INNOVATION INSIDER

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Cancer Center at Illinois

UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

CONTENTS

Innovation Insider is a Cancer Center at Illinois (CCIL) publication that highlights the interdisciplinary and translational work of CCIL faculty, staff, students, and external partners.

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DIRECTOR'S MESSAGE

The work we do each day at the Cancer Center at Illinois (CCIL) gathers around a common aim: to solve cancer problems for the benefit of individuals and communities affected by cancer. The CCIL's unique vision and mission guides our efforts and the pace of innovation is quickening. Ideas are moving to discoveries, discoveries are leading to the development of novel technologies, technologies and interventions are being translated to better diagnostics and therapies with our clinical partners, where physicians implement CCIL solutions—that's the pipeline of cancer research you'll read about in this latest edition of Innovation Insider. "Discovery to Use" is not just our guiding principle, you will read stories where it is put into action by our CCIL members, staff, and students.

You'll meet seven new CCIL members from various disciplines who recently joined our two research programs, including a clinician-scientist member in partnership with engineering-based Carle Illinois College of Medicine. You'll see the CCIL's robust, far-reaching educational pipeline spanning from high school to undergraduate to postdoctoral and on to alums performing innovative cancer research. You'll meet prominent CCIL members whose research has garnered national honors and awards. At the heart of our efforts are people—our own and all whom we hope to impact with our work.

I hope you will see this impact emerging from our highly collaborative, interdisciplinary research amongst the stories in this issue of Innovation Insider. These are just a sampling of what we could include in a magazine; I urge you to visit our website, visit us in person, and connect with the CCIL to learn more.

As always, I am deeply grateful for the faculty, students, staff, volunteers, and donors who work diligently to keep the momentum of this unique cancer center moving toward greater innovation and a better future for cancer patients, survivors, and their families.

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ROHIT BHARGAVA
CCIL Director

PAUL HERGENROTHER

RECEIVES 2023 NATIONAL CANCER INSTITUTE OUTSTANDING INVESTIGATOR AWARD

CCIL Deputy Director Paul Hergenrother is the first Illinois researcher to receive this celebrated award.

The prestigious NCI Outstanding Investigator Award (OIA) recognizes the outstanding research performance of cancer researchers, providing investigators with significant financial support to undergird current or future research programs of "unusual potential in cancer." Hergenrother is the first University of Illinois Urbana-Champaign researcher to receive this celebrated award.

The NCI established the OIA in 2014 for principal investigators with significant research accomplishments. The OIA supports investigators for seven years with up to $600,000 annually in direct costs, alleviating the burden of frequent grant applications and encouraging investigators to pursue bold research projects.

At the CCIL, Hergenrother is a member of the Cancer Discovery Platforms Bridging the Engineering-Biology Continuum research program's Drug Discovery theme. Hergenrother's primary cancer research focus is the identification of new anticancer compounds with unusual modes of action.

Hergenrother's lab has discovered multiple new anticancer compounds. His lab discovered the compound PAC-1, which has advanced through close collaboration with CCIL researcher Tim Fan and recently completed a Phase 1 clinical trial in late-stage cancer patients. In partnership with the laboratory of CCIL researcher David Shapiro, Hergenrother's lab discovered the compound ErSO, licensed for clinical development by Bayer AG in 2021, and the recently announced TEQ103 compound licensed by Oncoteq. In addition, the compound IB-DNQ was discovered in the Hergenrother lab and is advancing toward clinical trials.

"First and foremost, this award is a testament to all of my amazing current and former students, postdocs, and all the great collaborations over the years, most notably with Professor Fan, but also with Professors Shapiro, Nelson, Kranz, and many others," said Hergenrother. "This award gives our lab more flexibility in the research we can pursue, sustaining current projects and catalyzing more ambitious future projects. We want to discover more interesting and active compounds, and hopefully, ones with unique and effective ways to treat cancer patients that will have a positive impact on their lives. That's our goal. We're thrilled with this honor, but we know there's a lot of responsibility that comes with it."

Hergenrother is a professor of chemistry, the leader of the Anticancer Discovery from Pets to People theme at the Carl R. Woese Institute for Genomic Biology, the director of the NIH-supported Chemistry-Biology Interface Training Program, and the Kenneth L. Rinehart Jr. Endowed Chair in Natural Products Chemistry.

> We want to discover more interesting and active compounds, and hopefully, ones *with unique and effective ways to treat cancer patients* that will have a positive impact on their lives.

ZEYNEP MADAK ERDOGAN

RECEIVES AMERICAN ASSOCIATION FOR CANCER RESEARCH AWARD

CCIL Associate Director for Education Zeynep Madak Erdogan received the prestigious 2024 Michael B. Kastan Award for Research Excellence from the American Association for Cancer Research's (AACR) *Molecular Cancer Research* Journal.

> "The award is an encouragement to pursue more studies like this one. We had to work hard initially to prove that our system was an adequate representation of liver metastasis for breast cancer patients. *There was skepticism.* Science is always a process, though.

The award recognizes one paper annually with "the potential to shift paradigms, inspire translational activity, and raise awareness of new scientific areas." Madak Erdogan was honored as the corresponding author for this highly collaborative paper, "Targeting Metabolic Adaptations in the Breast Cancer-Liver Metastatic Niche Using Dietary Approaches to Improve Endocrine Therapy Efficacy," published in June 2022.

"The award is an encouragement to pursue more studies like this one. We had to work hard initially to prove that our system was an adequate representation of liver metastasis for breast cancer patients. There was skepticism. Science is always a process, though," said Madak Erdogan.

"At the time of our paper's publishing, our system was a novel and disputed concept, but as the paper was shared, cited, and tested, our system is now more mainstream in the lab and the field."

Madak Erdogan's system includes a hydrogel-based system to characterize how tumor cells behave in the liver microenvironment. Through a diverse collaboration that included CCIL members David Shapiro and Benita Katzenellenbogen and external partners

MD Anderson and Xylyx Bio using 3D models, mouse models, and in vivo and in vitro studies, the team developed a novel hydrogel system that allowed them to study the effects of a fasting-mimicking diet (FMD) upon endocrine therapies in metastatic liver tumors.

"Liver metastatic tumors are known to be difficult to manage for estrogen receptor-positive breast cancer patients. Treatments have not been effective. Our lab wanted to understand this phenomenon better and explore solutions to increase the efficacy of endocrine treatments upon the metastatic tumors," said Madak Erdogan.

Using a combination of RNA and ChIP sequencing and metabolomics to analyze molecular changes in cancer cells grown in novel hydrogels, her team found that the activity of metabolic pathways relying upon glucose increased. Combining this knowledge with the understanding that FMD reduces glucose metabolism, her team used FMD in models to determine if the liver tumors would present less resistance to the treatment. And that is indeed what happened. The synergistic effect of the diet and the treatment presented promising results.

"When you have a drug that targets a particular pathway, you almost always

have a side effect. And invariably, cancer finds a way to overcome the effects of a single chemical. You are dealing with millions of cells, and it only takes one or two mutations for the cancer to keep growing. With FMD, there are a multitude of effects on the body's overall system, not just on the cancer cells. So, on the liver, a tumor has direct access to every nutrient from the intestine. FMD changes liver physiology itself. We showed that tumors find ways to hijack a critical system that stores energy in the form of glycogen. Instead of liver cells, tumors hoard the glucose and store its energy. With the incorporation of FMD, the tumor was depleted of immediate energy sources. So, FMD can starve the tumor while the therapy is administered, facilitating less treatment resistance," explained Madak Erdogan.

"We are delighted and honored that AACR has selected Madak Erdogan's work for its significance and timeliness," said CCIL Director Rohit Bhargava.

"Characteristic of Zeynep's work, this study is not only of high scientific quality but can potentially change our thinking and inspire translational activity."

Madak Erdogan's team is working on a follow-up paper to expand this research and anticipates future clinical studies.

JUN SONG AWARDED FUNDING BY THE NATIONAL CANCER INSTITUTE

CCIL member Jun Song received a $319,585 award in January 2024 as part of his multi-year R01 grant from the National Cancer Institute (NCI) for his project "Predicting Transcriptional and Epigenetic Networks in Cancer from Sequencing Data."

The R01 research grant program, sponsored by the National Institutes of Health (NIH) and the NCI, provides principal investigators with support for health-related research and development consistent with the NIH's mission.

As an interdisciplinary cancer researcher, Song applies mathematics, physics, and computation expertise to biomedical research. Song's research uses integrative genomics to study the interplay among transcription factors, chromatin structure, non-coding RNAs, and gene regulation in the development of diseases. The Song lab studies how epigenetic and transcriptional changes are associated with cellular differentiation and cancer progression by reconstructing molecular interaction networks from high-throughput genomic data to identify actionable targets for improving regenerative medicine and precision cancer therapy.

Song is a Founder Professor in the Department of Physics, Director of the Fisk-UIUC Training of Under-represented Minds in Data Science and Quantitative Biology, and an affiliate of the Carl R. Woese Institute for Genomic Biology. Song is also affiliated with the NIH Center of Excellence in Big Data Computing and the NSF Physics Frontiers Center.

CCIL POWERS UP PIONEERING GLIOBLASTOMA RESEARCH TEAM

From left to right, Kim Selting, Sara Pedron Haba, Catherine Best-Popescu.

A $25,000 grant from the CCIL is catalyzing an interdisciplinary exploration of the relationship between neural networks and cancer cells in the brain. CCIL members Sara Pedron Haba, a research assistant professor in chemical and biomolecular engineering, and Kim Selting, an associate professor of veterinary clinical medicine, lead this innovative glioblastoma research project, along with Catherine Best-Popescu, a professor of bioengineering.

Building upon previous glioblastoma research collaborations with CCIL program leader Brendan Harley, Pedron Haba wanted to explore the frontiers of understanding how neurons and cancer cells interact. This prompted the application for a CCIL Planning Grant titled "Leverage of Biomaterial-Based Platforms in Cancer Neuroscience: Models for Multimodal Study of Radiotherapeutic Response in Brain Tumors."

"I was interested in looking into the tumor microenvironment to see how neurons in the nervous system affect the development of tumors. It's an incipient area of research. Our team will use our experience in neuroscience and oncology to better understand how neurons communicate with tumors," said Pedron Haba.

The 2023 CCIL planning grant was the first step for Pedron Haba's team, enabling follow-up work to generate a proof of concept, establish models, and publish data that would empower the team to pursue larger grants in the future. One such funding stream was the Elsa U. Pardee Foundation, which provided the team with a grant of $173,665 for their research proposal, "Use of Preclinical Models for the Implementation of More Precise Radiotherapeutic Approaches in Glioblastoma." The Elsa U. Pardee Foundation funds the discovery of new approaches for cancer treatment and cure.

Pedron Haba's team also sent undergraduate researcher Joseph Mueller, a junior in chemical and biomolecular engineering, to the 2023 AACR Annual Meeting, where he presented early work on the team's research: "Organotypic Models Reveal the Role of the Tumor Microenvironment in Glioblastoma Progression and Therapeutic Response." The CCIL sponsored Mueller's attendance at the AACR meeting.

