

Brown Cancer Center Research News

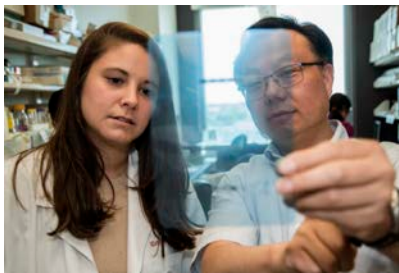
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BCC Research Newsletter

HAPPY SPRING!

A Publication of the Brown Cancer Center

UofL Researchers Use Trained Immunity to Reduce Tumor Activity in Pancreatic Cancer



Anne Geller and Dr. Jun Yan in the lab

Pancreatic cancer is one of the deadliest cancers, with a 5-year survival rate of just 10% for patients diagnosed with the most common type of pancreatic cancer – pancreatic ductal adenocarcinoma (PDAC). Furthermore, one promising area of cancer treatment, immunotherapy, thus far has not provided benefit for pancreatic cancer patients.

UofL researchers recently have shown that β -glucan, a natural carbohydrate, can generate enhanced immune responses to cancer in the pancreas and may lead to improved efficacy of immunotherapy for pancreatic cancer.

Jun Yan, chief of the Division of Immunotherapy in the Department of Surgery and Brown Cancer Center member, said one of the challenges for pancreatic cancer is that natural immune cells are not able to enter the pancreas to combat the growth of tumors, creating an immune desert.

“These tumors lack quality effector immune cells that can kill them,” Yan said. “In addition, pancreatic cancer has a unique tumor microenvironment that prevents the influx of anti-tumor immune cells.”

In new research published this month in *Nature Communications*, Anne Geller, an MD/PhD student, and a UofL research team led by Yan demonstrate that a type of β -glucan derived from yeast can alter the environment within the pancreas to promote anti-cancer immune cell migration to the site of the cancer. β -glucan, a naturally occurring carbohydrate found in plants, bacteria and fungi, is known to induce trained immunity, stimulating an immune

response to a specific stimulus, such as pancreatic tumor cells.

Trained immunity is a new concept in the field of immunology and is the idea that innate immune cells possess a form of “memory,” which typically only has been considered to be a feature of adaptive immune cells such as T-cells. Using animal models, Yan and his team found that when they injected particulate β -glucan into the peritoneal area, it accumulated in the pancreas and promoted anti-cancer immune cell migration to the area. These immune cells were found to have a trained immunity phenotype and effectively inhibited pancreatic cancer growth.

“This research demonstrates that a natural compound can stimulate trained immunity in pancreas,” Yan said.

The researchers also found that β -glucan-stimulated trained immunity can enhance PD-1 antibody therapy in pancreatic cancer. Anti-PD-1 immunotherapy has been approved to treat many types of cancer including melanoma and lung cancer. However, this therapy has failed in treating pancreatic cancer. This research could be a breakthrough in successfully applying immunotherapy to pancreatic cancer.

“This research has a great potential for clinical translation as it elucidates a strategy for delivering therapeutics directly to the pancreas, identifies a mechanism of enhancing anti-tumor immune responses against pancreatic tumors and provides insight into ways of unleashing the awesome power of immunotherapies against PDAC,” Geller said. “This could be a breakthrough in treating the deadly cancer that has evaded so many other forms of treatment.”

Yan, director of the Immunology Program at the Brown Cancer Center and study coauthor, and surgical oncologist Robert C.G. Martin II are conducting a clinical trial using β -glucan in pancreatic cancer patients as a proof-of-concept study.

“This publication demonstrates that a simple yeast-derived β -glucan supplement has the potential to enhance a patient’s immune system and then

respond more effectively to therapies in pancreatic cancer. The concept that patients’ immune systems can be ‘trained’ to see their pancreatic cancer as abnormal or foreign could be a crucial step in enhancing a patient’s overall survival and thus quality of life,” said Martin, professor and director of the UofL Division of Surgical Oncology and a co-author on the study.

According to the American Cancer Society, more than 60,000 adults are expected to be diagnosed with pancreatic cancer in the US in 2022 and nearly 50,000 patients will die from the disease. Alex Trebek, long-time host of the game show “Jeopardy!” shared his pancreatic cancer diagnosis and treatment journey beginning in 2019. Trebek died in 2020, just over 18 months after announcing his diagnosis.

