EVERYONE HAS A CANCER STORY. THAT’S WHY WE DO THE RESEARCH.
Greetings to friends and alumni of the School of Molecular and Cellular Biology at Illinois. A change of guard in the School leadership took place last August as I became the new director. I would like to acknowledge the past leadership of Dr. Stephen Sligar, who shepherded the School through fiscal challenges and led it during a decade of notable scientific advancements.

It is with great pride that I share this magazine with you. It highlights the inventive efforts of our faculty as they shoulder cancer. In his Pulitzer prize-winning book The Emperor of All Maladies, Dr. Siddhartha Mukherjee calls cancer the most elemental and magisterial disease known to our species. In relentless battle with this malady, researchers keep inventing and reinventing, learning and unlearning strategies. Our MCB scientists are exploring new avenues to develop effective treatments for this complex disease. They are playing important research and leadership roles in the newly established Cancer Center at University of Illinois at Urbana-Champaign and contributing to the Center’s goal of achieving national recognition and status.

This magazine also highlights the success of our research leaders in propelling bright minds and nurturing the careers of future scientists. Our graduates, with strong experience in research and innovation, are awarded postdoctoral fellowships in major laboratories that lead to a career in academia. They are also pursuing exciting employment opportunities in pharmaceutical industry or the government. Our undergraduates, equipped with fundamental, critical, and analytical skills imparted by MCB’s curriculum, are moving on to opportunities for further education, most notably medical school and graduate education in frontier areas of modern biology. The stories included in this magazine are a sample of the valuable development of both graduate and undergraduate students in our research laboratories.

We are committed to furthering MCB’s ability to attract and educate excellent undergraduate and graduate students, to support the continuing achievements of our faculty, and to promote MCB’s contribution to the overall distinction of the University. A testimony to our strong commitment to undergraduate education is the creation of a new learning center space, for which an update is included. The nurturing environment of learning and discovery in the School of MCB helps build successful careers. Many of our alumni have made great contributions to their fields with the strong foundation of an MCB undergraduate degree.

Alumni really are the key to MCB’s and the University’s success in all areas. Your accomplishments, distinctions, and awards are a source of pride and a beacon for future scientists. The diversity of alumni career trajectories gives our students hope and a broader vision of scientific contributions. Alumni also make it possible to retain and honor excellent faculty and students by supporting their research and distinctions. On behalf of our faculty and students, I thank you for your support, and importantly, your continued engagement in our academic mission.

The research conducted in our school solils the answers to fundamental questions about how organisms work at the molecular and systems level, how they evolve, and the resultant implications for life, health, and disease. Our science is foundational, translational, and transformative. I hope you will enjoy reading about the exciting work being accomplished by our faculty, students, and alumni.

Milan K. Bagchi
Director
School of Molecular and Cellular Biology
Several MCB faculty members are part of an exciting new campus unit known as The Cancer Center at Illinois. The Center is an interdisciplinary collaborative hub with more than 100 faculty members from departments ranging from kinesiology, human development and nutrition to electrical and computer engineering, as well as graduate students and postdoctoral researchers pursuing “cancer-related research.” The group has functioned as the Cancer Community at Illinois since 2011.

“Campus support is always helpful to have,” said Benita Katzenellenbogen, Professor of Molecular and Integrative Physiology and of Cell and Development Biology, of the center’s formal declaration. “It attracts outside money and it attracts additional colleagues. It allows for increased basic, translational, and clinical interactions.”

Erik Nelson, assistant professor of molecular and integrative physiology, agrees. “As a group, we are stronger than as individuals.”

However, cancer is a moving target. Often, once a cancer is diagnosed, the disease progresses to more advanced stages, and treatments become less effective and often combining two or more agents or approaches is best.”

MCB faculty are integral to the success of the Cancer Center by driving its scientific and education programs, as well as collaborations. I am grateful for their service on our steering committee and leadership in establishing the center,” said Bhargava.

Under the auspices of the Cancer Center, faculty members have hosted seminar series, meetings and poster sessions to increase campus networking and connections with other places battling cancer, including the Mayo Clinic and Carle Hospital.

MCB faculty collaborate with one another and, they collaborate with imaging experts who have developed “spectroscopic expertise and CRISPR” imaging modalities have become both more common and more specialized, the creation of the Cancer Center will further streamline and catalyze efforts and strengthen collaborations across campus, across the country, and even around the world.

“The next step for the center is to get National Cancer Institute (NCI) accreditation as a cancer center. As of 2017, there were 49 Comprehensive Cancer Centers, 13 Cancer Centers, and seven Basic Laboratory Cancer Centers. The University of Illinois is applying to be a basic laboratory cancer center. If it gets accredited, it would be the only such center in Illinois. Receiving the NCI-designation places cancer centers among the top four percent of the approximately 1,500 cancer centers in the United States, according to the NCI.

“This is a rigorous process, with different categories of designation,” said Nelson, who says the campus group is going for a basic cancer center designation similar to the one that MIT has.

An external advisory board, comprised of internationally renowned experts, visited the campus recently to evaluate the program and were very impressed with the work being done.

“We are very enthusiastic by what we’ve done so far,” said Nelson. “Both with the science we are doing and the current level of collaborations and our productivity... We showed that we are already rolling on many cancer-related interdisciplinary collaborations and we showed that, while we have some great core facilities, the University of Illinois is positioned to create additional unique and cutting-edge facilities, including one for tumor engineering and phenotyping.”

In addition to providing more translational opportunities, The Cancer Center provides special opportunities for students. One such initiative, OStar (Scholar-Translational and Applied Research initiative) scholarships for graduate students, pairs a student with a basic cancer research expert as a primary mentor, together with a clinician. The scholarship is jointly funded by Carle and the University.

