Cancer Scholars program graduates its first cohort
Researchers confirm that metabolism of drugs by cardioprotective enzymes can cause cardiotoxicity

Can Great Lakes fungi cure cancer?

Omics nanotechnology for cancer precision medicine

Ultrasound-guided nanobubbles could enhance cancer treatments

Illinois researchers achieve all-digital pathology of both tumor and microenvironment

Unsuspected flexibility offers new pathway to cancer drug development

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COVER STORY: The Cancer Scholars experience: Cohort 1 begins new adventures

Graduate Cancer Community at Illinois poised to chart a new course

Cancer Scholars for Translational and Applied Research (CSTAR)

Tissue Microenvironment (TiMe) Day Symposium

Bike ride, singing contest, workshops, lectures, institutes and seminars highlight cancer-related events on campus

PATHWAYS is a publication of the Cancer Center at Illinois, University of Illinois at Urbana-Champaign. Each issue highlights the interdisciplinary and translational work of Cancer Center faculty, staff, students and external partners.

ON THE COVER Cancer Scholars. The three hexagons vertically down the middle show May 2018 graduates from the first cohort.
With the end of the spring semester, we have entered into the “construction semester” on the Urbana-Champaign campus! Work crews seem to appear without warning, and the new growth seems to be on every university street and sidewalk. It’s all part of a bigger plan to improve the community and strengthen the infrastructure that supports our research, teaching, public engagement, and economic development missions.

In similar ways, the Cancer Center is under construction! We are deliberately putting infrastructure in place to connect our research community in new and exciting ways, building bridges among faculty, staff, students, physicians, and community partners to tackle the basic science and engineering questions that surround cancer.

When we “officially” established the Cancer Center at Illinois last July, we also laid out an ambitious plan to become designated by the NIH’s National Cancer Institute as the first new Basic Science Designated Cancer Center in nearly 30 years. Our first step in that process was preparation of a preliminary draft of a cancer center support grant (CCSG), which we shared with our External Advisory Committee last October. Our distinguished members of the EAC put in significant effort to strengthen our center and helped improve our application. I am deeply grateful for the quick work (and enthusiastic support) from our campus leadership — Chancellor Jones, Provost Cangellaris, and Interim Vice Chancellor for Research Martinis — in supporting the recommendations of the EAC and enabling amazing progress for the center. I am more confident than ever that we have the exceptional faculty and students, a great center team, institutional support, and the resources we need to be successful in building a truly unique and impactful Cancer Center.

While, as a researcher, I am delighted that we are making such significant progress, as an educator I am equally excited about our student programs. Our first cohort of Cancer Scholars graduated in May 2018, and our first group (2016-2018) of NIH-funded Tumor Microenvironment Training Fellows will wrap up their time with the program in August, making room for a new group to start their journey in the fall semester. We welcomed a new cohort of researchStart students this summer, and added to the C*STAR program. This cycle of growth and change — deliberately constructing opportunities for innovation, discovery, and learning — is a hallmark of the Cancer Center at Illinois. I hope you enjoy reading more about our progress and plans for the future in this latest edition of Pathways.

Rohit Bhargava

Steering Committee
There are many anti-cancer therapeutics that are effective at killing cancer, but some can have serious side effects, eventually causing heart attacks.

Researchers at the University of Illinois at Urbana-Champaign are studying the cardio-toxicity of doxorubicin (DOX), one of the most commonly used chemotherapeutic drugs. It’s also one of the oldest in its class, known as anthracyclines, and is considered an “essential drug” by the World Health Organization.

The Illinois team recently published their work in Biochemistry. “Arachidonic Acid Metabolism by Human Cardiovascular CYP2J2 is Modulated by Doxorubicin” outlined the findings about a new mechanism of doxorubicin cardiotoxicity. It was named an exemplary paper in its field by peer review service F1000 Prime, earning the designation of a “recommended article.”

“Doxorubicin can be very effective at attacking the cancer,” said Aditi Das, the research lead, who is an assistant professor of Comparative Biosciences in the College of Veterinary Medicine, of Biochemistry in the School of Molecular and Cellular Biology, Biophysics in the College of Liberal Arts and Sciences, in the Division of Nutritional Sciences in the College of Agricultural and Environmental Sciences, and member of Beckman’s 3D Micro- and Nanosystems Group. “However, patients undergoing doxorubicin treatment can reach a lifetime cumulative dose that becomes cardiotoxic,” she said.

“By figuring out what causes the cardiotoxicity, pharmaceutical companies can design better and better analogs that don’t harm the heart,” Das said.

The researchers studied cardiotoxic doxorubicin and two other non-cardiotoxic doxorubicin analogs to determine the mechanism causing the cardiotoxicity. Doxorubicin fights cancer by interfering with DNA replication so the cancer cells can’t divide, and they kill the cancer cells with reactive oxygen species.

“When we think of taking a drug, we think of its side effects,” Das said. “But we forget that the drug can be converted to metabolites that might produce a different type of side effect. Hence, we should study the pharmacology of the downstream metabolites as carefully as the primary drug.”

Cytochrome P450 enzymes metabolize all the foreign substances that enter the body including food and drugs. However, the new metabolites that are produced can work in either a positive or a negative manner leading to unpredictable outcomes. The cytochrome P450 enzymes are present in all the organs in the body, but drug development is often specifically targeted on the liver.

“It’s important to note that the enzymes are not only in the liver, but also in the heart, the brain, and in other organs,” Das said.

“We need to study the cardiotoxicity of drugs using cardiac enzymes, not just liver enzymes.
There are a lot of drugs that fail that way," Das said. "We need to make sure that drugs are safe, not just 'good enough.'"

The researchers want to understand how cardiotoxicity develops — which could be through multiple mechanisms — in order to provide important information to be used to make a new drug derivative that doesn’t hurt the heart.

“We think of food alone and of drugs alone, but we don’t think of the drug-food interactions that are mediated by all these enzymes," Das said. “Doxorubicin inhibits an enzyme that metabolizes an omega-3 or omega-6 fatty acid. So we’re looking at a drug-food interaction.”

“We know that fatty acids (omega-3s and omega-6s) have a positive benefit to our health," said William Arnold, Ph.D. student in Biochemistry. “One of the benefits is that they are converted in our bodies to help against things such as inflammation. And they help the heart in many ways, including combatting inflammation, so they are generally considered cardioprotective.”

“By figuring out what causes the cardiotoxicity, pharmaceutical companies can design better and better analogs that don’t harm the heart.”

— Aditi Das

The study focused on CYP2J2, a human cytochrome P450 that is strongly expressed in cardiomyocytes and is the primary enzyme responsible for turning fatty acids into cardioprotective compounds.

The researchers collaborated with the NIH Center for Macromolecular Modeling and Bioinformatics at the Beckman Institute, led by Emad Tajkhorshid, professor of Biochemistry, of Biophysics, and of Bioengineering.

Together with Javier L. Baylon, formerly affiliated with the Center for Biophysics and Quantitative Biology and the Beckman Institute, they performed the computational component of the research, which was critical to the molecular understanding of how the primary metabolite of the drug changed the site of metabolism of the omega-3 fatty acids leading to adverse drug-drug interactions.

“Seeing is believing,” Tajkhorshid said. “Through combining extended molecular simulation of the enzyme in its realistic environment of the cellular membrane with detailed analysis and visualization, we could provide a detailed picture of differential binding of these drugs to the binding pocket of the enzyme which helped with the design of experiments.”

The research was supported by an American Heart Association Scientist Development grant and a National Institutes of Health grant.
A cure to childhood cancer may be hidden in fungus discovered at the bottom of the Great Lakes and nurtured on Cheerios.

While the breakfast cereal came from Walmart, the fungi were found in the Midwest's own backyard: the bottom of the Great Lakes — which until recently have been hardly touched in the world of fungal research.

“I was shocked when I started doing the background research looking through the Great Lakes, and just thinking ‘holy crap, there’s basically nothing known about this,’” said Robert Cichewicz, a natural products professor at the University of Oklahoma. “That was just mind-boggling. One of the biggest freshwater sources on Earth, and no one knew what its fungal component was.

“A whole kingdom of life missing.”

A project that started four years ago led the team — Cichewicz and other researchers from universities in Michigan, Illinois, Oklahoma and Texas — to suspect the secret to fighting pediatric cancer may be found in this hidden world.

The National Institutes of Health awarded the team $2.5 million to research a cancer cure. The money wasn't necessarily intended for fungi research. But both Cichewicz and his colleague, Susan Mooberry, saw cancer-fighting potential in fungi because of its presence in life-saving drugs like penicillin and statin.

“I think they are the most brilliant chemists on earth,” Cichewicz said. “They make amazing molecules for their own purposes, of course; it just so happens we, as humans, can hijack them for other purposes.”

Cichewicz assembled a team that included Mooberry, a pharmacology professor at University of Texas Health Science Center in San Antonio; Andrew Miller, a plant biologist at the University of Illinois at Urbana-Champaign; and Mark Luttenton, an ecologist at Michigan's Grand Valley State University and Cichewicz's former mentor.

