is likely to be. They then applied that insight and single-cell profiling of RNAwhich carries information encoded by DNA during gene expression-to create an algorithm named CytoTRACE that's based on the number of genes expressed by a cell and the number of RNA copies per gene. Aaron and his colleagues applied CytoTRACE to triple negative breast cancer, which is notoriously difficult to treat. In homing in on stem-like cells in such tumors, CytoTRACE identified several known markers of triple-negative breast cancer and at least one novel marker that seems to be a prime target for future drug development.

# AN ENVIRONMENT OF RESISTANCE

A team led by Ludwig Harvard's Sandro Santagata and George Demetri reported in a February paper in JCO Precision Oncology their analyses of the mechanism(s) of resistance to TRK-fusion inhibitors (TRKi) in a patient diagnosed with a metastatic sarcoma that originated in the pelvis. Analysis of the sarcoma revealed that the cancer harbored a chimeric genomic fusion of the NTRK1 gene. After an initial major response to larotrectinib, a first-generation TRKi, disease progression occurred with subsequent response when treated with a second-generation TRKi, selitrectinib. Using a multiplex spatial imaging system developed at Ludwig Harvard, and nextgeneration DNA sequencing methods, Sandro, George and their colleagues analyzed the evolution of drug resistance in the patient's tumors. They identified a gain-of-function mutation in the KRAS gene that led to reactivation of the targeted signal transduction pathway and consequent tumor progression. The researchers also described how the activation of KRAS-induced changes in the infiltrating immune cell profile of the tumor microenvironment, including a significant increase in intratumoral cytotoxic T cells and macrophages. Their findings help define mechanisms of resistance to TRKis and suggest novel strategies to treat resistant disease. These could include a combination of immunotherapy and novel TRKis.



Sandro Santagata
 Ludwig Harvard



George Demetri
Ludwig Harvard



Frank Furnari 🕨 Ludwig San Diego

# **CRISPR REPLICAS**

The trouble with many models of cancer is that they do not authentically replicate the cellular and microenvironmental complexity of tumors that arise spontaneously and evolve over time in animals. In a January Nature Communications paper, Ludwig San Diego's Frank Furnari and colleagues describe their construction and evaluation of a new genetically engineered model for the brain cancer glioblastoma (GBM) that addresses this limitation. The model is developed from human induced pluripotent stem cells (iPSC)-which can give rise to a number of tissuesengineered using CRISPR (a method for directed gene editing) to replicate known genetic drivers of GBM. When engrafted into the brains of mice, the engineered iPSCs gave rise to authentic GBM tumors that, when re-engrafted into other mice, faithfully replicated the cellular heterogeneity and other common traits of patient-derived tumors. The models also enabled the tracing of the tumor's evolution and development of drug resistance. Frank and his colleagues plan to use their model to screen drugs and test other mutations in adult and pediatric brain tumors. They're also using their approach to model tumors in other tissues, such as the pancreas and lung.



Tammie Bishop Ludwig Oxford



Peter Ratcliffe Ludwig Oxford

## **VENTILATORY WARNING**

Hypoxia-inducible factors (HIFs) are master regulators of gene expression that play a central role in the cell's adaptation to oxygen starvation. They're also highly activated in a variety of tumors, which typically have hypoxic microenvironments, and experimental cancer drugs targeting HIF-particularly HIF-2 $\alpha$ -are well along in clinical development. Ludwig Oxford's Tammie Bishop and Peter Ratcliffe explored how one HIF-2 $\alpha$ -inhibitor affects ordinary physiological responses to low oxygen. They reported in a Journal of Clinical Investigation paper in January that the inhibitor PT2385 significantly compromises the hypoxic

ventilatory response, which normally boosts breathing rate in low oxygen environments. The drug also inhibits the proliferation of cells in carotid bodies, which sense the levels of oxygen and carbon dioxide in the blood and trigger adaptive physiological responses. Their analysis of the biochemistry of these effects suggest they're induced not by some coincidental effect of PT2385 but directly through its effects on HIF-2 $\alpha$ . All this, they argue, suggests a need for caution in using HIF-2 inhibition to treat patients with co-occurring respiratory disorders, or those living at relatively high altitudes.