"With Catherine's sophisticated imaging instrumentation and expertise in neuroscience and artificial intelligence, along with Kim's expertise in radiotherapy and access to cancer models in companion animals, our team will investigate how cancer cells interact with the healthy brain to improve treatments for patients with brain cancer," said Pedron Haba.
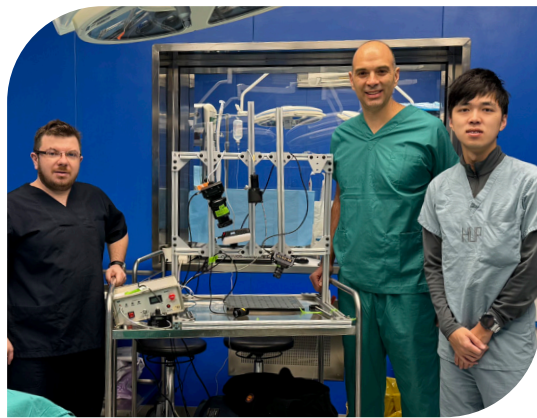
NSF ACCELERATES CANCER IMAGING THROUGH INTERDISCIPLINARY CONVERGENCE PROGRAM

A research team led by CCIL program leader Viktor Gruev, professor of electrical and computer engineering, was awarded a Phase I grant by the National Science Foundation's (NSF) Convergence Accelerator. This unique program funds the development and translation of multi-disciplinary research technologies for societal-scale impact. NSF's novel program focuses on the end-user, facilitating multi-disciplinary-inspired solutions for positive, real-world applications. "What's pioneering about the Convergence Accelerator is that we bring these teams together and manage them in a cohort of investigators," said Convergence Accelerator Program Director Linda Molnar.

The Convergence Accelerator recognized grant awardees according to targeted research themes, one of which is Bioinspired Design Innovations. "We knew that this theme was perfect for the work we have already been doing," said Gruev, whose co-principal investigators include CCIL member Shuming Nie, professor of bioengineering, Isak Ladegaard, assistant professor of sociology, and Thomas Cronin, a visual ecologist at the University of Maryland, Baltimore County. "Our diverse team, comprised of engineers, material scientists, physicians, visual ecologists, and social scientists, unites academia and industry in a collaborative effort to pioneer this groundbreaking technology," said Gruev.

From left to right: Borislav Kondov, Viktor Gruev, and ZHongmin Zhu, shown here in the operating room at the University Clinic Hospital in North Macedonia along with the NSF-funded research team's imaging instrument which allows for evaluation of ex vivo samples taken during surgery and evaluation of the presence of metastatic lymph nodes.

Gruev's team was awarded $650,000 for the 2024 fiscal year for their project, "Bioinspired Multispectral Imaging Technology for Intraoperative Cancer Detection," which aims to solve one of oncology's great challenges: detecting positive lymph nodes.

The team's innovative sensing technology, already in prototype form, is inspired by mantis shrimp vision. The sensor sits upon a single chip, enabling the simultaneous detection of cancer markers through near-infrared fluorescence and deep ultraviolet fluorescence. As previously reported by the CCIL, Gruev's lab has developed other novel cancer detection technologies inspired by the vision capabilities of the mantis shrimp and butterfly.

"We have three objectives in this project," said Gruev. "First, we will develop a multispectral, bioinspired imaging device to see specific tumor biomarkers. Second, we will validate the technology to guarantee its accuracy in detecting positive sentinel lymph nodes, both in vivo and ex vivo. Third, we will conduct a comprehensive evaluation of the practicality and transformative potential of this technology within the complex landscape of surgical environments."

Gruev's bioinspired innovations are no strangers to NSF funding, having come thus far through the Air Force Office of Scientific Research and NSF support.

"But this NSF grant is very different," said Gruev. "We are working directly with the end-user in the development of the technology, ensuring that the final product is tailor-made for cancer surgeons."

In Phase I, Gruev's team is collaborating with the University of Pennsylvania's Dr. Sunil Singhal, working with patients who have lung cancer, and a clinician at a resource-constrained north Macedonian hospital working with patients who have breast cancer. The Macedonian hospital context provides a similar model to community hospitals here in America, Gruev believes, and allows the technology's development to positively engage a global problem.

"Over my years of research and developing imaging technologies, I've witnessed dozens of cancer procedures," said Gruev. "It is an invaluable experience to bring back to our lab. As part of this project, I will contact dozens of clinicians using similar technologies to evaluate and refine our technology for the end user."

This year, Gruev and his team will be on-site in Philadelphia, Pennsylvania, and Macedonia to observe lung and breast cancer surgeries, ensuring that the development and translation of their prototype are effective for actual patients overcoming cancer. Convergence Accelerator Phase II will ideally move the technology to commercial application, pending FDA approval, added Gruev.

CCIL DEVELOPS NEXT GENERATION OF LEADERS

From left to right: Zeynep Madak Erdogan, Tim Fan, Erik Nelson, Rohit Bhargava, Kim Selting, Sayeepriyadarshini Anakk, and Cecilia Leal.

Members of the CCIL's Faculty Leadership Development Program (FLDP) graduated in fall 2023 after beginning the program's inaugural cohort in 2020.

The FLDP fosters leaders and develops a plan for succession within the CCIL. Members of the first cohort learned about leadership and building successful programs through a series of seminars. They met with members of the CCIL and broader Illinois campus and connected with the National Cancer Institute's Director of Comparative Oncology. Cohort members also developed a cancer-based project and were paired with a mentor from the CCIL leadership team to deepen their experience.

Organizers initially planned FLDP to be a one-year program, but it's been extended to two years so the cohort can dive into both theoretical and practical aspects of leadership development.

"The program is designed to be agile," said Margaret Browne Huntt, former CCIL Assistant Director for Strategic Research Initiatives.

"We developed the FLDP to address and identify who the next generation of leaders could potentially be. We wanted to start small and figure out the ebbs and flows of what the program would look like. These five individuals represent a cross-section of our programs, as well as represent diversity. Diversity is at the core of the program's design."

Upon completion of the program, Leal, Nelson, and Selting assumed leadership roles in the CCIL's new Breakthrough Engineering and Advanced Treatment (BEAT) of Cancer Initiative. Madak Erdogan was appointed as the new Associate Director of Education, and Nelson as a co-leader in the Cancer Discovery Platforms (CDP) Program.

Cohort Members

SAYEEPRIYADARSHINI ANAKK is an Associate Professor of Molecular & Integrative Physiology and co-leader of the CCIL's Cancer & Microbes Working Group.

ZEYNEP MADAK ERDOGAN is the CCIL's Associate Director of Education and Sylvia D. Stroup Scholar of Nutrition and Cancer, Associate Professor of Food Science and Human Nutrition, Associate Dean of the Graduate College, and the Director of the Women's Health, Hormones, and Nutrition Lab.

CECILIA LEAL is an Associate Professor of Materials Science & Engineering and a mentor in the CCIL's TiME Program.

ERIK NELSON is CCIL's Cancer Discovery Platforms Program co-leader, and an Associate Professor of Molecular & Integrative Physiology.

KIM SELTING is an Associate Professor of Clinical Veterinary Medicine and veterinary radiation oncologist.

CCIL COLLABORATIONS REACH FAR & WIDE TO ADDRESS CANCER PROBLEMS

CCIL members work each day to transform cancer research, detection, and treatment that will positively benefit cancer patients. Our research follows the path from discovery to development to translation and finally to impact. To make that impact, CCIL investigators start with the tedious and strenuous work of discovery in the lab, where they work collaboratively across disciplines at the University of Illinois Urbana-Champaign and around the globe. Innovation Insider's "By the Numbers" highlight on this critical feature of the CCIL's cancer research. In 2023 (January through October), the CCIL's discovery, development, and translation included the following unique external collaborators (cited in CCIL publications and grant awards).

TOP 10 EXTERNAL COLLABORATORS

Washington University in St. Louis	37
University of California, Los Angeles	35
Mayo Clinic	33
Stanford University	33
University of Toronto	31
University of Wisconsin, Madison	31
University of Pennsylvania	25
University of Texas Southwestern	25
University of California, San Diego	22
Northwestern University	21

~1,200
Total external collaborators

~800
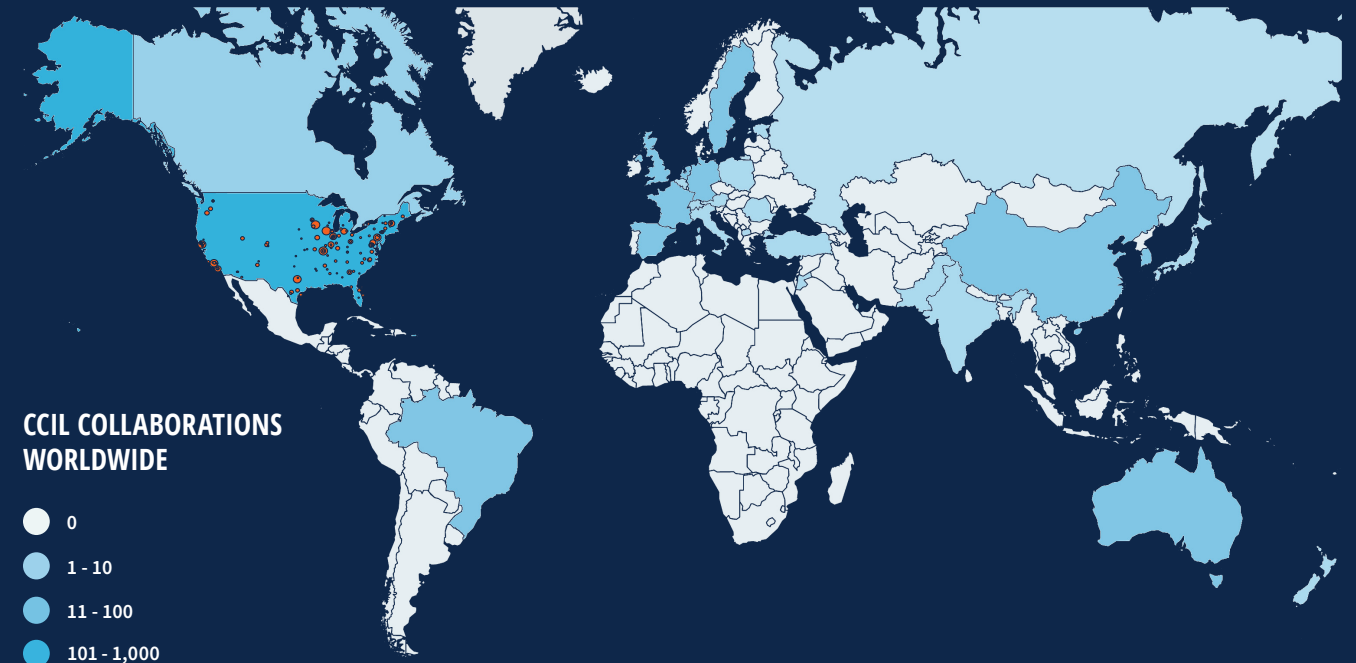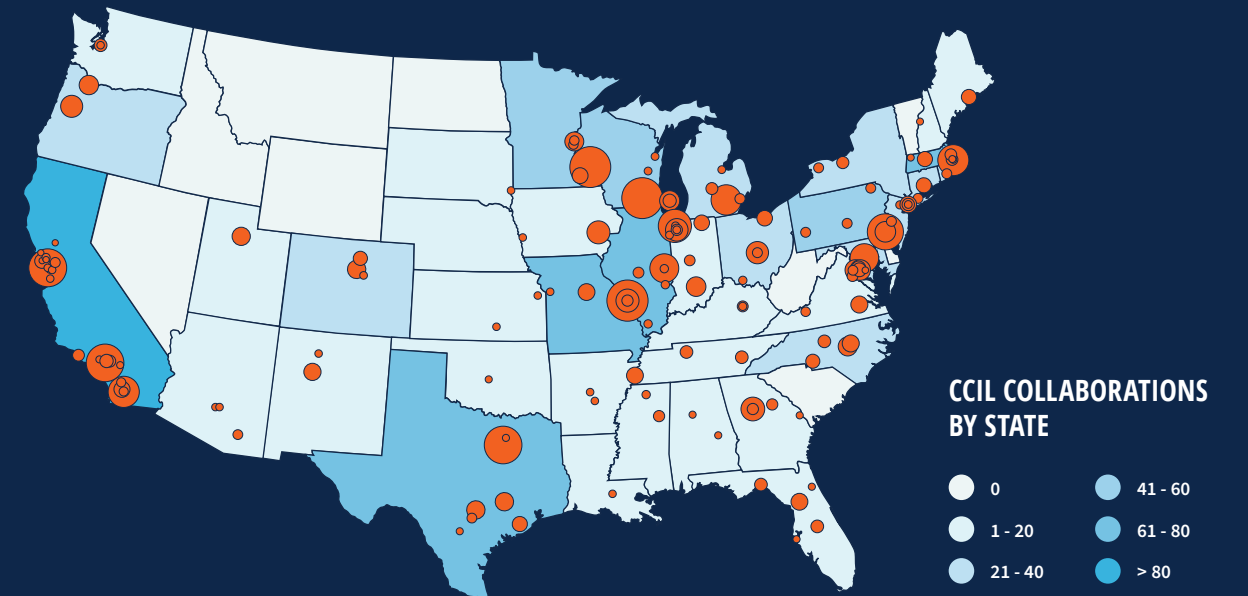**Total domestic external collaborators**