Members of the team were each assigned different roles. With access to research vessels, Luttenton and volunteers made trips to parts of lakes Michigan, Huron and Superior. They dropped a giant scoop called a Ponar dredge into the lake bed and collected whatever sediment lay at the bottom.

Then the sediment was divided up and mailed to both Miller and Cichewicz's labs for testing, Luttenton said. There the spores were isolated and grown.
That’s where the Cheerios come in.

“They grow great on it,” Cichewicz said. “They make tons of natural products. The fungi are very happy to be on it.”

The natural products — the chemical compounds found in fungi that are used in medicine — were then shipped to Mooberry’s lab, where she pitted them against cancer cells.

Toxins that kill everything have been studied quite a bit, Mooberry said. “We’re looking at things that have selectivity.”

The researchers want toxins that kill only cancer cells. After enough testing, they found one — a fungal toxin that eliminates only cancer cells associated with a rare type of the disease that grows on the bones of adolescents.

“We’ve come up with a lead for Ewing’s sarcoma that we’re pretty excited about,” Mooberry said. Lots of work lies ahead, but “even if we don’t discover the next drug, we could discover a target that people can then make molecules for,” she said.

There’s another benefit to the study beyond the laboratory research. Before Luttenton’s digging, 13 fungal species had been identified in the Great Lakes. By the end of his 200 digs, that number had climbed to 460 species, a boon for the fungi database.

Every time the scoop completed an excavation, several environmental factors were also documented, Luttenton said. Such measures as temperature, depth and available oxygen were recorded in hopes of discovering a pattern to the fungal types growing below.

Luttenton said the team pursued the question: “Can we better predict where we can expect higher fungal diversity, knowing what ecological conditions might be more conducive?”

“One of the biggest freshwater sources on Earth, and no one knew what its fungal component was.”

— Robert Cichewicz

Despite the optimism, the research has yet to emerge past the discovery stage. And the journey toward a marketed cure for cancer is far from certain.

“Our chance is one in a thousand,” Mooberry said. “When we get something we think is really good, it’s still one in a thousand that it will get to the clinics. The bar is very high, but ... you don’t know until you go out there.”

Editor’s note: This story was originally published by Great Lakes Echo, which is produced by the Knight Center for Environmental Journalism at Michigan State University.
Have you ever wondered how groundbreaking, innovative research ideas get their start? How does an interdisciplinary research team come together with just the right people to move the research forward? The Omics Nanotechnology for Cancer Precision Medicine (ONC-PM) theme is a good case study in how peer networking, collegiality across institutions, and interdisciplinary collaboration contribute to meaningful research that can change the world of medicine.

The theme got its start when University of Illinois at Urbana-Champaign professors Andrew Smith and Brian Cunningham co-organized a symposium in 2015 on the topic of “Super-Resolution Imaging Technologies.” Manish Kohli, M.D., medical oncologist at the Mayo Clinic, attended this symposium and talked with the Illinois professors about cancer diagnostics.

Cunningham, the team lead, explained, “The symposium led to some discussion between the three of us and (development of) some concepts for new cancer diagnostics that would be capable of being ultrasensitive for the most demanding applications, like detecting a handful of miRNA or mRNA molecules in a single droplet of blood.”

Cunningham explained that Kohli already had a great collaborator in Liang Wang, M.D., Ph.D., professor of pathology at the Medical College of Wisconsin, who has expertise in bioinformatics. “Together they already had been clinically validating which biomarkers had concentrations that tracked with successful response to drug therapy,” Cunningham said.

This core group of four people next sought to build the team’s bench strength to include collaborators with experience in genomics, bioinformatics, next-generation sequencing, cancer biology, chemistry, and biochemistry. Cunningham took the lead in preparing a proposal to establish a new theme at the Carl R. Woese Institute for Genomic Biology at Illinois.

Previously there had not been an IGB theme focused on genomics-based diagnostics, and Cunningham said, “A campus as strong as ours needs to be at the forefront of this area. IGB is the perfect environment for supporting interdisciplinary science with very ambitious goals.”

Kohli’s success in obtaining seed funding from a benefactor at Mayo Clinic helped the research team get the technical work off to a strong start and build some preliminary data that would strengthen their grant proposals.
The group has been very busy since establishing the ONC-PM research theme. For example, they have been preparing multiple proposals to the National Institutes of Health (NIH) and the U.S. Army to obtain additional funding to support the work. Kohli is acutely aware of the limitations of existing technology, and Mayo Clinic has been preparing an annotated bio-specimen repository, collecting blood samples from cancer patients and providing guidance on the type of diagnostics that would make a difference in the way that cancer is managed.

Wang, the team’s Wisconsin collaborator, continues to analyze DNA sequencing data from tumors to identify mutations measured from the blood of cancer patients, which is leading to the identification of more and more biomarkers that can be incorporated into the diagnostic tests developed by the research team. The team also hired Taylor Canady, an IGB Fellow and postdoctoral research associate at Illinois. And they set up lab space in IGB, where they are building a new photonic crystal microscope dedicated to diagnostic purposes.

Their chief goal is to develop use-at-home sample collection assays that can be employed to identify subclasses of cancer, as well as track treatment efficacy and progress. Facilities at the Micro and Nanotechnology Laboratory (MNTL) and the IGB will be used to conduct theme research.

The researchers envision the patient using a finger stick to collect a drop of blood that would then be placed into a cartridge and mailed to a laboratory for assessment. With this scenario, the patient should be able to reduce or eliminate clinic visits for routine blood work. The researchers also want to assist clinicians in identifying the distinct treatment that is most likely to work for a specific patient.

The team is framing the research in terms of increasing accessibility, reducing costs, and enhancing effectiveness. At the heart of their work is mitigating patient stress by making the ongoing testing process less invasive and reducing the need to travel to a clinic or medical facility.

As might be expected with MNTL involvement, developing instrumentation with a smaller, and less expensive, footprint is a primary objective. Cunningham described the goal as, “... a desktop-sized instrument that may cost only several thousand dollars, rather than a genome sequencing approach that requires a million dollar instrument.”
Ultrasound-guided nanobubbles could enhance cancer treatments

By Laura Schmitt, Department of Bioengineering

Widely available, portable, and relatively inexpensive ultrasound is well established as a powerful imaging technique for diagnosing disease. Increasingly though, researchers are exploring ultrasound as a therapeutic tool in the fight against cancer and other maladies.

At the University of Illinois at Urbana-Champaign, Bioengineering Founder Professor Joseph Irudayaraj and his team recently demonstrated a new nanotechnology- and ultrasound-based cancer treatment approach that could enhance existing chemotherapy and radiation regimens while reducing negative side effects for patients.

It’s well known that hypoxic tumor cells, which are starved of oxygen, become resistant to conventional radiation and chemotherapy treatments. When this happens, doctors typically increase the radiation dose or concentration of chemotherapy drug, which often adversely affects the patient.

To combat this, Irudayaraj and his recently graduated Ph.D. student Pushpak Bhandari, and two other researchers from Purdue University, used a Doppler ultrasound beam to precisely guide tiny oxygen-laden nanobubbles to hypoxic regions of a bladder cancer tumor in a mouse. At the same time, the researchers were using the ultrasound to image the process and determine the penetration depth of nanobubbles inside the tumor.

By altering the power of the ultrasound beam, the team could control the nanobubble speed, and by altering the beam’s angle, they steered the nanobubbles.

As a result, the hypoxic tissue was reoxygenated, and the tumor’s ability to grow was significantly suppressed.

“The dose of the chemotherapy drug, mitomycin-C — which is commonly used to treat bladder cancer — could be reduced by 50 percent and yet still be effective in reducing the tumor size,” Irudayaraj said. “Our unconventional approach provides an injectable, nanoscale delivery platform that significantly enhances the efficacy of chemotherapeutic agents by precise drug delivery and targeted re-oxygenation of hypoxic tumor regions.”

The work was funded by the National Institutes of Health through the Purdue University Center for Cancer Research and Indiana Clinical and Translational Sciences Institute, and by a W.M. Keck Foundation grant.

The paper, “Ultrasound beam steering of oxygen nanobubbles for enhanced bladder cancer therapy,” was published in Nature Scientific Reports and is authored by Purdue University’s Pushpak Bhandari, Gloriia Novikova and Craig Goergen; and Joseph Irudayaraj, who holds appointments at Illinois in the Carl R. Woese Institute for Genomic Biology, Beckman Institute for Advanced Science and Technology, and the Micro and Nanotechnology Laboratory.
Illinois researchers achieve all-digital pathology of both tumor and microenvironment

By Laura Schmitt, Department of Bioengineering

In the battle against breast cancer, identifying the disease’s molecular sub-type as part of a patient’s diagnosis is key to proper treatment and long-term prognosis. However, effective sub-typing requires not only an examination of the cancerous tissue but the surrounding microenvironment as well.