Working-from-home edition: Ask a scientist about COVID-19 and cancer research



# What lessons have you learned from the COVID-19 pandemic that might apply generally to the conduct, focus or planning of cancer research in the future?

Cancer is a much bigger threat to the world over time, especially with an aging population. The pandemic has demonstrated that it is possible to coalesce around an acute challenge, which will hopefully stimulate a greater and more coordinated focus on cancer research going forward.

> GEOFFREY GREENE Ludwig Chicago

Not being able to work in the lab has given me time to reflect on the big picture of my project rather than just focus on troubleshooting experiments. This has been very rewarding, and a practice that I would like to keep after the pandemic is over.

> EMILY H. HSIUE Ludwig Johns Hopkins

The COVID-19 pandemic has underscored how especially vulnerable early career investigators are to disrupted research time, shortfalls in funding and hiring freezes. To avoid a 'lost generation' in cancer research, academic institutions should implement bridge funding, extend tenure clocks and increase resource-sharing. If such measures remain available in the future to support investigators facing unforeseen crises, we will have learned the best lesson from the COVID-19 pandemic: 'we are all in this together'.

> SHEHERYAR K. KABRAJI Ludwig Harvard

A lesson that could apply to future cancer research: a sense of collective urgency can bring transformational change. We have witnessed a large marshalling of resources and an embrace of teamwork in science as people focus on finding solutions rather than protecting "ownership" of findings.

#### IAN MARTEN Ludwig Lausanne

Cancer research is dangerously underfunded. COVID-19 gets attention because patients can die in a short period of time, relatively speaking, and the lack of preparedness is glaring. Cancer kills many more over the long run.

> RALPH WEICHSELBAUM Ludwig Chicago

I believe it stresses the importance of solidarity and groups working together to tackle large problems in the understanding of cancer progression and treatment. Doing so requires ensuring adequate funding and resources to research groups.

> JASON BUGNO Ludwig Chicago

Being flexible in the projects we pursue and how we engage in them will be important. I'm now more interested in incorporating computational and other approaches that may be done outside of the lab, in case another stay-at-home order is implemented.

> SEAN FANNING Ludwig Chicago

Given that cancer patients are at greater risk of severe outcomes and death from COVID-19, and many cancer patients and COVID-19 patients are hypertensive, we are examining the role of angiotensin blockers in these patients using the available database. We are also developing mathematical models for this interaction—based on our previous math models of how angiotensin blockers can improve the outcome of cancer treatment.

> RAKESH JAIN Ludwig Harvard

The pandemic has given us no choice but to stop and think, analyze and synthesize our work. As a trainee, it's easy to get lost in the immediacy and urgency of the experiment in front of me. I've been struck by the value of taking this step back.

#### ADAM WOLPAW Ludwig Wistar

As a lab director, I focus on the big questions, or the forest, but pay attention to the trees being attended by trainees to test hypotheses. Often, we get lost in the details of the moment. The pandemic allows for time to step back and review the pertinent literature or data more thoroughly and plan for the future more strategically.

#### CHI VAN DANG Ludwig Scientific Director

I think the clear message that came from how rapidly many thousands of scientists around the world responded to COVID-19 by redirecting their research programs is that when faced with a challenge as immense as this, we absolutely can come together and collaborate in a truly open way to advance patient care as our sole priority.

> JOHANNA JOYCE Ludwig Lausanne

I think it is still too early to learn lessons from this pandemic. However, this is an opportunity for researchers to demonstrate the importance of science in the health and progress of humanity. The public is looking to the scientific community for answers: we must not fail. FRANCESCO BOCCELLATO Ludwig Oxford

One of the most striking aspects of the COVID-19 pandemic is the widespread willingness to collaborate, transparency when it comes to sharing efforts and data and a sense of shared responsibility. I hope to be able to use these lessons to conduct even more streamlined cancerrelated research in the future.