“UofL is committed to solving big, global challenges through research,” said Kevin Gardner, UofL’s executive vice president for research and innovation. “This work, leveraging the power of the immune system to better treat pancreatic cancer, could have a big impact in helping people live lives that are not just longer, but healthier and more resilient.”

Excerpted from UofL Today by Betty Coffman



Cruzin' for Cancer 2022

A Bullitt County tradition is returning for its 7th year as the Cancer Awareness Show brings a mix of two shows in one to the Hillview Community Center on Saturday, June 11, from 11 am to 4 pm.

One hundred percent of the proceeds from the day’s activities benefit patient support, community outreach and the research programs at UofL’s Brown Cancer Center.

The event is composed of 2 shows-in-one: an arts and crafts show and “Cruzin’ for Cancer” – a car, truck, motorcycle and model car show.

Levi Beverly, a BCC research scientist who examines the mechanisms of tumor initiation, progression and regression after treatment will be on hand to discuss his work and provide a general overview of the progress made in successfully beating

cancer in recent years. Proceeds from the show help to fund Beverly's lab, as well as services provided by the M. Krista Loyd Resource Center and the Kentucky Cancer Program.

UofL Scientist Receives 8-year NIH Grant to Learn How Metals Cause Lung Cancer



For nearly 30 years, John Pierce Wise Sr. (pictured above) has investigated the connection between exposure to metals and cancer, working both in the lab and in the field, reporting significant discoveries about the effects of metals on chromosomes in lung cancer and how those effects differ in humans and in whales.

Wise, professor of Pharmacology and Toxicology and member, Brown Cancer Center, now has received \$6.7 million over 8 years from the National Institute of Environmental Health Sciences through the Revolutionizing Innovative, Visionary Environmental health Research (RIVER) program to investigate how chromosome instability resulting from exposure to metals leads to lung cancer.

Lung cancer is the leading cause of cancer death in the US, and Kentucky has the highest rates of lung cancer incidence and mortality of any state. Despite the widely held perception that lung cancer is simply attributed to smoking, 1-in-5 women and 1-in-12 men who develop lung cancer never smoked. In addition to high rates of cancer, lung cancer has a 5-year survival rate of 21%, one of the lowest of any cancer site.

"Lung cancer has a substantial impact on human health, particularly here in Kentucky, and it is time the misconception that smoking is the only cause of lung cancer is dispelled," said UofL interim president Lori Stewart Gonzalez. "We are grateful for the institute's confidence in Dr. Wise and our university to lead this work in addressing such a significant health concern. I am excited to see this amazing research continue

and expand at UofL thanks to this grant."

Metals are some of the top environmental causes of human lung cancer, but scientists do not fully understand how the metals cause cancer. Wise's research has shown that one such metal, hexavalent chromium, causes chromosome instability, in which the chromosomes are increased, deleted or rearranged in inappropriate ways. This chromosome instability can lead to the development of cancer.

Wise has studied metals-induced chromosome instability in humans and animals. Through his field work in sampling skin and blubber from whales, Wise has discovered that while the animals are exposed to hexavalent chromium in the ocean, it results in much less chromosome instability and cancer.

"What's thought to underlie that is a double-strand break in the DNA helix. In human and whale cells, chromium induces the same number of breaks, so you would expect the same amount of effect on the chromosomes, but you don't see that," Wise said. "One of the things we've found is that chromium also inhibits the repair of these breaks in humans – you get the breaks and you can't fix them. In whale cells you get the breaks, but you can fix them. What about whales is protective or corrective? That's what we're digging into."

Wise has assembled a team of researchers from around the world to investigate this process further in the hope that this knowledge ultimately will lead to ways to prevent and reverse metals-induced lung cancer in people.

The research will include laboratory studies and then translate those findings to wildlife and human populations of workers exposed to metals. In addition to Wise, project researchers include KeJian Liu - University of New Mexico, who will lead lab studies and Tongzhang Zeng - Brown University, who will lead work with human populations. Doctoral students in Wise's lab and UofL faculty members Sandra Wise, Michael Merchant and Matt Cave also will participate, along with additional researchers in the US, Germany, China and Japan.