“Though it has been known to be important for over a hundred years, imaging the microenvironment is quite complicated today, and it’s not used for clinical diagnoses in most cancers,” said Rohit Bhargava, Founder Professor in Bioengineering and director of the Cancer Center at Illinois. “Further, using the full tumor and microenvironment information in manual diagnoses is too complicated for any practical use.”

Bhargava and members of his University of Illinois research group recently unveiled a new imaging method for simultaneously sub-typing cancer cells and the tumor microenvironment. Their approach used modern artificial intelligence algorithms to relate the information to disease to provide a powerful new all-digital, automated capability.

The group also developed a novel infrared (IR) microscope and combined it with machine-learning models. This enabled them to quickly and accurately sub-type breast cancer samples with greater accuracy compared to conventional lab analysis.


Lead author Shachi Mittal, Bioengineering Ph.D. student, developed two algorithms that diagnose cell-level tumors and discover tumor-associated microenvironments. One model, known as 6E, digitally examines breast cancer samples and classifies them according to epithelial sub-types normal, hyperplasia, atypical hyperplasia, and invasive — the same categories a pathologist uses.

“The model is basically detecting the hyperplasia (samples) and separating them from the normal or cancer samples,” Mittal said. “The second algorithm provides unique insight by identifying the reactions occurring around the tumor in the surrounding microenvironment.”

This microenvironment, which consists of many types of cells, including normal tissue, blood vessels, stromal cells, and immune cells, plays a critical role in the progression and metastasis of cancer.

After initial imaging of breast cancer tissue with a Fourier-transform infrared microscope (FTIR), Mittal tested her models on a novel confocal IR microscope built by Kevin Yeh, Bioengineering Ph.D. candidate and co-lead author.

“The image quality, noise performance, and resolution of our microscope exceeds all other instruments of this class,” said Yeh, noting that the instrument also cuts imaging time drastically from days to hours when compared to standard technologies.

As a result of this work, the team has advanced IR imaging as a viable clinical tool for clinical breast cancer diagnoses.

“As opposed to shape-based pathology, this is a practical approach to molecular pathology,” said Bhargava. “IR imaging offers an opportunity for cancer analysis to be truly all digital, in recognition of disease and in quantification of disease severity.”

The work was funded by the National Institutes of Health. The team also includes L. Suzanne Leslie, postdoctoral researcher in the UI Chemical Imaging and Structures group; Seth Kenkel, UI Mechanical Science and Engineering graduate student; and Andre Kadacsy-Balla, UIC physician and professor.
Blood vessels are the supply lines of the human body, bringing nutrients and oxygen to cells and carrying away waste. Controlling the growth of these supply lines can be an effective tactic to combat several different types of disorders, including cancer, stroke, and injury. A new study led by Assistant Professor of Bioengineering Princess Imoukhuede at the University of Illinois at Urbana-Champaign has added a layer of nuance to our understanding of the signals that direct blood vessel growth.

The Illinois research team also includes Ph.D. students Spencer Mamer and Si (Stacie) Chen, as well as other members of Imoukhuede’s laboratory group. Their work examined two distinct signaling systems within the body that influence blood vessel growth and discovered that molecules from one system were able to interact with molecules from the other. Scientific Reports recently published the work.

“If we learn how the proteins fit together and cause protein function, then you can imagine that drugs can be developed that block the way things fit together, and other drugs can be developed that enhance how things fit together,” said Imoukhuede, who is also a member of the Carl R. Woese Institute for Genomic Biology. “Unlocking this understanding would lead to better drug design for treating several diseases, including cancers and even cardiovascular diseases.”

Many aspects of development and growth are regulated by growth factors — molecules produced by the body that direct tissue growth and encourage cells to divide. Each type of growth factor plays a unique role in specific tissues and phases of development, and this individuality of function is reflected in individuality of form: the particular three-dimensional shape of each type of growth factor allows it to interact with a specific set of receptors — molecules that coat the surface of cells and translate external signals into internal ones. This interaction is called binding.

Two different growth factors — vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) — are known to play important roles in blood vessel growth. Drugs that influence the signaling activity of each of these molecules have been used to treat various disorders. In particular, drugs that influence VEGF signaling have been a major focus of cancer therapies.

“Many anti-VEGF drugs including Avastin (a drug used to treat a variety of cancers) have failed due to drug resistance, which makes treatment ineffective and difficult to manage,” Chen said. “Our initial research question was to better understand how the tumor microenvironment develops resistance towards anti-angiogenic drugs, and eventually build better models to predict drug efficacy.”

The group realized that drug resistance, as well as lesser efficacy in some individuals, might be explained if the body were somehow able to compensate for the loss of one type of signal by replacing it with another, similar one.
The researchers recalled a study showing that VEGF can sometimes interact with receptors for PDGF. What if PDGF did something similar, attaching to VEGF receptors and acting like a second-string football player, keeping the game going in the absence of the starting athlete?

Imoukhuede and her coauthors tested their idea by examining the strength of every combination of paired interactions between the two growth factors and their families of receptors. Because of indications from past research that the two growth factors might be flexible in their partnering with receptors, they were not surprised to see that PDGF could form a bond with one of the VEGF receptors. What did surprise them was the strength of that chemical attraction.

“Cross-family binding has kind of been observed, but it’s seen as very weak; the molecule is not the same (and) it doesn’t fit in well, so it’s never a tight binding to that receptor,” Mamer said. “We would have imagined it orders and orders of magnitude weaker, and some of the interactions that we did find were almost at the level of VEGF itself, which meant that they could be very clinically significant.”

These findings are in part a reminder that molecules are in no way bound by the names we give them. Names for cellular products are often chosen based on the context in which they were first discovered; while this system has some advantages, it also can lead to unconscious bias in what hypotheses are developed around those molecules and their functions.

“While people can be flexible in their thinking, I think these names often cause people to not explore the possibility that these are all similar proteins,” Mamer said. “If we weren’t worrying about their names too much, maybe we would be looking more for these interactions across (different signaling systems).”

The group hopes that exploring these types of complexities in growth factor signaling will eventually contribute to the development of more effective therapies either to promote signaling to aid recovery from conditions such as injury or stroke, or to inhibit it to block tumor growth. The next step toward this goal is to discover the functional results of cross-binding between the VEGF and PDGF signaling systems.

“Just because two molecules interact doesn’t mean this actually can induce the changes in structure that are necessary for all the signaling events that come out of it,” Mamer said.

“The next goal is to determine if the binding leads to protein activity, and if so, to measure how much activity we see and how that leads to cell growth and cell movement,” Imoukhuede said. “We eventually want to determine if this ‘second string’ can perform as well as our starters and to fundamentally determine whether they are playing the same game.”

Summary of novel cross-family VEGF and PDGF ligand-receptor interactions. The schematic illustrates an updated view of the VEGF and PDGF ligand-receptor binding patterns, adding newly discovered PDGF-VEGFR interactions. Specifically, only new interactions where the kinetic analysis fit $\chi^2$-to-Rmax ratio $<1.0$ were included. Previously known interactions are indicated with grey lines, and newly found interactions are indicated with red lines.
University of Illinois at Urbana-Champaign researchers are sending tiny drug-laden nanoparticles on a mission to seek and destroy cancer stem cells, the elusive and rare cells that can cause cancer to come back even when years have passed since the initial tumor was treated.

In a study led by Dipanjan Pan, associate professor and director of the M.Eng. program in Bioengineering at Illinois, researchers designed nanoparticles that specifically bind to a protein that marks the surface of breast cancer stem cells. Encapsulated in the particles is the drug niclosamide — a drug commonly prescribed around the world to treat tapeworm infections; but in cancer stem cells, it turns off key gene pathways that give the cells the stemlike properties that enable them to grow and spread.

"It is critical to administer treatments for already-developed tumors; however, long-term survival and not allowing it to come back are equally important," Pan said. "We want to destroy the cells that are hidden in the tissue and cause the cancer to come back or spread to other parts of the body."

Cancer stem cells represent a tiny fraction of cells in a tumor, but it only takes one or two to seed a new tumor, Pan said. The challenge for physicians and researchers is not only finding these cells, but treating them. Pan’s group created nanoparticles that target a protein called CD44, which only appears on the surface of cancer stem cells, and they tested them on breast cancer tumors in cell cultures and in live mice.

“I call them ‘GPS-enabled nanoparticles,’ because they seek out only the cells that have cancer stem cell properties. Then they latch onto the cells and deliver the drug,” said Pan, also a faculty member of the Carle Illinois College of Medicine and the Beckman Institute for Advanced Science and Technology. "To the best of our knowledge, this is the first demonstration of delivering cancer stem-cell-targeted therapy with a nanoparticle."

The researchers used the nanoparticles to deliver niclosamide, which is on the World Health Organization’s List of Essential Medicines, an index of the safest and most effective drugs in the world. Pan’s group previously found that niclosamide works on a particular gene-regulation pathway in cancer stem cells.