> CHETAN BETTEGOWDA Ludwig Johns Hopkins

This pandemic has brought most non-COVID related experimental lab work to a halt as researchers across the country have been physically distancing from one another and shifted to working remotely. This has brought about unprecedented collaboration, as many researchers have been refocusing at least some of their attention to COVID and thinking about the same problem from many different angles. The speed with which new research is being shared publicly and the extent of scientific discourse could present an enticing model for global scientific collaboration in non-COVID research as well.

> MICHAL CASPI TAL Ludwig Stanford

COVID-19 highlights the need for flexibility in research, yet it's difficult to simply abandon a direction you've invested years into. The lesson I've taken is the necessity of fostering many research interests, turning a lack of focus into a strength. So as doors are closed by the unpredictable, we can pivot to open ones.

> SPENCER S. WATSON Ludwig Lausanne

We can't count on the US government and its employees to keep politics out of science. For example, HHS banned the use of fetal tissues in research and the extra supplements for COVID-19 research and treatment included the ban. Discovery of HSC and CNS SC and leukemia stem cells, as well as the discovery of macrophage checkpoint inhibitors and blockers came from fetal tissue research, which are now late phase clinical trial antibody therapies. Recent COVID-19 research shows human fetal lung in SCID mice is successfully infected and gets ARDS, yet it cannot be used to test treatments and vaccines in NIH funded labs.

> IRV WEISSMAN Ludwig Stanford





# Will the coronavirus pandemic make medical science, including cancer research, nimbler long after this emergency has passed?

Research output during the COVID-19 pandemic has been rapid, focused and relevant. Scientists have asked clear research questions, shared patient samples and data worldwide, and enhanced cooperation between academia, government and industry. If continued and widely adopted, these best practices can make future cancer research more efficient and effective. SHEHERYAR K. KABRAJI Ludwig Harvard

Sheheryar K. Kabraji

I hope so. It has been remarkable to watch huge segments of the biomedical community refocus their expertise on COVID-19. We've recognized how our knowledge can translate to what we thought were unrelated fields, and I hope that this will make science more interdisciplinary in the future.

> ADAM WOLPAW Ludwig Wistar

Yes—people will be more willing to reach across departments to work together, and the connections already made by the forced collaboration due to coronavirus are maintained.

#### IAN MARTEN Ludwig Lausanne

It is easy to be cynical that we will just fall back into old ways, but the pandemic is a powerful and unanticipated stimulus and example of how to adjust our policies to alter ways in which we make decisions about funding and research priorities. We need to sustain that way of thinking. GEOFFREY GREENE

Ludwig Chicago

I don't think so.

RALPH WEICHSELBAUM Ludwig Chicago

That would be nice, and perhaps it could in some medical specialties. However, I don't clearly see that happening in cancer research.

#### JASON BUGNO Ludwig Chicago

The pandemic exposes the need for team science, and perhaps nimbleness will come in the form of a communal effort to solve some of the most challenging cancer problems for the public good rather than for the glorification of individuals.

> CHI VAN DANG Ludwig Scientific Director

I hope so. There are areas of overlap between the cancer and COVID-19 (i.e., cytokine storms), where we could make significant impact. COVID-19 has significantly increased my understanding of virology and immunology, and I am excited to start testing ideas.

> SEAN FANNING Ludwig Chicago

We have learned that many blood tests can be omitted, and that patients can be monitored online, and that medications can be shipped. So clinical trials may be easier to conduct. It is possible to design protocols more simply. It is possible to get them approved more swiftly. I hope that this can be maintained.

> GERBURG WULF Ludwig Harvard

Medical science including cancer research relies both on federal funding and private investments. The pandemic reinforced the need for continuation and even increase of such funding support and that may ultimately benefit cancer research.