~400
Total international external collaborators

~300
Total institutions
200 domestic institutions
100 international institutions

CCIL COLLABORATIONS BY STATE

- 0
- 1 - 20
- 21 - 40
- 41 - 60
- 61 - 80
- > 80

CCIL COLLABORATIONS WORLDWIDE

- 0
- 1 - 10
- 11 - 100
- 101 - 1,000

NEW INFRARED MICROSCOPE TRANSFORMS CHEMICAL IMAGING FOR PATHOLOGISTS

Visualization of colon tissue produced by the IR-LSM. The team's label-free imaging uses the intrinsic contrast (in this case, chemical contrast) of a sample for visualization and analyses, without using dyes or stains to highlight components of interest.

CCIL Director Rohit Bhargava's Chemical Imaging and Structures Laboratory developed a novel infrared microscopy system that dramatically improves the speed and quality of chemical imaging. The team's microscope holds the potential to shift the landscape of current pathology, opening new frontiers in the study and diagnosis of diseases such as cancer. Unlike a common light microscope that only measures the structure of a sample, this microscope can also measure the chemistry within the sample.

"In my journey as an imaging scientist, this is a milestone development. This system offers the high performance we've been aiming for at a speed that is just not available anywhere else," said Bhargava. "The imaging community has grappled for a long time with developing an instrument and imaging technology that is fast, reliable, robust, and acquires high-quality, useful data. We solved that challenge in this study by going back to the basics. We started from our expertise in theory and modeling and re-thought the image formation process. This is a reimagining of the infrared microscope from the ground up and is the culmination of years of effort by our large team to get that optimal instrument."

As reported in *Nature Communications*, the system is a mid-infrared confocal laser scanning microscope (IR-LSM) that enables label-free biomedical analysis of whole slide samples, providing high-throughput, low noise, and high spatial resolution images. When integrated with machine learning, the microscope facilitates efficient, comprehensive assessment of whole model organisms and histological assessments of disease in a manner compatible with the clinical environment. The benefits of mid-infrared spectroscopic imaging promise the highest optical molecular sensitivity due to light absorption

at mid-IR frequencies resonating with molecular vibrational modes. Sophisticated analyses of these data, in tandem with recent progress in artificial intelligence (AI), greatly expand the potential scope and speed of comprehensive chemical imaging for scientific and biomedical applications.

Using chemical imaging in cancer pathology presented noteworthy challenges for Bharava's research team over the years of developing their evolving instrument, which is now in its third iteration. For this milestone moment in the evolution of the imaging instrument, the team had two ambitious, simultaneous goals: speed and quality.

"The problem in acquiring infrared microscopy images is doing so quickly and with high fidelity," said Kevin Yeh, a postdoctoral researcher with Bhargava and first author of the publication. Yeh has led the development of multiple generations of infrared microscopes in the lab. Earlier generations were constructed from off-the-shelf and repurposed components and laid the groundwork for infrared microscope design with lasers. Building upon this research, members of the team designed and fabricated the microscope from custom optical components, hardware designed and tested at Illinois, and software they wrote. This careful engineering resulted in a microscope capable of collecting higher-quality data with clinically viable throughput. "In this current iteration detailed in our paper, we merged what we've learned from our previous system designs to build a deployable platform for fast, high-quality infrared microscopy that cancer clinicians and researchers will find easy to use," explained Yeh.

Adult Zebrafish
(i) Brain
(ii) Gills
Liver
Intestine
Pancreas
Muscle
(iii) Ovary
2 mm
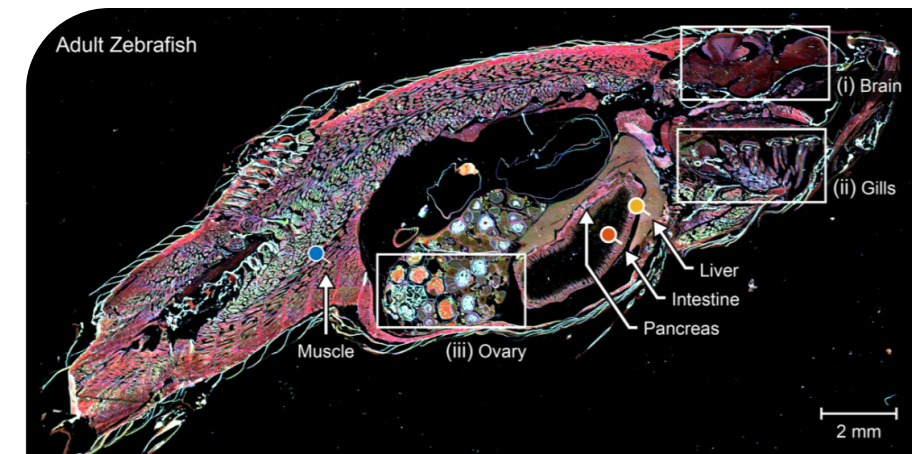
The team's IR-LSM speed and data quality allows them to perform experiments and diagnostics they otherwise would not attempt, such as the chemical imaging of a whole model organism. The adult zebrafish sample above was imaged in approximately 15 minutes. Traditional imaging methods may have taken as long as 2-4 weeks.

The first order of business for Bhargava's lab was to acquire data fast enough with both high chemical content and image quality. The second was to acquire the data with enough quantity that, when fed into an AI algorithm, the system gave desirable, dependable results.

"For a very long time, cancer pathology has relied on looking at structural changes in tissues. This is important because sometimes chemical changes precede structural changes in tissue. And now, with the availability of artificial intelligence, we can use our large reservoir of chemical data together with AI to make better diagnoses," said Bhargava.

The combination of chemistry and structure measured makes it ideal to use machine learning to extract information reliably and efficiently. With the assistance of pathology experts who can properly interpret the data, the team developed AI models to effectively extract cancer pathology information from the raw data. Postdoctoral researcher Kianoush Falahkheirkhah, a recent chemical engineering doctoral graduate, provided the leadership of the AI development.

"We are changing the way we measure and acquire data or images of cancerous tissues and how we interpret that data.

We want to use chemical imaging and look at the samples in a different way. We want to look at the chemical composition of the samples along with the spatial information. And that's where AI can play an important role because the data we acquire can be very helpful but not easily interpretable, unlike conventionally stained pathology samples. What we're trying to do is to make that data interpretable. And that's where the intersection of AI and our chemical imaging microscopes are coming from," said Falahkheirkhah.

The development of this instrument was possible due to the interdisciplinary strengths of a diverse team available at Illinois, bringing together mechanical and materials engineers; physics, biology, and chemical experts; software developers; and deep learning model systems researchers, as well as external clinical collaborators at Carle Foundation Hospital and Mayo Clinic.

What's next for the team? "Now we need to apply this technology to many different diseases and then try to make more sophisticated decisions about the data," explained Bhargava. "Can we find diseases other than cancer? Can we grade cancer? Can we use AI, together with the pathologist, to make more consistent, rapid, and more accurate decisions?

"Our goal is for our AI models to be clinically relevant," remarked Falahkeirkhah. "For us to be able to transition from research into the clinic, we need to increase the robustness and generalization of our models. We can't limit ourselves to the set of samples we've been given. In the real world, on new samples with unknown diagnoses, it still needs to work. That's the next step."

Bhargava believes this is precisely the kind of study that exemplifies the unique powers available at Illinois, making the CCIL a unique and attractive place among the nation's landscape of cancer research institutes.

"This project represents the kind of study that our cancer center exists to undertake," said Bhargava. "We bring in basic engineering, high-quality engineering at the University of Illinois and combine it with the strength of our clinical partners like Mayo and Carle. This combination helps us solve real problems. That's what our cancer center is all about – taking basic engineering developments and bringing them rapidly to our clinical colleagues to make useful, high-impact decisions."
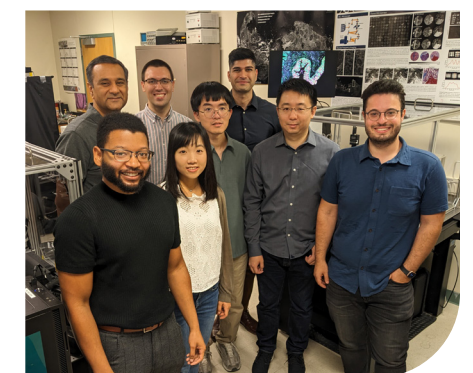
Researchers in CCIL Director Rohit Bhargava's Chemical Imaging and Structures Laboratory (from left): Andres Orr, Rohit Bhargava, Matthew Confer, Rou-Jing Ho, Yen-Ting Liu, Ishaan Sharma, Kevin Yeh, and Kianoush Falahkheirkhah.

CCIL RESEARCHERS IDENTIFY POTENTIAL TARGET TO TREAT BRAIN TUMORS

CCIL researchers have demonstrated that a specific mitochondrial protein plays an important role in glioblastoma and can therefore be a potential target to reduce tumors.

From left to right: Brendan Harley, Rex Gaskins, Andrew Steelman, and Payton Haak.

"Glioblastoma is notorious for its lethality. One of the major challenges is that it spreads invasively throughout the brain. We're interested in understanding what drives this process in order to identify new therapeutic strategies," said CCIL program leader Brendan Harley, the Robert W. Schaefer Professor of Chemical and Biomolecular Engineering.

In the current study, the researchers focused on the mitochondrial coiled-coil-helix-coiled-coil-helix domain-containing protein 2—also known as CHCHD2. The complicated name refers to the structure of the protein, whose subunits are coiled together like rope strands.

The researchers first looked at The Cancer Genome Atlas glioblastoma database to see whether they could spot any patterns that related CHCHD2 levels to cancer. Out of 577 samples, they found that the CHCHD2 genes had higher expression in tumor cells, compared to non-tumor tissue, and were higher in advanced cases of glioblastoma.

"We also learned that in humans, the gene encoding CHCHD2 was closely linked to the gene encoding the epidermal growth factor receptor, or EGFR, on chromosome 7. A mutated version of this protein is found in over 50% of glioblastoma patients," said CCIL member Rex Gaskins, the Keith W. and Sara M. Kelley Endowed Professor of Immunophysiology in Animal Sciences and author of the study.

When the results from the database showed that CHCHD2 expression was highest in the patients who harbored the mutation known as EGFRvIII, the researchers realized that understanding the interaction between these two proteins can be crucial to understanding glioblastoma progression.

To confirm their hypothesis, the researchers looked at the effects of CHCHD2 on tumor growth in mice. They compared mice that had CHCHD2 and the mutated version of EGFR to mice that did not contain CHCHD2, but still had mutated EGFR. The first group of mice survived for an average of 17 days, whereas the second group survived for 25 days. The researchers found that the mice that died earlier had more tumor growth infiltrating the surrounding brain tissue.