In the new study, “Targeted delivery of STAT-3 modulator to breast cancer stem like cells down-regulates a series of stem-ness genes,” published in the journal Molecular Cancer Therapeutics, the cancer stem cells lost their stemlike properties after treatment with the niclosamide-bearing targeted nanoparticles, making them less able to cause the cancer to recur or metastasize. The researchers also saw a significant decrease in overall cancer cell growth, both in the cell cultures and in the mice. By using an already-approved drug and easy-to-manufacture nanoparticles, Pan hopes that this system can become an accessible and cost-efficient treatment to prevent cancer recurrence in patients.
destroy elusive cancer stem cells

“We purposely used an extremely inexpensive drug. It’s generic, and we can mass produce it on a very large scale,” Pan said. “The nanoparticles are a polymer that we can make on a large scale. It’s highly defined and consistent, so we know exactly what we are delivering.

The rest of the process is just self-assembly.”

“This work also is important to future researchers working in the field of cancer stem cells,” said Santosh Misra, Illinois postdoctoral researcher, and first author of the study. “We described and confirmed the proteins and genes responsible for vital processes in these cells, and that is opening up new avenues to make better therapies.”

The researchers are working to create a combination therapy that can deliver drugs for the primary cancer, such as traditional chemotherapies, as well as targeted agents that can treat cancer stem cells. They also are testing the nanoparticle drug-delivery system in large animal models to bring it a step closer to the clinic.

The National Institutes of Health and the University of Illinois supported this work.

Welcome, Dr. Jin, to the Cancer Center

Zhaohui Jin, M.D., medical oncologist and hematologist at the Carle Cancer Center/Mills Breast Cancer Institute, recently joined the Illinois Cancer Center. Dr. Jin earned his M.D. at Peking Union Medical College in Beijing, China, and completed his internship and residency at Saint Barnabas Medical Center in Livingston, NJ. He completed fellowships in hematology and oncology at the University of Iowa, Iowa City, and advanced gastrointestinal oncology at Mayo Clinic, Rochester, Minn.
A drug that spurs cancer cells to self-destruct has been cleared for use in a clinical trial of patients with anaplastic astrocytoma, a rare malignant brain tumor, and glioblastoma multiforme, an aggressive late-stage cancer of the brain. This Phase Ib trial will determine if the experimental drug PAC-1 can be used safely in combination with a standard brain-cancer chemotherapy drug, temozolomide.

The trial is approved for patients who have seen their cancer progress after firstline therapy. This is an extension of an ongoing human Phase I clinical trial of PAC-1 alone in patients with various late-stage cancers. Phase I trials are designed to test the safety of new drugs in human patients.

PAC-1 is unusual in that it is able to cross the blood-brain barrier, a formidable obstacle to most anti-cancer drugs. The drug targets procaspase-3, an enzyme that is overexpressed in many cancer cells, said University of Illinois Chemistry professor Paul Hergenrother, who discovered PAC-T's anti-cancer effects more than a decade ago. After tests in human cell lines and rodents proved promising, Hergenrother and veterinary oncologist Timothy Fan, D.V.M., a professor of veterinary clinical medicine at Illinois, tested PAC-1 in pet dogs with a variety of naturally occurring cancers.

“Most cancers have elevated levels of procaspase-3,” Hergenrother said. “When it is turned on, procaspase-3 kills cells.”

Cancer cells override this normal cell-recycling pathway, however, he said.

“PAC-1 restores the activation of procaspase-3 and, because this enzyme is elevated in cancer cells, targets cancer cells over noncancerous cells,” he said.

PAC-1 has been evaluated in pet dogs with naturally occurring osteosarcoma, lymphoma and, most recently, glioma — a brain cancer similar to glioblastoma in humans. One 2016 study found that the combination of PAC-1 with doxorubicin, a chemotherapeutic agent that also is used in humans, saw tumor reductions in four of four dogs with lymphoma and in three of six dogs with osteosarcoma. The trials in dogs continue and, so far, have found PAC-1 to be safe, with few observable side effects apart from occasional gastrointestinal distress. The researchers report their latest findings in rodents and in dogs with brain cancer in the journal Oncotarget.

Dogs with certain naturally occurring cancers may be better than other animal models of human cancers because mice and rats used in many cancer drug-testing models must be implanted with human cancer cells to mimic specific types of tumors, Fan said.

“This requires that the rodents be immunocompromised to mitigate rejection of human cells,” he said.

“As such, most rodent tumor models do not faithfully recapitulate the tumor microenvironment — in particular, the body’s immune surveillance of the tumor,” Fan said. “Rodent models are limited, but they are still useful.”

Certain cancers in dogs are genetically similar to those in humans and respond to the same medications. Dogs also are more similar in size to humans, and so can be better models to evaluate how well drug agents perform on larger tumor masses.

“I look at pets with spontaneous tumors as being complementary to rodent models and recognize that not all discoveries in pet dogs will necessarily translate similarly to people,” Fan said.

The ongoing clinical trial of PAC-1 in human patients with late-stage solid tumors and lymphoma has shown that the drug is well-tolerated at tested doses up to 450 milligrams per day, said medical oncologist Arkadiusz Dudek, M.D, Ph.D., who chairs an advisory board for Vanquish Oncology, which is funding the trials.
The extension of the Phase I trial to brain-cancer patients begins with a PAC-1 dose of 375 mg per day and will increase the dose incrementally to test its safety in combination with the standard brain-cancer chemotherapy agent, temozolomide, Dudek said.

So far, the clinical trials of PAC-1 alone have seen no significant side effects in humans. None of the human patients in the first five dose levels of the single-agent trial has dropped out as a result of side effects, the researchers report. The team cannot report on clinical outcomes in a Phase I clinical trial, since such trials are designed to measure safety, not efficacy.

Surgery is a first-line therapy for anaplastic astrocytoma, followed by treatment with temozolomide, a chemotherapy drug that is one of the few effective treatments for brain cancer, Dudek said. Humans with glioblastoma multiforme usually undergo surgery to remove as much of the cancerous tissue as possible, followed by radiation and oral treatment with temozolomide.

"All three dogs had, at the very least, what we call a partial response, which means more than a 30 percent reduction in the tumor ..." — Timothy Fan

It is almost impossible to find and remove all glioblastoma cancer cells in surgery, however, Dudek said.

"Glioblastoma multiforme has this feature of spreading silently along the blood vessels inside the brain," he said. "That's a reason why most patients will unfortunately have disease coming back later on."

The median survival time for human patients with glioblastoma undergoing the standard treatment is about 15 months.

The three dogs in the glioma trial received daily oral doses of PAC-1 in combination with temozolomide and "curative-intent" radiation. Temozolomide is normally too expensive to use in canine patients, Fan said. The dogs tolerated the combination treatment very well and responded well to the therapy, he said.

"All three dogs had, at the very least, what we call a partial response, which means more than a 30 percent reduction in the tumor," he said. "And one of the dogs had a complete response, as identified with serial MRI scans, with a 100 percent reduction in the tumor mass 84 days after combination therapy."

Pretzel's brain tumor shrank more than 40 percent after treatment in a clinical trial for dogs with glioma.

Fan said a much larger study in dogs would be needed to determine whether the therapeutic effects were consistent and reproducible and to quantify how much PAC-1 contributed to the positive results.

Vanquish Oncology, a drug-development startup company Hergenrother helped found in 2011, has licensed the technology from the University of Illinois and is focused on moving PAC-1 into the clinic. As with any investigational agent, determining the true safety and efficacy profile of PAC-1 will take several years of human clinical trials.

Hergenrother is the chief science officer for Vanquish Oncology, Fan is vice president of preclinical development, and Dudek chairs the clinical advisory board. All have financial ties to the company.

The human clinical trials will be offered at the University of Illinois Cancer Center in Chicago; the Regions Hospital Cancer Care Center in St. Paul, Minn.; and Johns Hopkins University School of Medicine in Baltimore.

Hergenrother leads and Fan is a member of the research theme Anticancer Discovery: From Pets to People at the Carl. R. Woese Institute for Genomic Biology at Illinois.
Hormone therapy combination may benefit

Brazedoxifene is commonly prescribed in combination with conjugated estrogens to prevent postmenopausal osteoporosis. It is among a class of compounds known as selective estrogen receptor modulators, which bind to estrogen receptors and either promote or block their activity.

“Once women enter menopause and estrogens are lost, their metabolism is re wired, in the sense that they often start gaining weight, their bad cholesterol increases, their good cholesterol decreases and they may become pre-diabetic,” Madak-Erdogan said. “If they are prescribed a combination of brazedoxifene and conjugated estrogens, these symptoms often improve.”

“We wanted to see why this drug combination is helpful, so we used a genomewide approach where we looked at the gene expression profiles in the liver,” Madak-Erdogan said. “Because the liver is a major organ in metabolic control and regulates many of the chemicals in the blood, we looked at blood serum composition as well.”