> PAUL SURMAN Ludwig Johns Hopkins

COVID-19 researchers have benefited from the global spotlight, with shortcuts in bureaucracy, fast financing programs and dedicated technological platforms making research nimbler. Cancer research is unlikely to ever receive this widespread attention or emergency response. I believe the witnessed agility of medical science resides in its diversity and thus, after COVID-19, it is important that we return to focus on our respective scientific disciplines.

> FRANCESCO BOCCELLATO Ludwig Oxford

The pandemic has galvanized the entire scientific community to focus on one goal: defeating SARS-CoV-2. I have benefited from many collaborators and colleagues working as hard and as fast as they can towards the shared goal of making a difference in this pandemic. As the scientific community sees the benefits of establishing workflows that break down conventional barriers, I hope that, as the emergency passes, cancer researchers and institutions re-evaluate historical norms and find ways to expedite discovery and translation.

> CHETAN BETTEGOWDA Ludwig Johns Hopkins

I believe we will come to a new research norm after the pandemic. For instance, social distancing might still have to be practiced. Therefore, experiments will need to be redesigned to be less labor-intensive but still rigorous and reproducible.

> EMILY H. HSIUE Ludwig Johns Hopkins

Medical science requires rigor and replication, which are not well suited to the speed of data required to inform pandemic response. After this emergency, I hope that we will maintain the worldwide connectedness and collaborations that are currently taking place, but with the rigor required for meaningful, reproducible and translatable cancer research.

> MICHAL CASPI TAL Ludwig Stanford

Not in my view. The lack of appropriate and early response to the pandemic has severely damaged biomedical research and its translation, as well as public health oversight and direction to the extent that what is left must be less than what has been eliminated. It must be inhibitory to young people who hoped to make biomedical and cancer research and therapy their careers.

> IRV WEISSMAN Ludwig Stanford



The pandemic has forced the cancellation of scientific meetings and hampered travel worldwide. As a scientist, are you rethinking how you network and interact with potential collaborators? If so, how?

Limiting face to face meetings will help usher in greater acceptance of teleconferencing as the quality of conversation and presentation nearly matches an in-person meeting. Many will find screen sharing and audio control surprisingly good across various platforms. IAN MARTEN Ludwig Lausanne The ability to meet virtually during the pandemic should catalyze more nimble collaborative research meetings, but face-to-face meetings are irreplaceable for networking and building long-lasting friendships.

> CHI VAN DANG Ludwig Scientific Director

Climate change and the carbon consequences of air travel have already prompted many to rely on virtual meetings to network and maintain collaborations. With AACR and ASCO showcasing the first major annual academic meetings entirely online, I hope meetings become shorter, focused more on sessions where inperson interaction is key.

> SHEHERYAR K. KABRAJI Ludwig Harvard

No.

GERBURG WULF Ludwig Harvard

In the past, I conducted meetings with remote collaborators by sending them a PDF of slides and calling their cell phone. That seems laughable now. We've all grown accustomed to using virtual meeting software, sharing slides and seeing faces. I hope this ability will make distant collaborations more fruitful in the future.

#### ADAM WOLPAW Ludwig Wistar

I miss being able to casually discuss science with lab members on a daily basis, and I'm trying to substitute that by using digital avenues such as Twitter and Slack. The on-line AACR meeting held this year also provided a platform to virtually interact with other participants.

> EMILY H. HSIUE Ludwig Johns Hopkins

I finally activated my Twitter account, having been pretty skeptical for years about how useful this platform really was. I now find out about so much research that I probably wouldn't have seen otherwise, and it's been a great way to build a network of new contacts and share what we've experienced during the entire lab lockdown-restart process.

> JOHANNA JOYCE Ludwig Lausanne

The pandemic forced the cancellation or re-formatting of scientific meetings. As a result, we are relying more on electronic communications and multi-institutional video conferences to network with colleagues.

> PAUL SURMAN Ludwig Johns Hopkins

I have always used video calls to hear from my collaborators who are not on site, but I do not think that scientific conferences can be fully substituted by virtual events. In-person meetings will need to return after the pandemic has passed.