"UofL is one of the top institutions in the country in research and

discovery for how human health is influenced by our environment, and preeminent researchers like Dr. Wise are the reason," said Kevin Gardner, UofL executive vice president of research and innovation. "This grant is recognition of the incredible contributions Dr. Wise has made to the field and provides ongoing support for continued discovery for years to come."

RIVER grants are awarded to select investigators who have shown a broad vision and potential for impactful research. They allow the investigator increased flexibility and the freedom to set specific research goals toward a given objective, adjusting the research based on new findings, without seeking new funding.

This research is built on 20 years of previous support from the NIEHS as well as seed funding from the Kentucky Lung Cancer Research Program and the Jewish Heritage Fund for Excellence.

Excerpted from UofL Today by Betty Coffman

UofL Again Named a Top Research Institution

The UofL has once again been named a top US research institution.

The Carnegie Classification of Institutions of Higher Education once more has designated UofL a "Research 1" doctoral university with very high research activity. UofL is one of only 146 universities – approximately 4% of those considered – to receive this designation.

"UofL is a research powerhouse, and our consistent Research 1 designation is proof-positive of that fact," said Interim President Lori Gonzalez. "Our strength and growth in research is made possible by our faculty and staff, and their work to expand knowledge and tackle the grand challenges impacting the human condition."

In the past fiscal year, 2020-2021, UofL researchers received a record \$201.5 million in competitive research funding. That funding supported groundbreaking research to address the biggest global problems of our time, including climate change and providing robotic solutions and for manufacturing, health care and logistics challenges.

"Carnegie R1 status is highly competitive and is evidence of our dedication and commitment to research

and graduate education,” said Kevin Gardner, UofL’s executive vice president for research and innovation. “This continued designation shows our commitment to ensuring the work we do here at UofL has an impact here in our community and beyond.”

In addition to being a Research 1 institution, UofL also holds the Carnegie community-engaged designation, which recognizes institutions that work with community partners to exchange knowledge and resources for public benefit. UofL is one of just 79 U.S. institutions to hold both designations.

UofL’s dedication to community-engaged research has been especially apparent during the COVID-19 pandemic, when UofL researchers partnered with the community to lead widespread testing, develop and implement innovative wastewater monitoring methods, and further products that address the long-term health, economic and societal problems caused by the virus.

“Not only are we expanding the horizons of what’s considered possible,” Gardner said, “but we’re working hand-in-hand with our partners to use that knowledge to the benefit of our community. This is research with a reason; it’s innovation with impact.”

Excerpted from UofL Today by Baylee Pulliam



Humana and UofL partner on Health Innovation Hub

Humana and the University of Louisville are investing up to \$25,000,000 in a Health Innovation Hub with the goal of advancing health equity and outcomes for marginalized populations. The hub will focus on research, talent development, entrepreneurship, and skills to attain better jobs. Dr. Monica Wendel, a public health researcher with experience addressing these types of issues will lead the hub at UofL.



New Member Welcome



Karynn BrintzenhofeSzoc, Ph.D.

Preparing more social work students with knowledge to help their future

clients and patients manage chronic or life-limiting diseases is part of Dr. BrintzenhofeSzoc’s vision. She is the new Dr. Renato LaRocca Endowed Chair in Oncology Social Work at the Kent School of Social Work and Family Science, and member of the BCC.

Dr. BritzenhofeSzoc replaces Karen Kayser – recently retired – who served as the Kent School’s first endowed chair for the program.



UofL Researchers Lead the Call to Increase Genetic Diversity in Immunogenomics



Corey Watson, Ph.D., Melissa Smith, Ph.D., and Oscar Rodriguez, Ph.D., with the Pacific Biosciences Sequel IIe DNA sequencing system, housed in the UofL Sequencing Technology Center

Historically, most large-scale immunogenomic studies – those exploring the association between genes and disease – were conducted with a bias toward individuals of European ancestry. Corey T. Watson, assistant professor of Biochemistry & Molecular Genetics and member – Brown Cancer Center, is leading a call to actively diversify the genetic resources he and fellow immunogenomics researchers use in their work to advance genomic medicine more equitably.