The scientists fed 48 eight-week-old mice a high-fat diet in which 45 percent of the calories came from fat. To mimic the low-estrogen state of menopause, 40 of the mice had their ovaries removed when they reached 10 weeks old. The mice then were randomly divided into five groups, each of which was treated for six weeks with a different combination of conjugated estrogens and brazedoxifene.

The scientists measured the mice’s food intake and body weight weekly, and performed MRIs before treatment and at four weeks post-treatment to measure each animal’s whole body mass and lean body mass.

After the treatment period, the scientists euthanized the mice and weighed their adipose (fat) tissue, including their white adipose tissue — which stores energy in the form of lipids, and their mesenteric and perirenal adipose tissues, two forms of abdominal fat associated with the development of type 2 diabetes, insulin resistance, inflammation and other obesity-related diseases.
Using liver samples from each treatment group, the scientists examined the expression of various genes within the mice’s livers and measured the levels of nearly 150 metabolites in their blood, including cholesterol, free fatty acids and glucose.

Treatment with bazedoxifene and conjugated estrogens decreased the expression of genes along three parallel metabolic pathways that affect liver health — reducing lipid accumulation, levels of inflammation, and reactive oxygen species pathways in the liver, Madak-Erdogan said.

The researchers found that eight metabolites associated with the weight and health of the liver were down-regulated by the estrogen supplements — including several metabolites known to be misregulated in people with nonalcoholic fatty liver disease.

“Treatment with conjugated estrogens and bazedoxifene also prevented the weight gain that is often associated with postmenopausal decreases in estrogen and consuming a high-fat diet,” Madak-Erdogan said. “Animals in the treatment group had less fat mass and lower body weights than their peers in the control group. And their uteruses and mesenteric white adipose tissue weighed significantly less than those of their peers.”

Recent studies suggesting that hormone replacement therapy (HRT) increases women’s risks of reproductive cancers have prompted physicians to exercise caution in prescribing hormones — despite evidence that HRT may improve women’s metabolic functioning, lessen weight gain and lower their risks of serious health conditions such as cardiovascular disease and diabetes, Madak-Erdogan said.

“Although hormone therapy could reduce postmenopausal weight gain and many serious metabolic problems, physicians tend to avoid prescribing it because of concerns about elevating women’s risks of reproductive cancers,” Madak-Erdogan said. “Our study suggests that the combination of conjugated estrogens and bazedoxifene could improve metabolism without posing increased risk to the reproductive tissues.”

UI graduate students Karen Lee Ann Chen and Brandi Smith contributed to the research and were co-authors of the paper, along with Illinois alumnus Yiru C. Zhao, and Kadriye Hieronymi, who was a postdoctoral fellow at the university.

The research was supported by grants from the UI Office of the Vice Chancellor for Research, the Beckman Institute for Advanced Science and Technology, the U.S. Department of Agriculture National Institute of Food and Agriculture, and Pfizer Inc.
Study explores carbohydrates’ impacts on cancer recurrence and mortality

Consuming high amounts of carbohydrates and various forms of sugar during the year prior to treatment for head and neck cancer may increase patients’ risks of cancer recurrence and mortality, a new study reports.

However, eating moderate amounts of fats and starchy foods such as whole grains, potatoes and legumes after treatment could have protective benefits, reducing patients’ risks of disease recurrence and death, said lead author Anna E. Arthur, professor of Food Science and Human Nutrition at the University of Illinois at Urbana-Champaign.

In the study, researchers tracked the pre- and post-treatment diets and health outcomes of more than 400 cancer patients. Participants were followed for an average of 26 months after they were first diagnosed and treated for squamous-cell carcinoma of the head or neck; all were patients of the University of Michigan Head and Neck Specialized Program of Research Excellence. The study was published recently in the International Journal of Cancer.

Participants’ typical intake of food, beverages and supplements was assessed for the year prior to diagnosis and for one year post-treatment using the Harvard Food Frequency Questionnaire. Patients who consumed the lowest amounts of simple carbohydrates — which included refined grains, desserts and sugar-sweetened beverages — consumed about 1.3 servings daily, compared with about 4.4 servings by patients who were considered high intake.

Patients who consumed the most total carbohydrates and sugars — in the forms of sucrose, fructose, lactose and maltose — in the year preceding cancer treatment were at greater risk of mortality from any cause during the followup period, Arthur said.

Among the study population, the most commonly diagnosed cancers were in the oral cavity and the oropharynx, which includes the tonsils, the base of the tongue and surrounding tissues. More than 69 percent of participants were diagnosed when the disease was at stage 3 or stage 4. Patients’ average age at diagnosis was about 61.

During the followup period, more than 17 percent of patients experienced recurrence of their cancer, and 42 patients died from it. Another 70 participants died from other causes, according to the study.

Associations among carbohydrate intake and patient outcomes differed by cancer type and stage, Arthur said.

Higher mortality rates were found among people with oral cavity cancer who consumed the greatest amounts of total carbohydrates, total sugars and simple carbohydrates, but the researchers found no such associations among people who had oropharyngeal cancers.

Likewise, high carbohydrate consumption and glycemic load were significantly associated with increased risk of mortality from any cause among people with cancers.
in stages 1 to 3, but not in patients with stage 4 cancers.

“Although in this study we found that higher total carbohydrate and total sugar were associated with higher mortality in head and neck cancer patients, because of the study design we can’t say that there’s a definitive cause-effect relationship,” said Arthur, who also is an oncology dietitian nutritionist with the Carle Cancer Center at Carle Foundation Hospital in Urbana, Ill. “The next step would be to conduct a randomized clinical trial to test whether carbohydrate restriction has a protective effect on survival rates.”

“The next step would be to conduct a randomized clinical trial to test whether carbohydrate restriction has a protective effect on survival rates.” — Anna E. Arthur

Consuming a moderate amount — about 67 grams — of various forms of fat and starchy foods daily after cancer treatment appeared to provide some beneficial effects, lowering participants’ risks of mortality and cancer recurrence.

“Our results, along with the findings of other studies, suggest that diet composition can affect cancer outcomes,” said co-author Amy M. Goss, a professor of Nutrition Sciences at the University of Alabama, Birmingham (UAB). “We’d like to determine if this is true using a prospective, intervention study design and identify the underlying mechanisms. For example, how does cutting back on sugar and other dietary sources of glucose affect cancer growth?”

The study is believed to be the first to provide observational data on the therapeutic potential of carbohydrate-restricted, higher fat diets on head and neck squamous-cell cancers. Five-year survival rates among these patients continue to be low, in part because these cancers are often detected in later stages, putting patients at high risk of recurrence.

“This observational study is noteworthy because it focuses on a serious cancer that is difficult to treat, and little is known about how nutrition can best help a patient battling it,” said co-author Laura Q. Rogers, M.D., a professor of Nutrition Sciences at UAB. “This study reiterates the importance of additional intervention studies that test optimal diet recommendations for cancer survivors.”

The National Cancer Institute, the National Institutes of Health, and the U.S. Department of Agriculture National Institute of Food and Agriculture co-funded the study.

Additional co-authors on the paper were Wendy Demark-Wahnefried, William R. Carroll, Kevin R. Fontaine, Barbara A. Gower and Sharon A. Spencer, all of the University of Alabama, Birmingham; and Alison M. Mondul, Laura S. Rozek and Gregory T. Wolf, all of the University of Michigan, Ann Arbor. Yi Tang Chen of the University of Illinois also co-wrote the study.
King Li named fellow of American Institute for Medical and Biological Engineering

King Li, M.D., dean of the Carle Illinois College of Medicine, was admitted on April 9, 2018, into the AIMBE College of Fellows, comprised of the top two percent of medical and biological engineers. Li was nominated, reviewed, and elected by peers and members of the College of Fellows for outstanding technical and leadership contributions to biomedical imaging and its clinical translation.

College of Fellows membership honors those who have made outstanding contributions to “engineering and medicine research, practice, or education” and to “the pioneering of new and developing fields of technology, making major advancements in traditional fields of medical and biological engineering, or developing/implementing innovative approaches to bioengineering education.”

John Katzenellenbogen earns American Association for Cancer Research award

John Katzenellenbogen, Swanlund Professor of Chemistry, received the American Association for Cancer Research’s (AACR) award for Outstanding Achievement in Chemistry on April 17, 2018, at the association’s annual meeting in Chicago.

The AACR created the award in 2007 to “recognize the importance of chemistry in advancing cancer research,” and Katzenellenbogen is only the 12th recipient. The award is presented for “outstanding, novel, and significant chemistry research, which has led to important contributions to the fields of basic cancer research, translational cancer research, cancer diagnosis, the prevention of cancer, or the treatment of patients with cancer,” according to the AACR.

Katzenellenbogen and his research team have made major contributions to improve the diagnosis and therapy of breast and prostate cancers, and to illuminate the structure and function of nuclear receptors.