> FRANCESCO BOCCELLATO Ludwig Oxford

While the human aspects of in-person interactions will never be replaced, there are multiple platforms that enable the rapid communication of scientific and medical ideas during the pandemic. Given the robustness of these technologies, I plan to minimize travel for future scientific gatherings/meetings if they can be readily converted to online discussions.

> CHETAN BETTEGOWDA Ludwig Johns Hopkins

Yes. I have found it incredible to be able to virtually attend seminars and group meetings around the world from my home, and to closely connect with researchers outside of my institution at a whole new level. We will need to seriously harness this moving forward in trying to maintain this level of global collaboration while reducing the immense carbon footprint of academic travel.

> MICHAL CASPI TAL Ludwig Stanford

I'm amazed how my network of online collaborators has grown closer as the pandemic kept us further apart. We had Slack and Zoom before COVID-19, but necessity has really brought out their potential. The constant communication has made globally scattered individuals into a community. I hope this aspect of the pandemic continues.

> SPENCER S. WATSON Ludwig Lausanne

It is clear that current virtual methods to teleconference meetings are working, and hopefully can improve more to allow better results. It is an enormous savings in time and money to investigators to do this and allows many more students and fellows to participate. I have had the time and ability to organize many ad hoc meetings to consider COVID-19 research from stem cell and immunology perspectives and expect new alliances will come from it. That said, all of the businesses that count on conferences will be hurt if virtual conferences replace planned meetings at convention centers, etc.

> IRV WEISSMAN Ludwig Stanford



# During this time, many cancer patients are not receiving normal standard of care. What might be done to prevent this from happening in the future?

Sadly, our response to the epidemic through science, medicine, public health, and clinical trials all had to take a back seat to overwhelming lack of adequate and early response to scientific rather than political issues when the pandemic could have been controlled.

> IRV WEISSMAN Ludwig Stanford

Traditionally, the majority of cancer care is delivered in hospital. Recent events have increased the use of telemedicine, particularly communication of diagnosis and management plans. Future biological and technological developments could also facilitate remote diagnosis, therapy and surveillance of cancer, thus reducing unnecessary hospital visits without compromising patient outcomes.

> ASHVINA SEGARAN Ludwig Oxford

Our cancer center has transitioned to tele-visits for most patients requiring follow-up care or requiring second opinion consultations. As with any rapid transitions, the adoption of televisits encountered significant logistical hurdles. But we also gained invaluable experience and now have systems in place to accommodate all patient consultation needs. This will ultimately allow us to continue standard of care practices remotely during future pandemic events. By reducing the patient-physician consultation barrier, a wider adoption of tele-visit technologies may even improve cancer patient care and accelerate clinical trial recruitment in the future.

#### PAUL SURMAN Ludwig Johns Hopkins

There is a terrible risk of hospitalacquired infections and in order to allow for high risk patients to continue to safely receive care, we have to devise safe ways to isolate potential COVID-19 cases who could infect other patients coming in to receive care. This will require a much higher level of testing.

#### MICHAL CASPI TAL Ludwig Stanford

This pandemic has allowed us to examine the power of telemedicine. As the infrastructure and familiarity rises with virtual medical consults, it will allow for clinical medicine to be better prepared if the need arises in the future.

> CHETAN BETTEGOWDA Ludwig Johns Hopkins

The use of telemedicine, wearable technologies, more oral or injectable (rather than intravenous) medications—all have the potential to maintain delivery of standard cancer care in the face of future disruptions. Equally important is to use this opportunity to examine which 'standard of care' practices are truly evidence-based and which could use review.

#### SHEHERYAR K. KABRAJI Ludwig Harvard

For a pandemic related event, avoiding overloading the medical system would prevent loss of care. More investment in quickly deployable testing and tracing mitigates the worst-case scenarios.

> IAN MARTEN Ludwig Lausanne

It will be important to put into place safeguards that maintain essential care for cancer patients when an emergent threat occurs. If our medical care capabilities are kept at a level that can handle unexpected viral infections or similar crises, this should be possible.