Although it is evident that these proteins are interacting with each other, it is unclear how they affect glioblastoma progression. The authors have proposed several mechanisms, based on their experiments.

The first possibility is that CHCHD2 decreases the sensitivity of mutated EGFR to cytotoxic drugs. Patients with glioblastoma only survive for 15-20 months, despite being subjected to an arsenal of treatment procedures, including chemotherapy with the drug temozolomide. The researchers used this drug and tested cells that had the mutated EGFR protein and CHCHD2 and cells that only had EGFR. They saw that when cells did not contain CHCHD2, they were more sensitive to temozolomide. The researchers believe that this result highlights CHCHD2 as a potential therapeutic target.

Another possibility is that CHCHD2 affects how EGFR stimulates glioblastoma invasion. Using a hydrogel to replicate the tumor microenvironment in the brain, the researchers showed that cells with both CHCHD2 and mutated EGFR were able to grow and invade the surrounding area. This invasion was especially pronounced when the level of oxygen was lower, a condition commonly experienced by glioblastoma cells as they invade from the tumor into the brain.

The data also demonstrate that CHCHD2 profoundly affects cellular metabolism, which the researchers showed using different biochemical tests. "It's a multifaceted paper that used patient data, human cell lines, and a mouse model of glioblastoma," Gaskins said. "All of our data are aligned, and we can pursue any one of these mechanisms to see if it explains what is happening in the tumors."

The researchers are interested in figuring out why the invasive capacity of these cells change, especially under low-oxygen conditions. They also want to test whether these results hold true in other types of glioblastomas, which may not have a mutated EGFR.

"This study suggests that the role of CHCHD2 in glioblastoma progression was underappreciated, but it might be a significant new target as we try to improve clinical outcomes," Harley said. "The idea that this protein can change behavior based on its environment is valuable. We hope that researchers can start identifying new therapeutic strategies based on this key protein."

This story, written by Ananya Sen, first appeared in the IGB News on October 17, 2023.

COLLABORATIVE TEAM STARTS JOINT CENTER FOR MRNA DELIVERY AND CANCER IMMUNOTHERAPY

Illinois bioengineering faculty members are playing key roles in a new joint center for mRNA delivery and cancer immunotherapy.

This new center is being co-led by CCIL member Shuming Nie and Professor Youqing Shen from Zhejiang University (ZJU), with a collaborative team of eight faculty investigators, including CCIL member Hua Wang, and is part of a broader research and education collaboration between the University of Illinois Urbana-Champaign and the ZJU International Campus in China.

Inspired by the recent success of mRNA-based COVID vaccines, the center is focused on the exciting potential of mRNA delivery systems and cancer immunotherapy.

"While showing great success in the era of COVID-19, mRNA therapeutics have not been very successful for cancer treatment," said Wang, bioengineering and materials science professor and project co-investigator. "And that's the

motivation for this project. The goal is to develop an mRNA vaccine that can show robust immune response and therapeutic benefit against various types of cancer, especially solid tumors that are resistant to existing therapies."

mRNA vaccines work well against COVID in part because of the known targets (e.g., spike proteins) on the COVID virus. Vaccines can be designed to specifically and effectively target these proteins, where cancer cells tend to be less predictable and more specialized to individuals. Additionally, for a cancer vaccine to work, approaches to properly stimulate the adaptive immunity arm of the body, in addition to the humoral immunity that most viral vaccines are focused on, are essential.

In the face of these challenges, the team is optimistic that this new center could

help researchers make significant strides in the right direction. "There are some really interesting approaches and very innovative technologies to overcome these obstacles that I look forward to seeing in action," said Nie.

Some of these innovative technologies include identifying new antigens specific to tumor cells that will make it easier to target those tumors, and using nontraditional platforms, such as smart lipid nanoparticles and immune cell homing materials, to deliver mRNA to specific immune cells the body. Both of these methods are significantly different from the standard approach and have the potential to change the way mRNA vaccines are used in cancer treatments.

"This center offers a great potential to revolutionize mRNA-based therapeutic cancer vaccines with enhanced

antitumor efficacy, especially for solid tumors," said co-investigator Xing Wang.

In addition to the exciting potential in cancer research, the team looks forward to the opportunities for interdisciplinary research and discovery with their peers both in Illinois and at ZJU.

"As members of the CCIL, we are excited at this interdisciplinary opportunity presented to us through the UIUC/ZJU collaboration," said co-investigator and CCIL member Joseph Irudayaraj, a professor of bioengineering. "Although we are mostly from bioengineering, interestingly enough, we all have very different academic training and backgrounds. The amalgamation of this diverse expertise is the one that is most intriguing."

For more information, visit the UIUC/ZJU joint research enterprise online at zjui.illinois.edu.

This story, written by Bethan Owen in the Department of Bioengineering, appeared on October 17, 2023.

SEEING THE UNSEEN:

BUTTERFLY VISION HELPS SCIENTISTS DETECT CANCER BIOMARKERS

There are many creatures on our planet with more advanced senses than humans. Turtles can sense Earth's magnetic field. Mantis shrimp can detect polarized light. Elephants can hear much lower frequencies than humans can. Butterflies can perceive a broader range of colors, including ultraviolet (UV) light.

Inspired by the enhanced visual system of the Papilio xuthus butterfly, a team of researchers have developed an imaging sensor capable of "seeing" into the UV range inaccessible to human eyes. The design of the sensor uses stacked photodiodes and perovskite nanocrystals (PNCs) capable of imaging different wavelengths in the UV range. Using the spectral signatures of biomedical markers, such as amino acids, this new imaging technology is even capable of differentiating between cancer cells and normal cells with 99% confidence.

This research, led by CCIL members Viktor Gruev, professor of electrical and computer engineering, and Shuming Nie, professor of bioengineering, was recently published in the journal *Science Advances*.

SMALL VARIATIONS

"We've taken inspiration from the visual system of butterflies, which can to perceive multiple regions in the UV spectrum, and designed a camera that replicates that functionality," Gruev says. "We did this by using novel perovskite nanocrystals, combined with silicon imaging technology, and this new camera technology can detect multiple UV regions."

UV light is electromagnetic radiation with wavelengths shorter than that of visible light (but longer than x-rays). We are most familiar with UV radiation from the sun and the dangers it poses to human health. UV light is categorized into three different regions—UVA, UVB, and UVC—based on different wavelength ranges. Because humans cannot see UV light, it is challenging to capture UV information, especially discerning the small differences between each region.

Butterflies, however, can see these small variations in the UV spectrum, like humans can see shades of blue and green. Gruev notes, "It is intriguing to me how they are able to see those small variations. UV light is incredibly difficult to capture, it just gets absorbed by everything, and butterflies have managed to do it extremely well."

THE IMITATION GAME

Humans have trichromatic vision with three photoreceptors, where every color perceived can be made from a combination of red, green, and blue. Butterflies, however, have compound eyes, with six (or more) photoreceptor classes with distinct spectral sensitivities. In particular, the Papilio xuthus, a yellow Asian swallowtail butterfly, has not only blue, green, and red, but also violet, ultraviolet, and broadband receptors. Further, butterflies have fluorescent pigments that allow them to convert UV light into visible light which can then be easily sensed by their photoreceptors. This allows them to perceive a broader range of colors and details in their environment.

Beyond the increased number of photoreceptors, butterflies also exhibit a unique tiered structure in their photoreceptors. To replicate the UV sensing mechanism of the Papilio xuthus butterfly, the Illinois team has emulated the process by combining a thin layer of PNCs with a tiered array of silicon photodiodes.

PNCs are a class of semiconductor nanocrystals that display unique properties similar to that of quantum dots—changing the size and composition of the particle changes the absorption and emission properties of the material. In the last few years, PNCs have emerged as an interesting material for different sensing applications, such as solar cells and LEDs. PNCs are extremely good at detecting UV (and even lower) wavelengths that traditional silicon detectors are not. In the new imaging sensor, the PNC layer is able to absorb UV photons and re-emit light in the visible (green) spectrum, which is then detected by the tiered silicon photodiodes. Processing of these signals allows for mapping and identification of UV signatures.
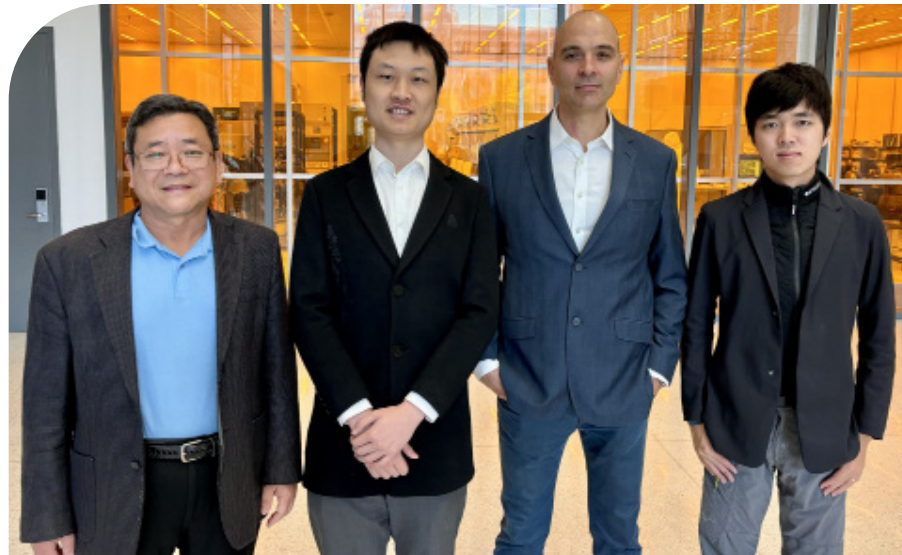
From left to right: Shuming Nie, Cheng Chen, Viktor Gruev, Zhongmin Zhu.

HEALTHCARE AND BEYOND

There are various biomedical markers present in cancerous tissues at higher concentrations than in healthy tissues—amino acids (building blocks of proteins), proteins, and enzymes. When excited with UV light, these markers light up and fluoresce in the UV and part of the visible spectrum, in a process called autofluorescence.

"Imaging in the UV region has been limited and I would say that has been the biggest roadblock for making scientific progress," explains Nie. "Now we have come up with this technology where we can image UV light with high sensitivity and can also distinguish small wavelength differences."

Because cancer and healthy cells have different concentrations of markers and therefore different spectral signatures, the two classes of cells can be differentiated based on their fluorescence in the UV spectrum.

The team evaluated their imaging device on its ability to discriminate cancer-related markers and found that is capable of differentiating between cancer and healthy cells with 99% confidence.

Gruev, Nie and their collaborative team envision the use of this sensor in oncology procedures. One of the biggest challenges is knowing how much tissue to remove to ensure clear margins and such a sensor can help facilitate the decision-making process when a surgeon is removing a cancerous tumor.

"This new imaging technology is enabling us to differentiate cancerous versus healthy cells and is opening up new and exciting applications, even beyond health," Nie said. There are many other species besides butterflies capable of seeing UV, and having a way to detect that light will provide interesting opportunities for biologists to learn more about these species, such as their hunting and mating habits. Bringing the sensor underwater can help bring a greater understanding of that environment as well. While a lot of UV is absorbed by water, there is still enough that makes it through to have an impact and there are many animals underwater that also see and use UV light.