Watson, along with UofL post-doctoral fellow Oscar Rodriguez, and visiting fellow Yana Safonova, are part of an international group of researchers who say the narrow studies limit their ability to identify variation in human adaptive immune responses across populations.

“We need to better understand how genetics influences immune system function by studying population cohorts that better represent the diversity observed across the globe if we are to fully understand disease susceptibility, as well as design more tailored treatments and preventative measures,” Watson said.

In an article published in *Nature Methods*, **Diversity in immunogenomics: the value and the challenge**, the group advocates for resources used in

immunogenomics research to actively include and specifically identify additional populations and minority groups. They say such diversity will make their research more relevant and help in understanding population and ancestry-specific gene-associated disease, leading to improvements in patient care.

“As scientists, we have a say in which populations are investigated. Therefore, it is critical for us to be actively inclusive of individuals representative of the world we live in. This is especially critical for genes that are as diverse and clinically relevant as those that encode antibodies and T cell receptors,” Rodriguez said.

Watson’s research focuses on immune function and molecular genetics. His team is studying a specific area of the genetic code that controls antibody function to better understand how differences in an individual’s genes determine their susceptibility to certain diseases or immune responses to vaccines.

In collaboration with Melissa Smith, assistant professor of Biochemistry & Molecular Genetics and Brown Cancer Center member, the team is conducting the largest sequencing efforts of the antibody gene regions in humans and in animal models, Watson said.

“Specifically in humans, we are working to build catalogs of genetic variation in samples from multiple ethnic backgrounds and are engaged in projects that seek to understand how this genetic variation influences the immune response in infection, vaccination and other disease contexts,” he said.

Watson is involved in efforts to improve the resources and data standards for antibody and T cell receptor genes for immunogenomics researchers around the world.

The article in *Nature Methods* was co-authored by researchers from the United States, Canada, Norway, France, Sweden, the United Kingdom, Russia, Saudi Arabia, Israel, South Africa, Nigeria, Chile, Peru, China, Japan, Taiwan and French Polynesia with expertise in biomedical and translational research, population and public health genetics, health disparities and computational biology as well as immunogenomics.



UofL Researchers' Health-Tech Projects Selected for KYNETIC Funding

In late 2021 the Kentucky Network for Innovation & Commercialization (KYNETIC) selected its first round of promising university-born health and medical technologies, each of which is receiving training and \$33,000 for development.

Two of the 6 projects selected in this first round are from UofL:

- *Pediatric NeuroRecovery Posture Control System* (researcher Andrea Behrman)
- *Verify Probe: Intraoperative Device for Measurement of Bone Quality* (researchers Stuart Williams, Maxwell Boakye and Michael Voor)

KYNETIC is a statewide program supported by \$6.6 million in funding, including a \$4 million Research Evaluation and Commercialization Hub (REACH) grant from the National Institutes of Health and matching funds. The goal is to advance the most promising biomedical research innovations – including pharmaceuticals, devices and apps – from the state's 8 public universities and the Kentucky Community & Technical College System (KCTCS).

KYNETIC grants support 6-month, milestone-driven projects focused on quickly determining whether or not each technology is viable as a commercial product. Awardees will receive funding for product-focused research and development, attend trainings, and get advice from program staff, industry, investors and other experts on identifying needs, navigating regulations and protecting their intellectual property.

Paula Bates, professor of medicine and BCC member, who co-leads KYNETIC, said the idea is to spur innovation and economic development through collaboration.

"I'm very pleased with the strong projects awarded in this cycle of KYNETIC, each of which will have a positive impact on human health," she said. "Collaboration and innovation go hand-in-hand, and that's our goal with KYNETIC. It's a really powerful way to use our collective expertise to help to turn great ideas from our state into products that improve people's health and wellbeing."

Funding cycles are offered twice a year and are open to faculty, staff,

trainees and students. Competitive renewal opportunities are available. Applications for KYNETIC funding require a two-page pre-proposal.

Launched in 2019, the KYNETIC program builds on UofL's strong history of translational research support, which includes a prestigious suite of programs for turning research into products.

"Through these programs, UofL supports commercialization of the work being done by our researchers," said Jessica Sharon, UofL's director of innovation programs. "The goal is to translate research into products that can improve, or even save, lives."