Rashid Bashir named 2018 Royal Society of Chemistry Fellow

Rashid Bashir, executive associate dean of the Carle Illinois College of Medicine and Grainger Distinguished Chair of Bioengineering has been selected as a Royal Society of Chemistry (RSC) fellow, in recognition of his research contributions in the broad field of BioMEMS and biomedical nanotechnology.

RSC fellowships are the highest level of membership in the organization, and eligibility is determined by having made significant impact in the chemical sciences and attaining a high professional standing.

Bashir’s research focuses on integrating engineering and technology with biology, and innovations of his research group include various lab-on-a-chip technologies, miniature biological robots (biobots), microfluidics, and point-of-care diagnostic devices, leading to the creation of multiple startup companies.

Saurabh Sinha one of six Urbana faculty members named University Scholars

Saurabh Sinha, professor of Computer Science, was recognized on January 31, 2018, as a University Scholar for his excellence in teaching, scholarship and service. The University of Illinois created the award in 1985, and it provides selected faculty with $15,000 for each of three years to be used to enhance the recipients’ careers.

Sinha is among the top researchers in the field of bioinformatics whose work aligns with the campus vision to excel in health and medicine. He has worked on computational models of the genetics of animal development, behavior and evolution, and is collaborating with researchers at the Mayo Clinic to develop the computational foundations of an emerging field called pharmacogenomics.
The Cancer Research Advocacy Group (CRAG) is a group of cancer advocates supporting and bridging the fundamental, translational, and clinical science at the Cancer Center at the University of Illinois at Urbana-Champaign. CRAG supports critical science and influences fundamental research, clinical trials, outreach, and education, as well as facilitates discussions among cancer survivors, researchers, and clinicians. This work informs research and creates a bench-to-bedside, bedside-to-bench information flow that advances the fight against cancer.

**CRAG visits IU Cancer Center and Komen Tissue Bank**

CRAG members recently visited the Indiana University Cancer Center, which is home to the Komen Tissue Bank. During this trip, members heard from Connie Rufenberg, a well-known advocate who is the founder of the Catherine Peachy Fund and was also instrumental in establishing the Komen Tissue Bank. The visit also included a talk about the tissue bank from Jill Henry, a tour from Natascia Marinon, and Hari Nakshatri’s description of the importance of the Komen Tissue Bank and how specimens could be utilized.
After graduating in May, several alumni from the first cohort of Cancer Scholars reflected on their time in the program. Here they share their thoughts and plans for the future with Pathways.

**What were your ambitions coming into the program?**

**Miranda Dawson:** “(I wanted) to perform research and maybe consider (doing) a Ph.D.”

**Pierce Hadley:** “At first (during the summer before college), I was not really sure what I wanted to do. I began to form an unbiased interest in research and medicine, but these aspirations did not become realized until receiving the invitation into the program. I saw a perfect opportunity to really explore the research space to see what exactly I wanted to do.”

**Madelyn O’Gorman:** “I wanted to add not only a focus but a challenge to my standard Bioengineering curriculum. Sometimes when you get caught up in the coursework of classes, especially freshman year, you lose a sense of the impact your work can have when applied in the real world. Through Cancer Scholars, I wanted to learn about and become a part of that application and the translation of what I was learning into viable treatments, technologies ...”

**Christian Presnall:** “(I wanted to) learn more about the mechanisms of cancer and to be a part of a lab that researches cancer.”

**Kinsey Schultheis:** “I wanted to work in cancer research.”

**How did your summer experiences influence your career path?**

**Dawson:** “My summer at the National Cancer Institute helped me realize my love for health-related microbes.”

**Hadley:** “My summer experiences were similar to the semesters, just continued research. I did not — (as did) some of my other cohort members — travel around to other institutions for research experiences.”

**O’Gorman:** “My summer experiences at Mayo Clinic allowed me to see the translational potential of my work firsthand ... I had independent projects where I was able to find a gap, address the medical issue, and formulate novel therapeutics and diagnostics that are now in clinical trials. Seeing and experiencing the entire process of idea to reality, or ‘bench to bedside,’ inspired me to pursue a career where I can apply my background in engineering at the research-patient interface and directly improve people’s lives.”

**Schultheis:** “I really enjoyed research, but I realized it moved too slow for me.”

**What did you learn from being a part of the CSP program?**

**Hadley:** “The CSP program initiated most of the success that I have today by transforming my mindset when I was a freshman. During our first class with Prof. Bhargava, he really took the time to answer my numerous questions and discuss..."
Cohort 1 begins new adventures

ideas that I had ... I felt extremely comfortable from then on to not just ask questions ... but to follow those questions with my own ideas and to search current literature to support or reject the idea.”

O’Gorman: “I learned how to think as an intellectual, to question the current bounds of healthcare technology and to formulate potential solutions for some of the most complex medical issues in the modern world.”

Presnall: “I learned a lot about the mechanism of cancer and the cutting-edge technology being researched to treat and diagnose cancer ...”

Schultheis: “I gained an understanding of various aspects of the cancer research fields.”

What impact did being a part of the CSP program have on you or your future goals?

Dawson: “It helped me start early getting the experience to qualify for a competitive Ph.D. program.”

Hadley: “Because I was not sure what I wanted to do before coming to college, CSP provided me a fast-track program for discovering my interests in research and medicine.

O’Gorman: “I will use the knowledge, critical thinking ability, and connections gained through CSP to move forward my career in translational medicine and make a difference in the lives of patients.”

Schultheis: “I gained an appreciation for the work going into cancer research. Additionally I realized how unique approaches are necessary to really improve cancer treatment outcomes.”

CSP THEN: First cohort of Cancer Scholars in Year One

Photos courtesy of Department of Bioengineering
The Graduate Cancer Community (GCCIL) debuted in Fall 2014 as a student-run group designed to bring together graduate students and researchers involved in cancer research from across various disciplines. The group also was designed to bridge the gap between on-campus research and the greater community as a whole. From its inception, the GCCIL has collaborated with local and national cancer researchers and has now embarked onto new horizons, charting new courses.

Following are reflections from four members of the founding team who related their GCCIL experiences for Pathways’ audience.

Why was establishing the Graduate Cancer Community at Illinois important?

SARAH HOLTON: It was important to me to create a space for people on campus who were studying cancer from multiple perspectives to come together and discuss their research findings. I felt that the biochemists and the molecular biologists should talk to the engineers and sociologists. I also wanted to create an open forum for discussion between cancer researchers and cancer patients.

KERIM KAYLAN: Establishing the GCCIL brought together students and faculty from a diverse set of departments to collectively explore all facets of this brutal disease, ranging from the biochemical to the humanistic. In doing so, we anticipated that members of the GCCIL would return to their own work with a fresh perspective on their own research problems — and perhaps (with) new collaborators, empowering more impactful work than they might have otherwise produced.

MATTHEW KOLE: There are a large number of different departments and disciplines at Illinois ... involved with cancer. Coming from a biochemistry background, I once had a very narrow view of what cancer research looked like. I am a more well-rounded researcher for having interacted with students of different academic backgrounds, and I would imagine that this could apply to all other students as well.

MICHAEL TENCATI: The Graduate Cancer Community at Illinois allowed me to maintain my interest in cancer research upon joining.
the University of Illinois. While I had a background in cancer cell signaling, this group opened my eyes to all the impressive work being done in the campus and the many different ways researchers are approaching the goal of improved outcomes in cancer patients.

What did you learn as a result of forming the group and developing activities?

HOLTON: I learned a lot about being a leader during this experience. Being passionate is not enough! You have to give people an idea and let them take ownership, and you have to understand that their vision may be different than yours.

KAYLAN: I personally see one of the key lessons of the activities of the GCCIL to be awareness of cancer not just as a disease but as a reflection of social practice (e.g., what we eat, whether we drink or smoke) and government policy (e.g., what checks and laws ensure our surroundings our safe for us?). Similarly, our treatment of cancer patients should be sensitive to the circumstances not always captured by objective, medical descriptions of the disease.

KOLE: It is surprisingly easy to ask ‘big-name’ researchers to help out with your project. While they might seem intimidating on paper, leaders in the field are very often willing to lend their time and expertise to enthusiastic students. These sorts of interactions make collaborative research — often seen as the difficult-to-obtain ideal — seem so much more achievable.

What is your most memorable GCCIL moment?

HOLTON: After our first symposium, we had a dinner (that included) a large group of breast cancer survivors who were able to speak with cancer researchers. After the dinner was over, one of the survivors came up to thank me for the opportunity to attend. It was everything I had wanted the community to become.

KAYLAN: Dr. John Condeelis of the Albert Einstein School of Medicine spoke on the tumor microenvironment of metastasis in 2014 as part of our Pioneers in Cancer Research Seminar Series. I still remember vividly his descriptions of macrophages moving and interacting with tumor cells ... His talk expanded my understanding of tumors as highly dynamic and changing landscapes — the very opposite of the static homogeneity to which one might default.