# GEOFFREY GREENE

Ludwig Chicago

No patient should have received something other than the standard of care. I can see modifications, but a breach of the standard even under these circumstances is unacceptable.

RALPH WEICHSELBAUM

Ludwig Chicago

Not receiving the standard of care won't do. I would hope that we learn from this experience to be better prepared to ensure proper care even during unforeseeable events.

> JASON BUGNO Ludwig Chicago

I'm not an oncologist, but I would say that improvements to rapid testing along with new building engineering approaches will be needed to protect patients in the next few years.

> SEAN FANNING Ludwig Chicago

I don't think this is true. I have not encountered any patients not receiving standard of care. We do have instances in patients with advanced metastatic disease where the diagnosis of additional COVID disease accelerates the decision to move towards inpatient hospice care. We cannot accrue patients to clinical trials currently. This is, in many instances, a disadvantage for patients.

#### GERBURG WULF Ludwig Harvard

Lessons learned will have to come from major oncology clinics that are willing to share best practices during the pandemic slow-down and collectively provide guidelines for the good of patients during future pandemics.

> CHI VAN DANG Ludwig Scientific Director

Clinically, we've learned a great deal from this pandemic about how to minimize interactions between providers and staff while maximizing patient care. Hopefully, early implementation of similar interventions will allow us to continue to provide close to standard care during any future events.

> ADAM WOLPAW Ludwig Wistar

Managing cancer during COVID-19 has resulted in treatment variations, guided by national protocols and clinician discretion. Accumulating data on shortterm and long-term outcomes stratified by confirmed COVID-19 cases will guide future decisions on the extent of modifying cancer treatment in response to epidemics and pandemics. See the UK cancer and COVID-19 monitoring project: https://ukcoronaviruscancermonitoring. com/

> PAUL MILLER Ludwig Oxford

This extraordinary time is a good opportunity to build up telemedicine infrastructures, which in the long run, would make healthcare more accessible. Some of the actual treatment can be done by mailing the therapies to the patients to be administered at home or by local pharmacies.

> EMILY H. HSIUE Ludwig Johns Hopkins

# Required reading

#### **Ludwig Chicago**

#### Journal of Experimental Medicine 2020 March 6

Intratumoral accumulation of gut microbiota facilitates CD47based immunotherapy via STING signaling.

Shi Y, Zheng W, Yang K, Harris KG, Ni K, Xue L, Lin W, Chang EB, Weichselbaum RR, Fu YX.

#### **Ludwig Harvard**

#### Cancer Cell 2020 April 2 [Epub]

A deregulated HOX gene axis confers an epigenetic vulnerability in KRAS-mutant lung cancers.

Guerra SL, Maertens O, Kuzmickas R, De Raedt T, Adeyemi RO, Guild CJ, Guillemette S, Redig AJ, Chambers ES, Xu M, Tiv H, Santagata S, Jänne PA, Elledge SJ, Cichowski K.

#### JCO Precision Oncology 2020 February 14 (Epub)

Response and mechanisms of resistance to larotrectinib and selitrectinib in metastatic undifferentiated sarcoma harboring oncogenic fusion of NTRK1.

Hemming ML, Nathenson MJ, Lin JR, Mei S, Du Z, Malik K, Marino-Enriquez A, Jagannathan JP, Sorger PK, Bertagnolli M, Sicinska E, Demetri GD, Santagata S.

#### Nature Cell Biology 2020 February 3 (Epub)

# HSF1 phase transition mediates stress adaptation and cell fate decisions.

Gaglia G, Rashid R, Yapp C, Joshi GN, Li CG, Lindquist SL, Sarosiek KA, Whitesell L, Sorger PK, Santagata S.

#### Proceedings of the National Academy of Sciences USA 2020 February 3 (Epub)

Combining microenvironment normalization strategies to improve cancer immunotherapy.

Mpekris F, Voutouri C, Baish JW, Duda DG, Munn LL, Stylianopoulos T, Jain RK.