This story, written by Amber Rose, was first published by the Grainger College of Engineering on November 3, 2023.
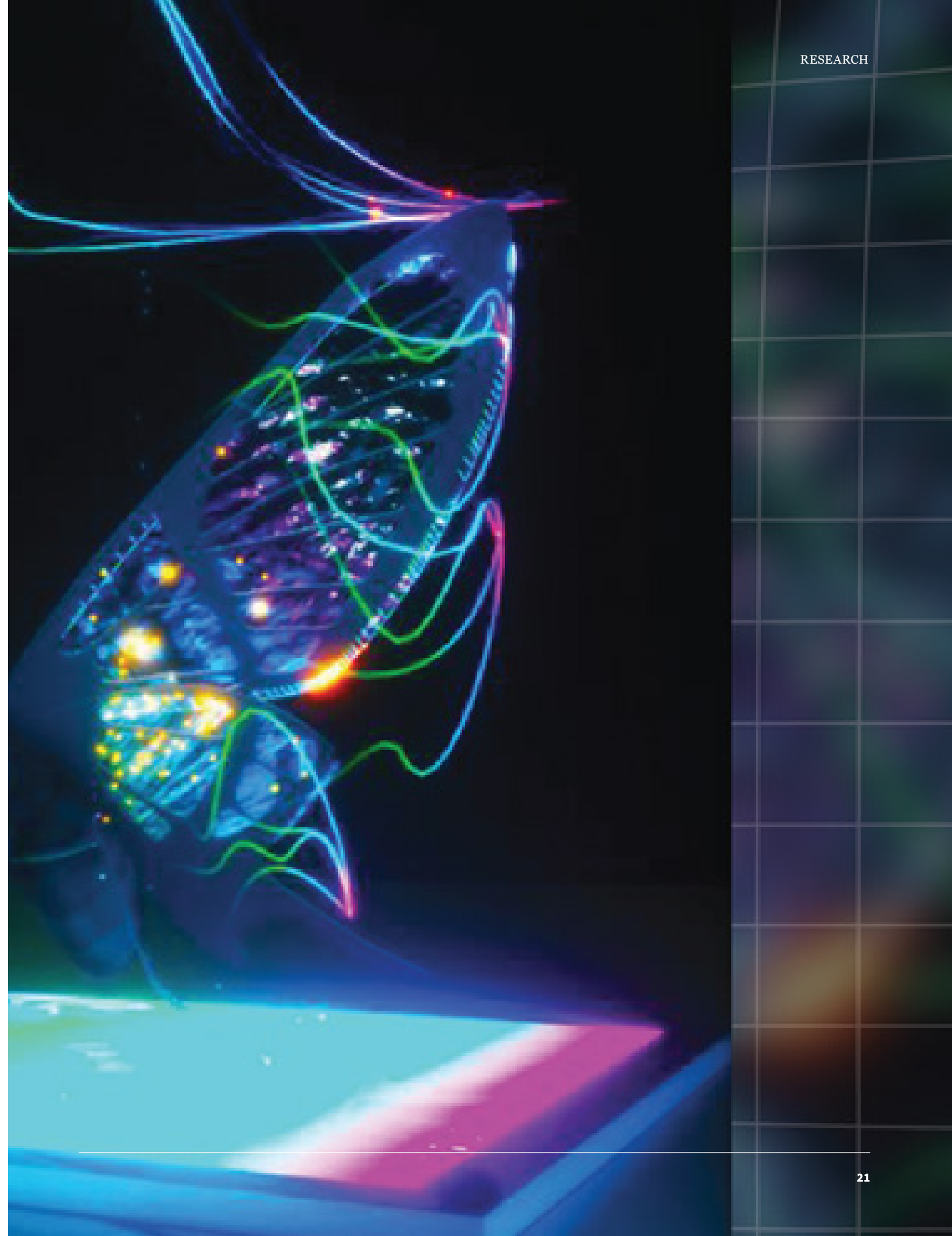
UNPRECEDENTED COMPOUND TAKES A STEP TOWARD BREAST CANCER CLINICAL TRIALS

Estrogen receptor-positive breast cancer is the most common form of breast cancer, affecting approximately 75% of breast cancer patients. In advanced and metastatic form, it is lethal, claiming the lives of nearly 350,000 individuals annually. Presently, no drug is able to eradicate these advanced tumors.

CCIL researchers Paul Hergenrother and David Shapiro are working to change that with the anticancer compound developed in their collaborative labs and now licensed for pre-clinical development.

The biotech company Oncoteq announced in November 2023 the licensing of the novel compound TEQ103 from Systems Oncology. TEQ103 is the product of the collaboration between CCIL researchers Hergenrother and Shapiro, who developed the molecules for the activation of anticipatory unfolded protein response (a-UPR), and Systems Oncology, who advanced the novel technology for clinical viability.

TEQ103 targets estrogen receptor alpha (ERα) positive breast cancer cells and kills only the cells with an activated stress response, the so-called a-UPR. "The a-UPR is already on in cancer cells and helps shield them from other anticancer drugs. Our compounds are unique in that they work by over-activating this pathway, switching into a lethal mode that kills the cancer cells." Shapiro said. Presently, endocrine breast cancer treatments function by slowing tumor growth or modulating estrogen levels; however, the efficacy of current treatments falls short in eradicating advanced ERα-expressing breast cancers.

This compound emerging from the Hergenrother-Shapiro collaboration is their latest effort aimed at eradicating ERα-expressing breast cancer. As reported in 2020, Bayer AG licensed the breast cancer therapeutic ErSO for clinical development, which was born from Hergenrother and Shapiro's cancer research. In 2021 and 2022, Hergenrother and Shapiro reported developments in two scientific papers, "A Small-Molecule Activator of the Unfolded Protein Response Eradicates Human

> "We've never seen a class of compounds that looks this good. *It is really, really remarkable.* This is a very promising compound for breast cancer treatment.

Breast Tumors in Mice" in Science Translational Medicine and "Activators of the Anticipatory Unfolded Protein Response with Enhanced Selectivity for Estrogen Receptor Positive Breast Cancer" in the *Journal of Medicinal Chemistry.*

The 2021 paper spoke of unprecedented tumor "eradication" in mouse models.

"We've never seen a class of compounds that looks this good," said Hergenrother. "It is really, really remarkable. This is a very promising compound for breast cancer treatment."

Now in the hands of Oncoteq, this new compound will undergo pre-clinical drug development to advance it to human clinical trials in late-stage metastatic breast cancer patients by 2025. "It's great to find a partner in Systems Oncology, and now Oncoteq, that has the resources to take it all the way through to clinical trials," explained Hergenrother.

"Metastatic breast cancer is still a major problem and needs much better treatments. I am thankful to work with great colleagues such as Professor Shapiro, and also Professors Tim Fan and Erik Nelson, to move these promising compounds forward to help patients. It's a trailblazing experience, hopefully making it easier to advance the next technology coming out of the CCIL," said Hergenrother.

The CCIL is home to a large collaborative of breast cancer researchers, working together and crossing disciplines to understand the causes of breast cancer, improve diagnostics, create more effective treatments with fewer side effects, and ultimately, save lives. As always, it takes a team of scientists to arrive at such a milestone as licensing a new cancer therapeutic. The labs of CCIL researchers Tim Fan and Erik Nelson have also provided instrumental research support in the development of the novel anticancer compound TEQ103.

Paul Hergenrother and David Shapiro.

HACKING CELL COMMUNICATION:

RESEARCHERS DEVELOP PROMISING CANCER VACCINE

An Illinois research team led by CCIL member Hua Wang published new research with promising developments for the future of personalized cancer therapeutics.

CCIL member Hua Wang published new research with promising developments for the future of personalized cancer therapeutics. In a *Nature Communications* paper, the Wang lab–in collaboration with Illinois professors Shelly Zhang, an assistant professor in the Department of Civil & Environmental Engineering (CEE), Wael Mostafa, a clinical assistant professor in the Carle Illinois College of Medicine (CIMED), Qian Chen, an associate professor in the Department of Materials Science & Engineering (MatSE), and CCIL member Erik Nelson–reports a novel extracellular vesicle (EV)-based cancer vaccine.

Wang's research focuses on the discovery of cancer immunotherapies, and these latest findings are a noteworthy milestone in that journey.

"Compared to other immunotherapies we're developing in our lab, EV-based immunotherapy is a type of personalized medicine with huge potential for translation to the clinic," said Wang.

EVs are nanosized vesicles secreted by nearly all types of cells including tumor cells. They are critical players in cell communication, carrying essential molecular signals to the interacting cells. Like a delivery truck, tumor-secreted EVs

transport antigen mail to immune cell recipients with critical instructions for how to get to work. As such, EVs have been the focus of decades of immunotherapy research. However, there has been little success for cancer treatment applications.

That stands to change with a bold, new immunotherapy approach developed in the Wang lab that introduces a universal metabolic tagging technology to the EV, supercharging its capacity to upregulate the body's immune system response. Standard practice for improving conventional vaccines is to include an adjuvant that will activate dendritic cells (DCs). However, in practice, simply mixing adjuvants with EVs often results in inefficient DC activation and low antitumor efficacy. This problem motivated Wang's lab to develop a new approach that can integrate large quantities of the adjuvant directly onto the EV surface for increased modulation of DCs and elicitation of potent cytotoxic T lymphocyte (CTL) response.