KOLE: The 2012 symposium featured an incredible number of inspirational speakers, but even more impressive was the response from the Illinois community. Both researchers and community members packed the event for two days straight — the definition of outreach in action.

TENCATI: I am very proud to have been a part of the Graduate Cancer Community at Illinois 2012 Symposium and see it as a great accomplishment. Despite little prior experience putting together a conference, our ... group of dedicated student volunteers managed to host one of the best conferences I have seen. ... This conference inspired me and will serve as the ideal for any future conference (in) which I am involved in planning.
**Cancer Scholars for Translational and Applied Research Teams**

**“Health-Related Quality of life (HR-QOL): Relationships among Dietary Patterns, Eating Behaviors, Nutritional Status, and Patient-Centered Survivorship Outcomes”**

Team (left to right): Anna E. Arthur, Sylvia Crowder, and Kalika Sarma

Head and neck cancer squamous cell carcinoma (HNSCC) caused by an etiologic factor, human papillomavirus (HPV), is associated with improved prognosis. While the overall rate of HNSCC has decreased in recent decades, the prevalence of HPV+-related HNSCC have increased dramatically. HPV+ HNSCC is associated with younger age and improved treatment response as compared to HPV-HNSCC. Therefore, the overall number of HNSCC survivors have increased over the last decade. Evidence suggests 90-100% of these patients are prone to acute (during/immediately following treatment) nutrition impact symptoms (NIS) as a result of tumor location and treatment received. NIS refers to any impediments likely to compromise oral intake. While most adverse events following treatment occur during the acute phase, some may fail to resolve, resulting in permanent, chronic challenges. Interventions are needed to ameliorate the prevalence and consequences of chronic NIS.

**“The Impact of Cholesterol on the Ovarian Tumor Microenvironment and Cancer Progression”**

Team (left to right): Erik Nelson, Sisi He, Marta Spain, and Ronald Kimball

Ovarian cancer continues to have a high mortality rate (53.8%) and a high recurrence rate (70%). Hence, there is an urgent need for new therapeutic or lifestyle strategies to prolong progression free survival (PFS). Importantly, epidemiological studies have implicated elevated cholesterol as a negative prognostic factor. Conversely, ovarian cancer patients taking cholesterol lowering drugs (HMGCoA-R inhibitors; statins) exhibit significantly increased PFS. Consistently, our preliminary data also shown increased ovarian tumor growth in mice fed a high-cholesterol diet. These observations strongly suggest that cholesterol impacts ovarian cancer progression. 27- hydroxycholesterol (27HC) is a primary metabolite of cholesterol, and its circulating levels are closely correlated with those of cholesterol. We speculated that cholesterol promotes ovarian cancer progression via the active signaling of 27HC. Our long-term goal is to understand the molecular mechanisms responsible for the link between high cholesterol and increased ovarian cancer recurrence. Our specific goal for this project is to explore the effect of elevated cholesterol and 27HC on tumor progression and the tumor microenvironment.
**“Fluorometric Microculture Cytotoxicity Assay for Personalized Medicine”**

Team: Maria Grosse Perdekamp (left), Evijola Llabani (right), and (not pictured) Paul Hergenrother

Metastatic cancers are extremely challenging to treat with an overall 5-year survival rate ranging from 2% (pancreatic cancer) to 55% (thyroid cancer). The number and location of the metastases present challenges for curative surgical resection, thus systemic chemotherapy serves as the backbone for cytoreduction at most of the sites. Multiple chemotherapeutics have been approved for advanced-stage cancers, but there are still cancers such as metastatic breast cancer that have no standard of care. Therefore, there is a critical need to determine the best drug for each metastatic patient. Here, we describe the establishment of an efficient method to assess ex-vivo the effect of the FDA-approved chemotherapeutics in fresh primary tumor samples, circulating tumor cells, and in metastatic tumor tissues.

**“Development of a microRNA Panel to Facilitate Prognosis Stratification and Personalized Nutritional Intervention in Colorectal Cancer”**

Team: Suparna Mantha (left), Laura Moody (right), and (not pictured) Yuan-Xiang Pan

Colorectal cancer (CRC) is the third most common cancer worldwide and accounts for roughly 50,000 U.S. deaths annually. Currently, endoscopy is the primary tool used to screen and diagnose CRC. Non-invasive techniques have tremendous potential to assist in identifying individuals at risk for CRC. We are investigating circulating microRNA (miRNA) as a CRC biomarker. MiRNA are 22 nucleotide sequences that regulate gene expression by inhibiting translation, destabilizing mRNA, and inducing mRNA degradation. Circulating miRNA are thought to be excreted from multiple organs and reflect a systemic state. Indeed, circulating miRNA profiles have been shown to be affected by both lifestyle factors such as diet and exercise as well as disease states such as cancer. We are examining the relationship between nutrition, cancer, and miRNA. By understanding the interplay between disease and lifestyle, we hope to show that circulating miRNA can be used as CRC biomarkers. Furthermore, we hope to elucidate possible dietary interventions that will promote overall health in CRC.

**“Determination of Tumor Aggressiveness by Real-Time Label-Free Nonlinear Imaging and Characterization of Tumor-Associated Microvesicles”**

Team: Yi (Edwin) Sun (left), Stephen Boppart (right), and (not pictured) Zheng (George) Liu

Tumor-associated extracellular vesicles (TEVs), as a special kind of cellular communication carrier, have been found to play vital roles in directing the invasion and metastasis of tumor cells. However, because human tumor microenvironments and TEVs significantly degrade or lose vitality over long periods of time after breast cancer surgical excision, lab-based studies with fresh human tissue specimens cannot provide accurate TEV information. By designing and building a portable label-free nonlinear imaging system, we have been able to conduct intraoperative imaging of unperturbed breast tissues immediately after excision. Various features of the breast tumor microenvironment from our images are characterized to indicate tumor progression, invasiveness, and tumor grades. Particularly, TEV counts from intraoperative images correlate well with tumor aggressiveness and closest margin distance. Acquisition and interpretation of these intraoperative image data not only provide assessment of the human tumor microenvironment, but also offer the potential to intraoperatively assess tumor margin distance and determine tumor aggressiveness.
The TiMe cohort hosted the second annual Tissue Microenvironment (TiMe) Day Symposium and Poster Session on April 13, 2018, at the Beckman Institute for Advanced Science and Technology. More than 70 people attended, representing 14 departments across campus and industry guests. The symposium explored different aspects of the tissue microenvironment through six faculty research talks.

Lani Wu and Steven Altschuler from the University of California, San Francisco, delivered the keynote address as guest faculty speakers. Altschuler and Wu spoke about tissue patterning and dysregulation in gut epithelium and the proliferation-senescence cell fate decision.

Illinois faculty provided additional discussions about the tissue microenvironment with plenary talks by Erik Nelson on “Cholesterol, its Metabolites and the Tumor Microenvironment,” Stephen Boppart on “Shedding Light on the Dynamic Tumor Microenvironment,” and Jefferson Chan on “Development of Photoacoustic Probes for Non-invasive Imaging of Tissue Environments.” Chandrakjit Bajaj from the University of Texas at Austin and a Cancer Center at Illinois (CCIL) External Advisory Board member spoke about his research on infrared imaging, “The Promise of Machine Learning for Infrared Spectroscopy.”

Peter So from the Massachusetts Institute of Technology, and Bruce Wheeler from the University of California, San Diego — both CCIL External Advisory Board members — provided additional support, questions and comments throughout the event.

Hailey Knox, Sisi He, Sushant Bangru and Whitney Sinclair gave graduate student rapid talks to conclude the research portion of the symposium.

Twenty-four participants presented during the poster session and competition, and Thomas Gaj and Shannon Sirk selected the top posters. Competition was so fierce that the judges were unable to choose only three winners, so the day closed with four taking the top honors: Hailey Knox, Liqian Ma, Phuong Le and Whitney Sinclair.

The event was sponsored by NIH T32 Award T32EB019944, the Cancer Center at Illinois, and the Beckman Institute, with additional support from the College of Engineering, Carl R. Woese Institute for Genomic Biology, and the Department of Materials Science.
Reception for Illini 4000

The Cancer Center at Illinois (CCIL) sponsored a “welcome home” reception on June 5, 2018, at the Beckman Institute to honor the Illini 4000 cycling team as they bike across the United States to raise awareness of cancer and raise funds for cancer research.

“The Illini 4000 is a non-profit organization dedicated to documenting the American cancer experience through the Portraits Project, raising funds for cancer research and patient support services, as well as spreading awareness for the fight against cancer through an annual cross-country bike ride,” said Margaret Browne Huntt, CCIL associate director.

The team began their 2018 trip in New York City on May 18 and will end in San Francisco on August 2.

A short program at the reception included welcoming remarks by David Kranz of the Cancer Center, and recognition from Chancellor Robert Jones, who rode into town with the Illini 4000 students. Jones thanked them for their commitment, passion and hard work and encouraged the audience to “Join our team! Support our team! With the fortitude and sheer sweat and laser-focused determination that is demonstrated by these Illini 4000 students — and by dedicated faculty, researchers, students, clinical partners and community members working together every day — there is no doubt we will be victorious!”