KYNETIC is led by the UofL, University of Kentucky, Kentucky Cabinet for Economic Development, and Kentucky Commercialization Ventures and works closely with Kentucky's regional universities and KCTCS.

Recently Issued Patents

UofL researchers Shin-je Ghim, A. Bennett Jenson and John Trent, all with the BCC, are inventors on a recently issued patent - U.S. 11,008,367. Research colleague Jenson was honored upon his recent passing for many remarkable achievements during his tenure at the BCC. This patent describes a parvovirus B19 vaccine using immunogenic virus-like particles (VLP). This technology received funding from the UofL ExCITE Program. The researchers are currently working with the Commercialization EPI-Center to find commercial opportunities for the technology.

John O. Trent, deputy director of basic & translational research at the BCC, received a recently issued patent, U.S. 11,013,673. This patent describes compounds that can be formulated into cosmetic compositions for topical application to enhance DNA repair and/or prevent sun-related DNA damage. This technology resulted from a collaboration between UofL, Cornell University and Repairogen, which has exclusively licensed this technology. The researchers are currently working with the Commercialization EPI-Center to ensure there is continued commercial development of this valuable innovation.

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Researchers Paula Bates, Kyung Kang and Mohammad Tariq Malik are inventors of a newly issued international patent in Hong Kong. This technology, patented in the United States in 2016, is for an anticancer aptamer that can be used for early detection and treatment of a wide number of cancers. This technology has been exclusively licensed by Qualigen Therapeutics, Inc. The researchers are currently working with UofL Innovation & Commercialization to ensure there is continued commercial development.

The High-School Summer Research Internship Program Returns for 2022

The HSSRIP at the Brown Cancer Center (BCC) is back for the summer of 2022, despite a number of changes which have been made, not least being the change of department for oversight by the UofL.

The Program will run for 8-weeks over the summer, ending with a poster session on Friday, August 5.

If you have been wondering what to do with your free-time this summer, the program is looking for mentor volunteers.

For more information and/or to volunteer, contact Diane Konzen at diane.konzen@louisville.edu or visit the BCC research website at <https://louisville.edu/medicine/research/cancer/edu-and-train> and click on 'summer research internship program'.

Student Research Support Awarded

Researchers Suzanne King, Shae Morgan and Jeffrey Bumpous in the department of Otolaryngology-HNS and communicative disorders and BCC member (JB), were awarded funding from The AR-Hale Family Foundation that will be used as a mechanism to support student research. The goal is to involve students in research projects during their clinical training to help develop their critical thinking and evidence-based decision-making.

New Grants Awarded

On the next page is a partial listing of new NIH grants awarded over the last

few months:

Zhong-bin Deng – P.I.

NIAID/NIH R21

Defining the Role of S1p and Myeloid Cells during Enterotoxigenic B. fragilis Infection

[09/22/21-07/31/22]

Gautam Gupta – P.I.

NCI/NIH R21

Supplment: *Bio CaRGOS: Capture and Release Gels for Optmiized Storage of Cancer Biospecimens*

[09/20/21-07/31/22]

Kenneth E. Palmer – P.I.

NCI/NIH G20

Upgrading Infectious Disease Research Facilities at University of Louisville RBL

[09/23/21-02/28/23]

T. Mike Sabo – P.I.

NIGMS/NIH R01

Linking the Conformational Landscape to Enzymatic Function through Functional Site Distant Mutations

[12/21/21-12/31/26]

Jill Steinbach-Rankins & Hermann

Frieboes, co-PIs

NIAID/NIH R01

3D-bioprinting of Sustained- and Phased-release Antibiotic and Probiotic Scaffolds to Treat Bacterial Vaginosis

[02/25/22-01/31/27]

Lori D. Phinney & Sucheta Telang –

co-PIs

EKSNICHHD/NIH UG:

Neonatal Opioid Withdrawl Syndrome (NOWS) in Kentucky: Improving Outcomes for Infants

[09/17/21-08/31/23]

John P. Wise, Sr. – PI

NIEHS/NIH – R35 RIVER program

Chromosome Instability Drives Metal-Induced Lung Cancer

[08/01/21-06/30/29]

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