"Scientists have been trying to exploit tumor EVs as a form of therapeutic cancer vaccine for years with the goal to improve the processing of EVs by DCs, the prominent type of antigen presenting cells in the body. The typical EV vaccine has not been effective to date," said Wang. "That brings us to our project. We wanted to better integrate EVs with the adjuvant
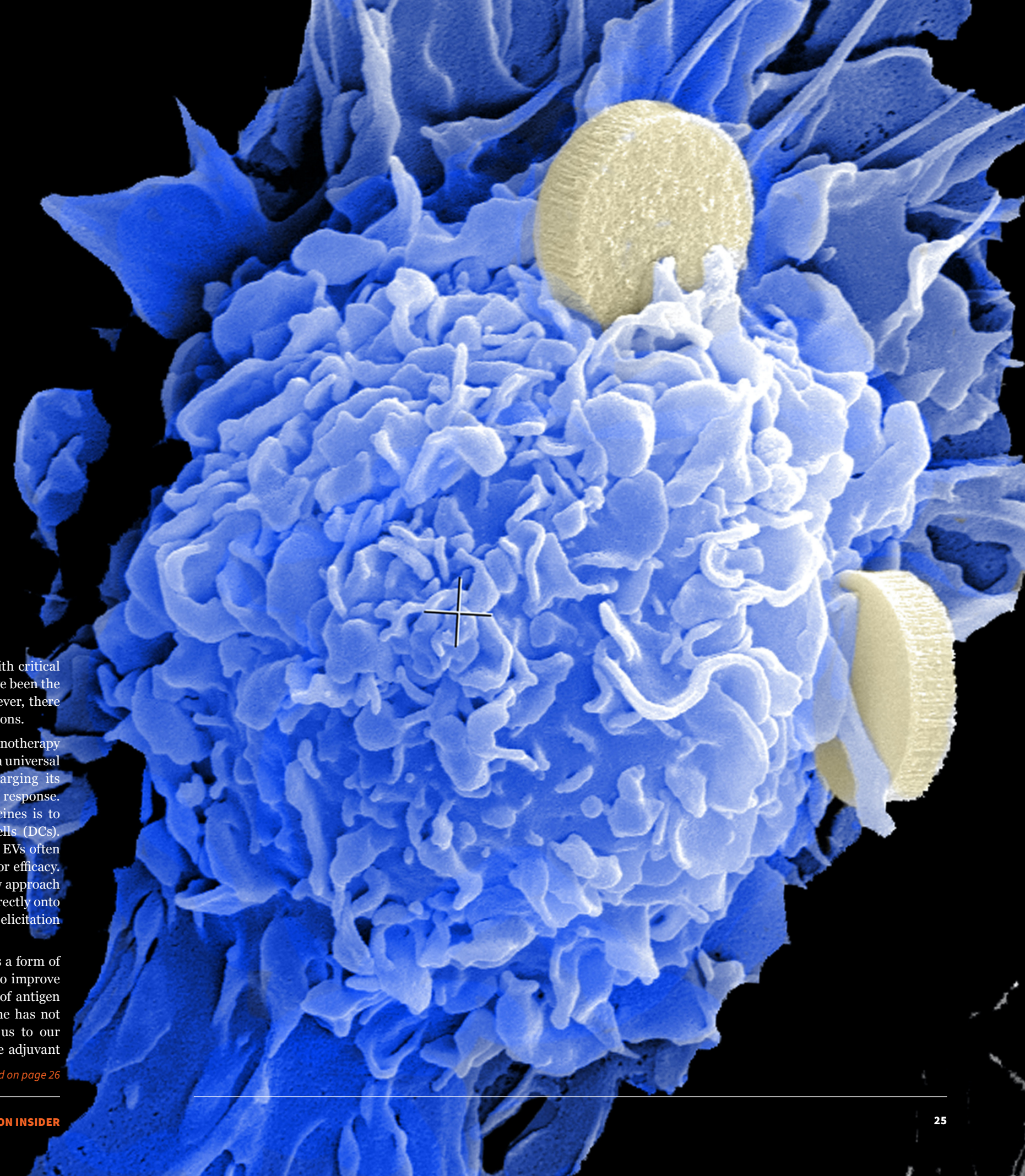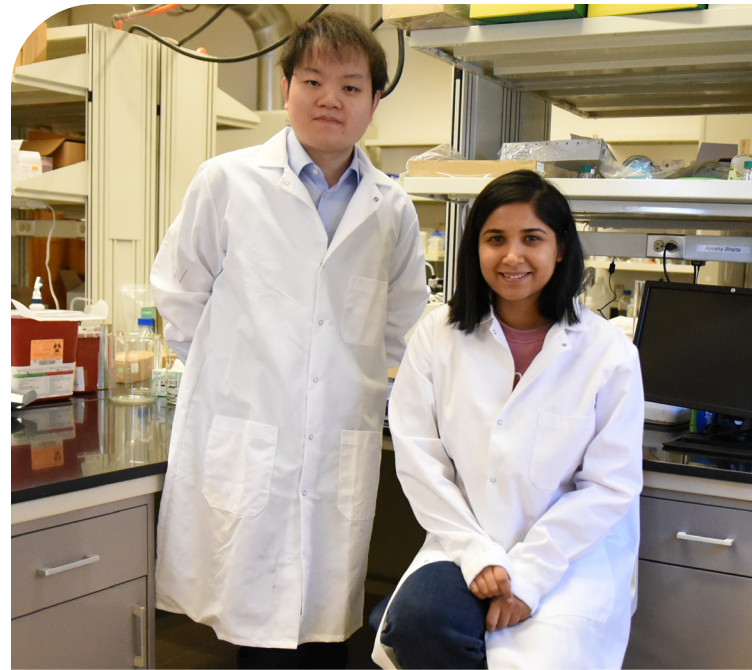
Professor Hua Wang and graduate student Rimsha Bhatta.
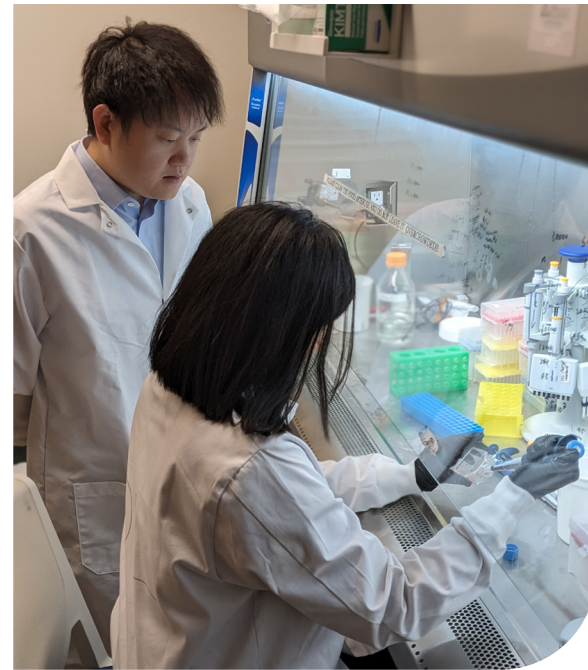
to amplify the CTL response and antitumor efficacy. One key challenge, though, was the lack of an effective strategy to functionalize EVs and bind sufficient adjuvants onto EVs. We now have a metabolic labeling technology that lets us do that, though. We found that when we label the cancer cell with the chemical tag, the EV carries the chemical tag and allows for the conjugation of a good number of adjuvants. These adjuvant-conjugated EVs can efficiently activate DCs during the cellular internalization process."

"The results are a superior DC activation effect, robust T-cell response, and antitumor efficacy against lymphoma, melanoma, and other types of cancer."

Wang's lab uses a metabolic glycan labeling of parent cells, which can introduce chemical tags (e.g., azido groups) in the form of glycoproteins and glycolipids to the membrane of each cell, generating chemically tagged EVs. They demonstrated that this EV-tagging approach is universally applicable to EVs secreted by various types of cancer cells, mesenchymal stem cells, dendritic cells, and T cells.

This project not only marks a promising development in the big picture of personalized cancer immunotherapies, but it is deeply meaningful for Rimsha Bhatta, an Illinois doctoral student who has worked for years studying EVs.

"This project has been very close to my heart. I've worked on EVs since my first year as a Ph.D. student in Prof. Wang's lab. When I learned about this important area of cancer research, I wanted to work on developing a vaccine for human application.

The CCIL and the Department of Materials Science and Engineering allowed me to combine my interest in EVs and vaccines and bring a solution to the table for cancer patients. Our results have been very encouraging, and I am hopeful for the future of this project," said Bhatta.

This foundational research into an EV-based cancer vaccine demonstrates the critical role of the CCIL, which provided the seed funding to help Wang generate an initial proof of concept, enabling the team to move forward on the research project. "The CCIL is a natural home for our lab and has been critical for our research. I appreciate the opportunity with the CCIL to build a growing collaboration network," said Wang.

"Hua's idea to develop an EV-based vaccine was very risky. Historical efforts to vaccinate against cancer haven't proven successful. So, his bold research proposal required investment by the CCIL to generate proof of concept. Hua's team took that initial data with support from the CCIL and acquired federal funding. It was a high-risk proposal, but the results are promising. This will be the first publication among many, no doubt," said CCIL Cancer Discovery Platform (CDP) program leader Erik Nelson, who collaborated on this project.

Moving forward, Wang said that his lab plans to collaborate with Mustafa to obtain patient-derived glioblastoma tissue, culture the samples in the lab, generate chemically tagged EVs, test in humanized-mouse models, and move toward human clinical trials.

TWO CLINICAL TRIALS AIM TO HELP CANINES

Veterinary comparative oncology researchers at the University of Illinois Veterinary Teaching Hospital, including CCIL members, are making progress on their investigations into new immunotherapy options for canines with osteosarcoma and malignant melanoma.
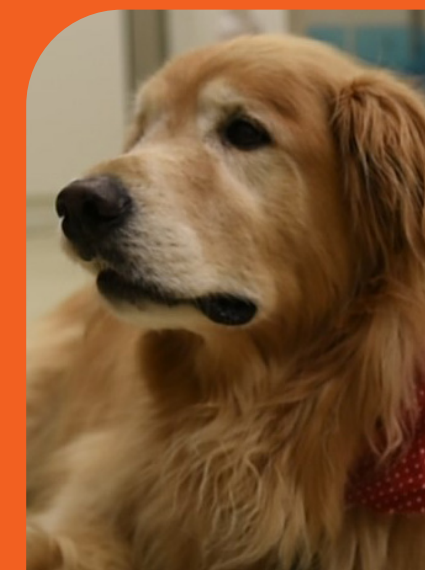
Micah Joy (Patient with osteosarcoma).

OSTEOSARCOMA

The trial evaluates the novel combination of using radiation therapy with an innate immune-stimulating molecule called CpG oligodeoxynucleotide (ODN) injected into the tumor site.

"This is hopefully working as a vaccine effect. We're trying to amplify the immune response locally. Then the immune system can have this body-wide surveillance to kill cancer cells that have already spread from the tumor location to other parts of the body," said Dr. Matthew Berry, a veterinary oncologist.

This study, supported by the Morris Animal Foundation, will lay the groundwork for the treatment's safety and ability to activate the immune system. Researchers plan to launch a future clinical trial with a larger group of dogs to determine if the treatment is as effective as traditional chemotherapy. Their findings could eventually have implications for the treatment of osteosarcoma in humans.

"One of the big barriers in people with osteosarcoma is that it would take 10 years for you to run a clinical trial in people because of the rarity of the tumor," said Dr. Timothy M. Fan, a professor of veterinary oncology and CCIL Associate Director for Development and Translation.

"Those barriers are dramatically reduced when we look at dogs with osteosarcoma. Instead of 1,000 people a year, we have 50,000 dogs a year affected with osteosarcoma, and the turnaround time to know if the therapy works is about a year for the dog versus five to seven in a person."

MALIGNANT MELANOMA

In a clinical trial sponsored by Ankyra Therapeutics, researchers injected pet dogs that have naturally occurring melanoma with a cytokine, a protein that activates the immune system. High levels of cytokines in the bloodstream can cause toxicity, so to avoid this problem the cytokine, called Interleukin 12, is anchored to aluminum hydroxide. Aluminum hydroxide has been used for almost 100 years as a vaccine adjuvant. Given the physical properties of aluminum hydroxide, anchored Interleukin 12 is retained locally at high concentrations within the sites of tumor injection.

The goal is to elicit an immune response strong enough to shrink the tumor and alert the immune system to fight cancers found in other areas of the body. The strategy is similar to the study discussed in a recent article, but the current technology using aluminum hydroxide as a cytokine anchor can be used effectively in any solid tumor regardless of the protein components within different tumor types.

"We have recruited and treated 14 dogs in this clinical trial. Many of these dogs have tolerated the therapy very well. Excitingly, there are dogs that are showing robust positive responses," said Fan.

The technology used in this clinical trial has been approved to start phase one human clinical trials. The first human cancer patients were enrolled and treated at Massachusetts General Hospital and other sites at the end of 2023.

"We hope that the studies we did in dogs will be very important in recognizing what aspects we need to look for in people," said Fan.

Researchers plan to continue their study with another cohort of canines who will receive an optimal dose of anchored cytokine in combination with checkpoint inhibitors, another type of immunotherapy. It is expected that the greatest anticancer activities will be achievable through a rational combination of multiple immunotherapy strategies.

CCIL TRAINS FUTURE CANCER RESEARCHERS IN ResearcHStart PROGRAM

In summer 2023, six high school students from central Illinois gained hands-on laboratory experience, a network of mentors, and a newfound understanding of what CCIL members are doing to transform cancer detection and treatment.

Those students, and their peers from the Chicago area, presented their projects to family, friends, and scientific community members at a researcHStart symposium at CCIL on August 4, 2023. ResearcHStart is an intensive cancer research experience and partnership between the University of Chicago, University of Illinois Urbana-Champaign, University of Illinois Chicago, Northwestern University, and Rush University.

Many students in the program plan to pursue STEM careers. For at least one of them, this experience was more personal. Kenzie Hales, a rising senior at Shiloh High School, applied to researcHStart shortly after her grandfather started treatment for his fourth cancer recurrence. "Had this come at some other time, I may not have considered it as much, but I thought, 'You know what, if it came at this exact moment, this is a sign I need to take it,'" said Hales.