Bill Brown of the Urbana City Council, on behalf of the twin cities of Champaign and Urbana, announced a joint proclamation designating June 5, 2018, as “Illini 4000 Day.” The team thanked everyone, acknowledged Neutral Cycle for its sponsorship, and asked the crowd to follow the cyclists as they ride across the nation by visiting the website at illini4000.org.

Event highlights continued on page 30 ...
The Nexus: Social and Behavioral Science Research Institute and the Cancer Center

More than 45 faculty members participated in the first workshop sponsored by the Cancer Center and the Social and Behavioral Science Research Initiative (SBSRI) on April 25, 2018. The workshop was designed to bring together social scientists and cancer researchers across all disciplines to provide an interactive forum to facilitate synergistic collaborations and explore the resources and services that would spearhead innovative cancer research endeavors.

Brent Roberts, SBSRI Chair, and Margaret Browne Hunt, Cancer Center at Illinois associate director, presented opening/welcoming remarks and the introduction. The workshop facilitators — Barbara Fiese, Family Resiliency Center director; and Hillary Klonoff-Cohen, Saul J. Morse and Anne B. Morgan Professor in Applied Health Sciences and Director of the MPH program — provided the workshop overview, which led into a series of lightning talks by Anna Arthur, assistant professor of Nutrition; Erik Nelson, assistant professor of Molecular and Integrative Physiology; and Florin Dolcos, associate professor of Psychology. Individuals then broke up into groups and discussed topics of interest. Rohit Bhargava, CCIL director, closed out the workshop with a discussion of the next steps alongside the SBSRI Chair.

Prairie Dragon Paddlers: “Sing for the Health of It”

The Prairie Dragon Paddlers, Illinois’ first breast cancer survivor dragon boat team, held a competition, “Sing for the Health of It,” on Thursday, April 5, 2018, at the City Center in Champaign. Ten area finalists competed in a variety of genres to win the grand prize trip to Nashville. Performances in support of the cause included a duet by Champaign Mayor Deb Feinen and Urbana Mayor Diane Marlin, singing “Anything You Can Do I Can Do Better;” a group from the Cancer Center at Illinois led by Rohit Bhargava, the center’s director; and Lester Fahrner, M.D., who sang with several of his Christie Clinic colleagues.
The Role of Data, Computing, and Visualization in the Future of Cancer Research

Cancer research is becoming more reliant on data, computing, software, and visualization. At Illinois, the National Center for Supercomputing Applications is a hub of transdisciplinary research and digital scholarship where collaborators can unite to address grand research challenges like cancer. This March 14th workshop explored resources and services available to campus researchers and partners to help address computing and data challenges, and it fostered discussion of collaborative opportunities for scientists, engineers and scholars.

Olga G. Nalbandov Lecture: A Synthetic Biology Approach to Epigenetic Therapy for Cancer

On March 2, Karmella A. Haynes, assistant professor in the Ira A. Fulton School of Biological and Health Systems Engineering at Arizona State University, spoke about cell and tissue engineering.

Researchers have more ability than ever before to control genes and manipulate cell and tissue development. Haynes focused on emerging synthetic biological approaches to the advancement of new cancer therapies. She highlighted that recombinant DNA technology has empowered scientists to control gene expression at will. Fusion transcription factors (TF) are customizable proteins that can activate and repress virtually any target gene of interest. Typically, the mode of target site recognition is an interaction of the TF peptide (e.g., Gal4, TAL, ZF, etc.) or an RNA adapter (i.e., CRISPR) with DNA at promoters or enhancers near target genes. She discussed her current work representing a unique approach to TF targeting: the use of fusion proteins that bind epigenetic marks on histones rather than DNA sequences and talked about her previous work where her lab developed and characterized the “Polycomb-based transcription factor” (PcTF), a fusion protein that reads histone modifications through a protein-protein interaction between its N-terminal Polycomb chromodomain (PCD) motif and trimethylated lysine 27 of histone H3 (H3K27me3).

Faculty Seminar Series, Spring 2018

MAY 3
Saurabh Sinha, professor, Computer Science
“Knowledge-Guided Analytics for Cancer Research”

Joseph Irudayaraj, professor, Bioengineering

Prasanth Kannanganattu, associate professor, Cell and Developmental Biology
“Role of Long Noncoding RNAs (IncRNAs) in Cancer Progression”

APRIL 5
Ling-Feng Chen, professor, Biochemistry
“From Bench to “BET”side: Regulation of NF-kappaB Signaling in Cancer”

David Shapiro, professor, Biochemistry
“Targeting Breast and Ovarian Cancer through ER-Mediated Hyperactivation of the Unfolded Protein Response”

Hong Chen, associate professor, Food Science and Human Nutrition
“MicroRNA as Markers for Nutritional Interventions in Cancer Patients”

MARCH 1
Roy Dar, assistant professor, Bioengineering
“Engineering Fluctuations in Gene Expression for Biasing Cell-Fate Decisions”

Dipanjan Pan, associate professor, Bioengineering
“In Silico to In Vivo Molecularly Targeted Imaging and Therapy for Liver Cancer”

Paul Hergenrother, professor, Chemistry
“Traversing the Valley of Death in Anticancer Drug Discovery”

FEBRUARY 1
Aleksi Aksimentiev, professor, Physics
“Modeling DNA for Cancer Research: Detecting a Cause and Building a Cure”

Andrew Smith, assistant professor, Bioengineering
“Counting Molecules in Cancer Cells and Clinical Biospecimens with Next-Generation Quantum Dots”

Shuming Nie, professor, Bioengineering
“Image-Guided Minimally Invasive and Robotic Cancer Surgery: Opportunities”

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Cancer-related events on campus—cont’d.

Dr. Oguzhan Alagoz, invited speaker

On February 26, the Tissue Microenvironment class was privileged to talk with Oguzhan Alagoz, professor in Industrial and Systems Engineering and in Population Health Sciences at the University of Wisconsin-Madison. Alagoz was invited to speak to the ISE Graduate Seminar students but graciously took time to also speak to the TiMe students about his experience in data informatics. Alagoz discussed his work on developing a mammography screening schedule for different populations based on prior screening history and personal risk characteristics of women. Although data analysis and tissue engineering seem far removed, students were able to ask about the specific markers the screening looked at, as well as how engineering and the hospital setting can be intertwined. Alagoz also serves as the director of NIH-funded Institute for Clinical and Translational Research (ICTR)-Simulation Center, as well as the associate director for the Wisconsin Institute for Healthcare Systems Engineering (WHSE).

Seminar: “Is Computational Genomics the Key to Future Breakthroughs in Cancer Research?”

The interdisciplinary and collaborative field of computational science uses advanced computing abilities including software, algorithms, networks and storage to tackle challenges in engineering, and biological and social sciences. Cancer research, in particular, is becoming more and more dependent on computational sciences to create problem-solving methodologies and tools. This half-day seminar on March 2 showcased successful applications of computational tools and identified computational resources to assist researchers.

Grady Carlson lecture: “Phenoptics for Immunoncology”

Grady Carlson is a field applications scientist with experience in basic and translational pathology-based research, with a focus on assay development for detection and characterization of biomarkers in tissues and circulating tumor cells. Carlson joined PerkinElmer from the Baylor College of Medicine, where he researched breast cancer metastasis as a postdoctoral associate. Carlson noted that, to advance the understanding of disease mechanisms in cancer, it is critical that one sees everything the tumor has to show. With his team’s phenoptics platform, one can visualize and measure tumor cells and multiple immune-cell phenotypes simultaneously in FFPE tissue. Phenoptics integrates multiplexed immunohistochemistry and imaging to quantitatively capture systems biology data with cellular detail. It reveals multi-parameter cellular expressions and interactions while retaining spatial context, offering insights into the complexity of immune cell-cancer interactions.

Lecture by SimBioSys’s John Cole

You wouldn’t put a brain cell in a petri dish and expect it to think, and you wouldn’t put a lung cell in a liver and expect it to help filter blood, says John Cole, co-founder and director of scientific development for SimBioSys Inc. Why? Because cellular function depends on both the cell’s internal state (what genes are expressed, or if there are any mutations, etc.), and its broader context (what other cells and chemicals are around). In cancers, both of these are disrupted, and drug-development research focused to heavily on the internal cellular state has proven to be expensive and prone to high failure rates. SimBioSys is developing a software environment that enables computational biologists to integrate -omics and imaging data in order to build unified 3D models of cancers and their surrounding tissues, with the hope that it aids in the discovery of new drug targets and investigates why some drugs fail and others succeed.

Watch for these coming 2018 events:

- Lecture Series, Fall
- Faculty Seminar Series, September
- Cancer Center Annual Meeting, October
- researchStart applications accepted, December