#### Ludwig Johns Hopkins

#### Journal of Clinical Investigation 2020 April 30 [Epub]

Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists.

Konig MF, Powell MA, Staedtke V, Bai RY, Thomas DL, Fischer NM, Huq S, Khalafallah AM, Koenecke A, Xiong R, Mensh B, Papadopoulos N, Kinzler KW, Vogelstein B, Vogelstein JT, Athey S, Zhou S, Bettegowda C.

# Science 2020 April 28 (Online ahead of print)

#### Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention.

Lennon AM, Buchanan AH, Kinde I, Warren A, Honushefsky A, Cohain AT, Ledbetter DH, Sanfilippo F, Sheridan K, Rosica D, Adonizio CS, Hwang HJ, Lahouel K, Cohen JD, Douville C, Patel AA, Hagmann LN, Rolston DD, Malani N, Zhou S, Bettegowda C, Diehl DL, Urban B, Still CD, Kann L, Woods JI, Salvati ZM, Vadakara J, Leeming R, Bhattacharya P, Walter C, Parker A, Lengauer C, Klein A, Tomasetti C, Fishman EK, Hruban RH, Kinzler KW, Vogelstein B, Papadopoulos N.

#### ArVix Version 5 2020 April 21 Preprint

Alpha-1 adrenergic receptor antagonists for preventing acute respiratory distress syndrome and death from cytokine storm syndrome.

Vogelstein JT, Powell M, Koenecke A, Xiong R, Fischer N, Huq S, Khalafallah AM, Caffo B, Stuart EA, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S, Bettegowda C, Konig MF, Mensh B, Athey S.

#### Ludwig Lausanne

#### Cell 2020 May 28 (Epub)

Interrogation of the microenvironmental landscape in brain tumors reveals diseasespecific alterations of immune cells.

Klemm F, Maas RR, Bowman RL, Kornete M, Soukup K, Nassiri S, Brouland JP, Iacobuzio-Donahue CA, Brennan C, Tabar V, Gutin PH, Daniel RT, Hegi ME, Joyce JA.

#### Nature Immunology 2020 February 17 (Epub)

#### CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors.

Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, Mohmood SR, Fernández-García J, Tsai CH, Schulze I, Picard F, Meylan E, Silverstein R, Goldberg I, Fendt SM, Wolchok JD, Merghoub T, Jandus C, Zippelius A, Ho PC.

#### Nature Biotechnology 2020 February 3 [Epub]

A computationally designed chimeric antigen receptor provides a small-molecule safety switch for T-cell therapy.

Giordano-Attianese G, Gainza P, Gray-Gaillard E, Cribioli E, Shui S, Kim S, Kwak MJ, Vollers S, Corria Osorio AJ, Reichenbach P, Bonet J, Oh BH, Irving M, Coukos G, Correia BE.

#### Ludwig MIT

#### Science Translational Medicine 2020 April 1

#### Urinary detection of lung cancer in mice via noninvasive pulmonary protease profiling.

Kirkpatrick JD, Warren AD, Soleimany AP, Westcott PMK, Voog JC, Martin-Alonso C, Fleming HE, Tammela T, Jacks T, Bhatia SN.

#### Ludwig MSK

#### Nature 2020 April 15 (Epub)

Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells

Campbell C, McKenney PT, Konstantinovsky D, Isaeva OI, Schizas M, Verter J, Mai C, Jin W-B, Guo C-J, Violante S, Ramos RJ, Cross JR, Kadaveru K, Hambor J, Rudensky AY.

#### Nature 2020 February 19 [Epub]

#### ILC2s amplify PD-1 blockade by activating tissue-specific cancer immunity.

Moral JA, Leung J, Rojas LA, Ruan J, Zhao J, Sethna Z, Ramnarain A, Gasmi B, Gururajan M, Redmond D, Askan G, Bhanot U, Elyada E, Park Y, Tuveson DA, Gönen M, Leach SD, Wolchok JD, DeMatteo RP, Merghoub T, Balachandran VP.