As her grandfather battled the disease this summer, she learned what researchers are doing to help patients like him and solidified her interest in the medical field, including a possible career in oncology. Other students in the program said they gained a deeper understanding of the complexities of cancer research, including how to pivot when there are unexpected circumstances.

"It takes a group effort. It takes getting your work published so that others can look at it and collaborate and expand on it," said Hailey Downs, a Tuscola High School graduate headed to Parkland College this fall. "Much of my project changed because we had an issue with a cell line that we're pretty sure got contaminated. It really changed my work from being in the wet lab to a lot of analysis."

Central Illinois high school researcHStart students.

Another recent graduate, Kara Mathias of University Laboratory High School (Uni High), was grateful for the opportunity to get a head start on studying the same concepts she'll be diving into at Carnegie Mellon University. "This is pretty cool to get experience right now, before college, so next year, I'm prepared," said Mathias.

Aya Surheyao also feels more prepared to enter a laboratory setting in the future. The Uni High student said the lab felt like a safe place to learn and gain independence. "It's been good to be able to make mistakes. I was having trouble with the multi-channel pipette. My handwriting is bad when I write on the tiny vials. I can make those small mistakes now, so it's useful," said Surheyao.

Hands-on experience was critical for several participants who took their high school biology courses during the height of the COVID-19 pandemic when they could only do virtual experiments. "I applied [to researcHStart] because I love math and science, but I didn't have any practical experience," said Charlotte Chesser of Champaign's Central High School.

In addition to learning the inner workings of the lab, students worked closely with mentors and learned how to think like a scientist, including how to analyze articles and answer their questions by conducting thorough research.

"Starting to work with experts in a field may be intimidating for an early researcher, especially if one feels like they don't know as much as their peers," said Chesser's mentor and Ph.D. candidate, Rishee Iyer. He said it's important for young scientists to enjoy the process of uncovering a mystery. "In cancer research, there is an additional satisfaction of creating immediate impacts on a prevalent and real-world problem."

"All the things I've learned, not just about my project specifically, but also about research and lab work, are some of my favorite parts of the researcHStart program," said Savindi Devmal, a Uni High student.

While they may have only spent a summer in the program, the lessons these students learned will last much longer as they continue their education and find a path toward a successful future.

CCIL UNDERGRADUATE WORKS TOWARD IMPROVING HEALTHCARE DISPARITIES

Cindy Mu.

During her junior year at the Illinois Mathematics and Science Academy (IMSA), Cindy Mu traveled from Aurora, Illinois, to Northwestern University every Wednesday to perform Parkinson's disease research. In a position normally reserved for graduate students, Cindy was a formative member of Jones Parker's research group while helping to start the new lab. While performing behavioral and surgical studies in mouse models initially pushed Cindy out of her comfort zone, she still works in the same lab today during her summer breaks and enjoys the highly collaborative and fast-paced research environment.

With such a unique opportunity to dive into scientific research in high school, on top of taking college-level courses such as organic chemistry, biochemistry, and cancer biology, Cindy began to think about her values and the goals of her education. "Before transferring to IMSA, I didn't think about the integral role of education in my life, but saw it as something that is just required," says Cindy.

Now a junior pre-medical honors student at Illinois, double majoring in chemistry and molecular & cellular biology with a minor in creative writing, Cindy continues to challenge herself to find meaning in her education and apply it in the future. This motivated her decision to join the CCIL's Cancer Scholars Program. "I think it's really cool that we are educating others about cancer, while also navigating how to perform and discuss cancer research ourselves. We have even done a project where we made lesson plans to teach middle schoolers about cancer," explains Cindy.

Looking forward to a future career in medicine, Cindy is passionate about addressing health disparities and advocating for healthcare accessibility. She reflects, "My parents were the first of my entire family to go to college and were able to immigrate to the United States. They both pursued their master's degrees in engineering, which is really inspiring and makes me appreciate these opportunities that I wouldn't otherwise have without my parents and grandparents."

Cindy continues, "I lived in China for a short time and saw my grandparent's house in the village where my dad grew up. I was young, but old enough to recognize the cultural differences in the societal structures and medical systems in China and the United States. My grandmother lived in poverty as a child and never received medical care for her ailments, which led to chronic illness. So, it's very personal for me to use the opportunities that the United States offers to help make a difference by eliminating health disparities."

Cindy has taken full advantage of the opportunities on campus to enrich her college education and fulfill her personal goals to help alleviate healthcare disparities. Her free time is filled by training dogs with the Illini Service Dogs group for people in the community, working as an emergency medical technician in the Illini Emergency Medical Service, and participating in a cancer health disparity initiative with Marci Pool, the CCIL's Assistant Director of Education.

"Right now, I'm working with Prof. Pool on a CCIL pilot program in collaboration with Plaksha University in India and their own grand challenge to address health disparities. We're investigating ways to increase treatment accessibility for patients. We are currently recruiting people for the study and hoping to involve more CCIL students in the research project," remarks Cindy.

As she gears up to apply to medical school, Cindy reflects on her time as a cancer scholar. She says, "It's really cool how the CCIL is involving the public. That's something I want to be a part of—to go out into the community and make an impact. I think that we as cancer scholars represent the mission of the CCIL by trying to inspire people to prioritize cancer research in medicine."

POSTDOC RESEARCHER ENJOYS SMALL PART IN BIG CHANGES FOR CANCER RESEARCH

Kia Falahkeirkhah.

When Kianoush (Kia) Falahkheirkhah came to the University of Illinois Urbana-Champaign in the fall of 2016, he wasn't too sure about America. "Growing up in Tehran, I was familiar with life in a big city surrounded by mountains. But here it was very different in a quiet college town in the middle of cornfields," remembers Kia. "And people were putting pineapple on pizza! 'What is that,' I thought. It was so strange," laughs Kia.

More worrying for him, though, was America's political landscape and the associated stresses impacting international students. "It was very stressful for me and my fellow Iranians," he recalls. "But the University was always very supportive of us in those uncertain times. I am so grateful for that."

Seven years later, Kia is now a postdoc researcher in CCIL Director Rohit Bhargava's Chemical Imaging and Structures Laboratory, and he couldn't be happier. "I was accepted to four American universities: University of Southern California, Penn State, University of Maryland, and Illinois. My Iranian friends recommended Illinois; I chose well," acknowledges Kia, who graduated in May 2023 with a Ph.D. in chemical engineering. "When I was investigating my options for Ph.D. advisors, I received some advice to choose carefully because your 20s are a 'golden time' in life, and you don't want to be miserable with your Ph.D. advisor. When I sat down with Rohit for an interview, we had an immediate connection, and seven years later, we still like each other," says Kia with a characteristic smile. "I really like Rohit's advisory style; he's very results-oriented, which allows me the flexibility to work productively."

So, how exactly did a boy from Tehran end up working as a cancer researcher? "If it were up to me, I would have become a musician," admits Kia, an only child whose early world was quite small, walking five minutes to elementary school and ten minutes to high school. "I loved playing the guitar, writing music, and listening to music, but my parents saw art as something to do on the side, not a career," remarks Kia.

"My dad was a mechanical engineer at an automobile manufacturer, and he was big on teaching me math in the context of card games we would play together. In high school, I discovered I liked solving problems and began to see math and science as a possible path. Certainly, without my parents, I wouldn't have chosen a career in engineering, but I'm glad I did," he exclaims. As a chemical engineering student, Kia found himself interested in the computer applications of his field, which ultimately led him to the role he holds now as a postdoc researcher in Bhargava's lab, where he is designing artificial intelligence (AI) models to support the team's microscopy innovations for pathology.

"One thing I like about the cancer research we are doing is that you can feel the impact you are going to have. In five to ten years, our research will change how we look at pathology. I get to play a small part in that big change, and that makes me feel really good," says Kia, who enjoys working in an interdisciplinary lab environment focused on improving cancer diagnosis methods.

"I want to push forward our research to be transformational in healthcare and in low-resource hospitals. Many people lose their lives not because of cancer itself but because their diagnosis was inaccurate or comes too late. We are interested in advancing our research so that it has the potential to reach more people in everyday clinics."

Kia wants to see more young scientists consider cancer research, specifically the applications of AI in the field of pathology. "Many aspects of pathology haven't changed for 125 years. There is much room for improvement, and we need fresh minds to push forward this area of cancer research. If you want to have an impact in the world, consider cancer research," offers Kia.

IMAGING TECHNOLOGY GRADUATE STUDENT FOCUSES ON NOVEL TECH FOR BIOMEDICAL OPTICS

Janet Sorrells.

In the summer of 2017, Janet Sorrells arrived at the University of Illinois to perform undergraduate research in CCIL researcher Stephen Boppart's Biophotonics Imaging Laboratory as part of a National Science Foundation Research Experience for Undergraduates (NSF-REU).

Today, Janet is a Ph.D. candidate in that same lab, working on developing novel nonlinear optical imaging technologies. She is also a trainee in the CCIL's Tissue Microenvironment (TiME) program, a university-wide training program for graduate students focused on studying tissue microenvironments to advance biomedical science.

Originally from Massachusetts, Janet didn't ever expect to live in the Midwest after her REU, especially after applying primarily to graduate programs on the East Coast. However, "after visiting, I decided that it had to be Illinois," she said. "It's such a large school with diverse people and tremendous resources. I knew that I wanted to join the Boppart lab because he was such a supportive mentor and advocate, and the lab had a good environment during the NSF-REU. I'm really happy with my choice."

When Janet learned that pursuing a doctorate was an option, it felt like a natural choice to continue her education. "I didn't know anything about obtaining a Ph.D., but I had some really fantastic mentors for undergraduate research who introduced me to the concept of attending graduate school and how the funding works. That helped it become a possibility," Janet explained.

Growing up, Janet loved learning new things, whether at school or as a hobby, like juggling flaming clubs and knives. In fact, she chose to major in biomedical engineering at the University of Rochester because it combined her many academic interests in biology, physics, math, and medicine.

At Rochester, Janet serendipitously discovered her passion for biomedical optics, starting the chain reaction that led her to the Boppart group. She reminisced, "Rochester has a really big optics program, and I didn't know anything about it before I got there. When I showed up and learned about it, I decided to take a class to try it out, and just by chance I realized I liked it and figured out that it was what I wanted to do."

After taking a break from engineering to study Chinese language and culture during her fifth year at Rochester, Janet moved to Illinois in 2018 to start her doctorate program in bioengineering and officially joined the Boppart group. "My first couple years of grad school, I spent a lot of time sitting alone in the dark waiting for data to be acquired on really sensitive detectors," she laughed, referring to her research on the development of improved technologies for fluorescence lifetime imaging microscopy. Janet continued, "I created a method 40 times faster than the current gold-standard methods." This novel technology enables the study of fast, dynamic processes such as cancer cell death and extracellular vesicles implicated in cancer metastasis.

Currently, Janet is focused on new developments in coherent anti-Stokes Raman scattering imaging, another form of label-free nonlinear optical microscopy. Enhancing the speeds of these various nonlinear imaging techniques opens the door to new clinical applications and enables novel biological discoveries, including studying the tissue microenvironment.

"I think one of the significant benefits of nonlinear optics is being able to characterize the tissue microenvironment. That's what pushed me to apply to the TiME program, and it has been rewarding so far," remarked Janet. "I would like to thank Professors Rex Gaskins, Marci Pool, and Rohit Bhargava because they have done a great job in supporting the trainees in the CCIL. I'm appreciative for everything they've done to develop the TiME program and empower students to excel."

WHERE ARE THEY NOW?

EGE GUNGOR ONAL

Ege joined the CCIL's Cancer Scholars Program (CSP) as a freshman in 2018. Inspired by his CSP classes, he joined CCIL program leader Brian Cunningham's lab to perform cancer diagnostics research, which included developing a cancer liquid biopsy device. In 2020, he became a CSP mentor, assisting young cancer scholars with personal growth and career plans.

"My experience as a Cancer Scholar made me realize the need to expand the sphere of cancer research advocacy across the Illinois campus. To that end, I co-founded the Cancer Center at Illinois Student Organization (CCIL-SO) and served as its first president. Together with 26 students across seven committees, we led fundraisers, spread awareness for cancer research, and hosted cancer research seminars and alumni events to encourage support for cancer research. I would suggest to any student interested in joining the fight against cancer to check out CCIL-SO."

After graduation, Ege went on to become a technical associate in Robert S. Langer's laboratory at the Massachusetts Institute of Technology (MIT), where he focused on engineering a tumor-selective nanotherapy for solid tumors. Ege continues his ongoing research project at MIT in parallel with additional clinical research projects he performs now as an M.D./Ph.D. student at The Warren Alpert Medical School of Brown University.

"I am energized each day to learn about the human body, diseases, treatments, doctor-patient interaction, and areas we need to improve in clinical practice. The CCIL really empowered me to embark on this cutting-edge cancer research journey. The mentorship I received from Prof. Cunningham and my experiences in the lab motivated me to pursue additional research endeavors on campus and over the summer at Mayo Clinic. Those experiences have resulted in multiple journal publications and conference abstracts. Furthermore, these experiences have uniquely prepared me to be creative in the laboratory and independently run my experiments at MIT. "

"One of the greatest strengths of CCIL lies in the *foundation of the people.*

The support and mentorship I received from CCIL leaders have been the cornerstone of my success. I am very grateful to many people, including Brian T. Cunningham, Marci Pool, Andrew M. Smith, Rohit Bhargava, Amber Lannert, and many more. It was an honor to be a part of the CCIL, and I am forever grateful for the people and experiences the CCIL brought to my life."

QIANYING ZUO

In 2018, Qianying Zuo won the Kathryn Van Akken Burns Memorial Fund Merit Award while working in Zeynep Madak Erdogan's lab. As a graduate student, Qianying was the first author on a paper recognized in 2024 by the AACR for its scientific significance in the field of molecular cancer research.

"Our research project looking at endocrine drug resistance in liver metastasis excited me for several reasons. First, estrogen receptor-positive (ER+) metastatic tumors represent a significant clinical challenge, resulting in many deaths. Addressing this challenge is critical in improving patient outcomes and quality of life. The emergence of liver metastasis adds another layer of complexity to the management of ER+ breast cancer, as effective treatments for liver metastasis are currently limited. Therefore, the potential to discover novel therapeutic strategies for liver metastasis was highly compelling. The findings of our study regarding the synergistic effects of a ketogenic diet with endocrine therapy in reducing breast cancer liver metastasis were very promising. Overall, the opportunity to contribute to cancer research that addresses a pressing clinical need and offers novel insights into therapeutic strategies for breast cancer liver metastasis is what truly excited me about this project."

Today, Qianying is a postdoctoral researcher at Princeton University where she works under the mentorship of Yibin Kang. Her research centers on investigating how nutrients shape the tumor microenvironment, uncovering metabolic vulnerabilities, and devising food-based interventions that complement existing cancer therapies to impede or treat cancer progression.

"As a researcher, I firmly believe in conducting work that is not only rigorous and pioneering but also holds significant societal relevance. My aim is to make substantive contributions to academia and society alike, by conducting research that ultimately enhances the well-being of individuals worldwide."

Looking back, Qianying is filled with gratitude for the foundational experience of working under the cancer research mentorship of Madak Erdogan.

"Working under Zeynep's scientific leadership was invaluable. Weekly one-on-one meetings involved close discussions on experimental results and planning future work, fostering my independent and critical thinking. Her guidance not only facilitated my understanding of the research process but also empowered me to take ownership of my work. Moreover, her mentorship extended seamlessly into the paper-writing process, where she provided invaluable insights and guidance, ensuring that our findings were effectively communicated and disseminated within the scientific community. Overall, it has been an enriching experience that significantly contributed to my growth as a researcher."

TUMOR ENGINEERING & PHENOTYPING FACILITY ACCELERATES DISCOVERIES FOR CAMPUS RESEARCHERS

The CCIL's Tumor Engineering & Phenotyping (TEP) Facility is the largest space dedicated to cancer research at Illinois. The TEP is a campus shared resource supporting CCIL members and all other researchers at the university, as well as external users.

The TEP is a one-stop shop for biological and engineered materials analysis to accelerate your discoveries.

NEW EQUIPMENT INSTALLATIONS

The TEP recently installed new equipment to further expand the TEP's robust capacity to support a diverse array of experiments and analyses.

The TEP's custom-made hypoxia chamber now houses the TEP's Seahorse Analyzer. The hypoxia chamber enables real-time analysis of metabolic function, performed at a wide range of oxygen concentrations (including hypoxia) and allowing for analysis of in vitro cellular and organismal metabolic functions at relevant in vivo oxygen levels.

The TEP's new NanoGenerator™ Flex-M applies microfluidic approaches to synthesize nanoparticles (e.g., lipid nanoparticles or LNP) in a continuous mode. The system provides a wide throughput range from 1 to 12 mL, meeting a variety of applications from early screening to animal studies.

The TEP's new PhenoCycler-Fusion System performs comprehensive spatial phenotyping across whole slides to detect protein and RNA in situ at single-cell resolution. The system is part of an integrated spatial biology workflow, including single-step tissue staining, image acquisition and on-board processing. It can analyze 100+ protein and RNA biomarkers for deep spatial phenotyping in 24 hours.

NEW PERSONNEL

The TEP hired Renee Walker to support the TEP's growing histology services. Renee comes to the TEP after two decades working as a histologist at Illinois' College of Veterinary Medicine.
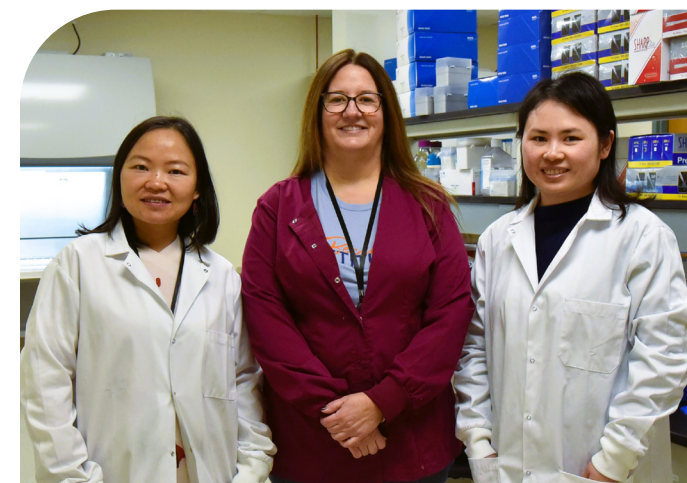
From left to right: TEP staff Huimin Zhang, Renee Walker, and Hui Xu.

"

TEP's support has been vital in navigating the complex landscape of cancer research and pushing our work's boundaries. The support we've received has *expedited our research and enhanced its quality.* The availability of TEP's resources and expertise is a testament to the CCIL's mission to foster cutting-edge cancer research and its translation into meaningful health solutions.

**— YUN-SHENG CHEN
CCIL member, Assistant Professor of Electrical & Computer Engineering**

OUR NEWEST MEMBERS

SEVEN RESEARCHERS JOIN THE CCIL'S GROWING TEAM OF 100+ FULL AND ASSOCIATE MEMBERS

RACHEL ADLER
Associate Professor, School of Information Sciences

Research Program: Cancer Measurement Technology and Data Sciences

Strategic Theme: Computational Biology and Engineering

Adler's research interests are in human-computer interaction, accessibility, and computer science education. She is particularly interested in designing applications for and with people with disabilities. Some of her recent projects include co-designing a mobile health application to empower cancer survivors with disabilities, co-designing a mobile health peer navigator intervention for people with disabilities, and creating simulation games to teach students about accessible design.

YUN-SHENG CHEN
Assistant Professor, Electrical & Computer Engineering

Research Program: Cancer Measurement Technology and Data Science

Strategic Theme: Imaging

Chen's research focuses on developing innovative, translatable imaging, diagnostic, and therapeutic techniques utilizing light and ultrasound. Chen is a faculty member of the Beckman Institute and the Holonyak Micro and Nanotechnology Laboratory and an affiliate of the Department of Bioengineering and the Carle Illinois College of Medicine.

CLAUDIUS CONRAD
Professor, Carle Illinois College of Medicine
Medical Director of Surgical Strategy and Innovation, Carle Health

Research Program: Cancer Measurement Technology and Data Science

Strategic Theme: Imaging

Conrad is a world-renowned surgeon, researcher, and expert in minimally invasive procedures to treat liver, pancreatic, and biliary tract cancers. His research seeks to improve minimally invasive cancer surgery and explore the mechanisms of the disease.

BUMSOO HAN
Professor, Mechanical Science and Engineering

Research Program: Cancer Discovery Platforms Bridging the Engineering-Biology Continuum

Strategic Theme: Natural and Model Systems

Han's research explores biotransport phenomena for cancer research and tissue engineering. His current work focuses on drug transport at the tumor microenvironment, engineered microphysiological disease models, and cell-matrix interaction in the stroma tissue.

SAMY MEROUEH
Professor, Biochemistry

Research Program: Cancer Discovery Platforms Bridging the Engineering-Biology Continuum

Strategic Theme: Drug Discovery

Meroueh develops small molecules that modulate the function of proteins that are considered undruggable, such as members of the RAS and Rho GTPase superfamily, transcription factors and co-activators such as Hippo pathway TEAD and YAP, and proteins involved in tight protein-protein interactions like the urokinase receptor or the HPV E6 oncogene.

YANG LIU
Professor, Bioengineering

Research Program: Cancer Measurement Technology & Data Science

Strategic Theme: Imaging

Liu investigates the future of precision medicine through multiscale optical microscopy, automation and robotics, artificial intelligence, and large-scale bioimage informatics. Her imaging techniques span seven orders of magnitude—from the nanoscale to the mesoscale—enabling transformative advancements in precision medicine. Liu's fusion of cross-scale imaging and AI-driven systems biology sets the stage for unprecedented scientific discoveries and transformative personalized medicine.
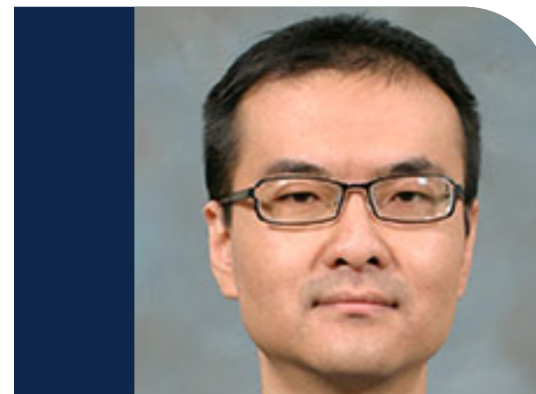
HUANYU (JOE) QIAO
Associate Professor, Comparative Biosciences

Research Program: Cancer Discovery Platforms Bridging the Engineering-Biology Continuum

Strategic Theme: Pathways and Mechanisms

Qiao's laboratory explores how post-translational modifications, such as SUMOylation (Small Ubiquitin-like Modifier) and ubiquitination, regulate various checkpoint pathways in mammalian cells. This work has the potential to provide insights for developing treatments for infertility, miscarriage, congenital disabilities, cancer, immune dysregulation, neural degeneration, and aging-related diseases.

Cancer Center
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