# Required reading

#### Ludwig Oxford

#### Genome Biology 2020 March 3

Accurate targeted longread DNA methylation and hydroxymethylation sequencing with TAPS

Liu Y, Cheng J, Siejka-Zielińska P, Weldon C, Roberts H, Lopopolo M, Magri A, D'Arienzo V, Harris JM, McKeating JA, Song CX.

# Journal of Clinical Investigation 2020 January 30

Marked and rapid effects of pharmacological HIF-2α antagonism on hypoxic ventilatory control.

Cheng X, Prange-Barczynska M, Fielding JW, Zhang M, Burrell AL, Lima JD, Eckardt L, Argles I, Pugh CW, Buckler KJ, Robbins PA, Hodson EJ, Bruick RK, Collinson LM, Rastinejad F, Bishop T, Ratcliffe PJ.

#### Ludwig San Diego

#### Nature Communications 2020 January 28

Longitudinal assessment of tumor development using cancer avatars derived from genetically engineered pluripotent stem cells.

Koga T, Chaim IA, Benitez JA, Markmiller S, Parisian AD, Hevner RF, Turner KM, Hessenauer FM, D'Antonio M, Nguyen ND, Saberi S, Ma J, Miki S, Boyer AD, Ravits J, Frazer KA, Bafna V, Chen CC, Mischel PS, Yeo GW, Furnari FB.

#### **Ludwig Stanford**

#### Nature Medicine 2020 April 27 (Epub)

#### Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/ rhabdoid tumors.

Theruvath J, Sotillo E, Mount CW, Graef CM, Delaidelli A, Heitzeneder S, Labanieh L, Dhingra S, Leruste A, Majzner RG, Xu P, Mueller S, Yecies DW, Finetti MA, Williamson D, Johann PD, Kool M, Pfister S, Hasselblatt M, Frühwald MC, Delattre O, Surdez D, Bourdeaut F, Puget S, Zaidi S, Mitra SS, Cheshier S, Sorensen PH, Monje M, Mackall CL.

# Nature Biomedical Engineering 2020 April 6 [Epub]

#### A mountable toilet system for personalized health monitoring via the analysis of excreta.

Park SM, Won DD, Lee BJ, Escobedo D, Esteva A, Aalipour A, Ge TJ, Kim JH, Suh S, Choi EH, Lozano AX, Yao C, Bodapati S, Achterberg FB, Kim J, Park H, Choi Y, Kim WJ, Yu JH, Bhatt AM, Lee JK, Spitler R, Wang SX, Gambhir SS.

#### Nature 2020 March 25 (Epub)

#### Integrating genomic features for non-invasive early lung cancer detection.

Chabon JJ, Hamilton EG, Kurtz DM, Esfahani MS, Moding EJ, Stehr H, Schroers-Martin J, Nabet BY, Chen B, Chaudhuri AA, Liu CL, Hui AB, Jin MC, Azad TD, Almanza D, Jeon YJ, Nesselbush MC, Co Ting Keh L, Bonilla RF, Yoo CH, Ko RB, Chen EL, Merriott DJ, Massion PP, Mansfield AS, Jen J, Ren HZ, Lin SH, Costantino CL, Burr R, Tibshirani R, Gambhir SS, Berry GJ, Jensen KC, West RB, Neal JW, Wakelee HA, Loo BW Jr, Kunder CA, Leung AN, Lui NS, Berry MF, Shrager JB, Nair VS, Haber DA, Seguist LV, Alizadeh AA, Diehn M.

#### Science 2020 January 24

# Single-cell transcriptional diversity is a hallmark of developmental potential.

Gulati GS, Sikandar SS, Wesche DJ, Manjunath A, Bharadwaj A, Berger MJ, Ilagan F, Kuo AH, Hsieh RW, Cai S, Zabala M, Scheeren FA, Lobo NA, Qian D, Yu FB, Dirbas FM, Clarke MF, Newman AM.



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