“This is one of several student opportunities offered through the Cancer Center. Another one, Research@Ill, is targeted at high school students, who work full time with faculty mentors, including Nelson and MCB professor Kannanganattu Prasanth, who are established cancer researchers.

The new Cancer Center is, above all, a highly collaborative undertaking. And, because MCB faculty members have a long history of extensive and interdisciplinary collaboration, it is a perfect fit. Katzenellenbogen, for example, collaborates with numerous groups, not only on campus, with faculty in bioengineering, food science and nutrition, but also in Korea and France and across the United States.

In her view, interdisciplinary collaboration is, without a doubt, a key way to advance the science of cancer. There is no down side. “With stronger science, we make better progress,” she says. The Cancer Center is part of that progress.”
they have figured out ways to target specific mechanisms at work, the more targeted those treatments have become, meaning that they effectively treat the cancer with greatly reduced side effects. A panacea. Even with the exciting results of targeted treatments, some cancers figure out a way to fight back? Those cancers that become drug resistant? Those cancers that go rogue, so to speak. Katzenellenbogen’s lab has found an increase in the expression of the transcription factor FOXM1, another “aggressiveness factor.”

In one recent collaboration with oncologists in Korea, Katzenellenbogen’s lab observed an upregulation of FOXM1 in treatment-resistant cancers. Typically, FOXM1 is only found at significant levels during embryonic development. When it shows up in cancer, it makes the cancer much more robust and difficult to treat. “High levels of FOXM1 are associated with proliferation, invasiveness, and resistance to treatments,” she added.

As with the constitutively active estrogen receptor project, Katzenellenbogen is collaborating with John Katzenellenbogden’s laboratory to develop small molecule inhibitors that can effectively block FOXM1. For example, they are looking for compounds that might block FOXM1’s interaction with DNA or in some other way block its activity. Some inhibitory molecules have been identified previously, but they are not active enough or are not selective enough, meaning they interfere with too many other cell activities, says Katzenellenbogen. One finding that has Katzenellenbogden intrigued is that FOXM1 upregulation is present in triple-negative breast cancers. These are breast cancers that do not respond to hormonal therapies, including tamoxifen and aromatase inhibitors. If the action of FOXM1 can be blocked, that might represent a possible breakthrough in treatment for this especially challenging subgroup of cancer, which comprises about 15% of all breast cancers.

Katzellenbogden rarely stops to consider how far the field has come, but when she does, it is to appreciate that cancer is no longer the disease one survives; they are not always lethal. The numbers of people effectively treated even 20 years after diagnosis continues to increase.

Of the ER positive cancers that metastasize or resist treatment, 30-40% of them have these mutated ERs. So, finding a way to inhibit them would be a major breakthrough.

Benita Katzenellenbogden Lab

Hitting the (Moving) Target of Drug Resistant Cancers

by Deb Aronson

Benita Katzenellenbogden has delved into the causes and treatments for breast cancer and other hormone-dependent cancers for virtually her entire career. Her tireless work in the field has established her as a world-renowned expert. Lately, Katzenellenbogden, Professor of Molecular and Integrative Physiology and of Cell and Developmental Biology, and her research group are “very much focused on targeted therapies.”

Cancer treatment approaches have changed in the past decades. As researchers learn more about cancer biology, including identifying subtypes that respond to different treatments, they have figured out ways to target specific cancer cells with a more precise approach. And the more they understand about the mechanisms at work, the more targeted those treatments have become, meaning that they effectively treat the cancer with greatly reduced side effects. Of course, targeted therapies are not always a panacea. Even with the exciting results of targeted treatments, some cancers figure out a way to make a comeback. Why and how do cancers fight back? Those cancers that become “treatment-resistant” currently present one of the major challenges in the field. Working to describe the biology by which cancers change in response to these targeted therapies, and looking at certain “aggressiveness factors” that block treatment has motivated Katzenellenbogden's lab for several years.

Several effective treatments for hormone receptor (HR)-positive cancers (which comprise about 70% of initial breast cancers) block the action of estrogen, turning the estrogen receptor (ER) off and thus thwarting the cancer. In cases where this treatment stops working, it is often because the ER becomes “constitutively active,” which means it no longer needs estrogen to turn on. This is one so-called aggressiveness factor, when the ER goes rogue, so to speak. Katzenellenbogden’s lab has been working to understand how it is that the ER becomes constitutively active and then why that makes the cancer more resistant to treatment. Her lab is collaborating with John Katzenellenbogden and his laboratory in the Department of Chemistry to develop anti-estrogen molecules that might be able to inhibit the activity of these mutated estrogen receptors.

“The ER positive cancers that metastasize or resist treatment, 30-40% of them have these mutated ERs,” said Katzenellenbogden. So, finding a way to inhibit them would be a major breakthrough. In another recent finding that holds promise for some of the most difficult-to-treat breast cancers, Katzenellenbogden’s lab has found an increase in the expression of the transcription factor FOXM1, another “aggressiveness factor.”

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Katzellenbogden rarely stops to consider how far the field has come, but when she does, it is to appreciate that cancer is no longer the disease one survives; they are not always lethal. The numbers of people effectively treated even 20 years after diagnosis continues to increase. Through better subtyping of cancers we know better the risk of recurrence so people are better monitored and even treated differently.

And that is progress worth celebrating.

(Professor Katzenellenbogden gratefully acknowledges research support from the Breast Cancer Research Foundation, the John and Mary Lelandfield Cancer Research Fund, and the National Institutes of Health.)

Dr. Benita Katzenellenbogden, Swanlund Professor of Molecular and Integrative Physiology and Cell and Developmental Biology. Photo by L. Brian Stauffer
Harnessing and Boosting T-cells to Fight Disease
David Kranz Lab

by Brian Wallheimer

Last summer, the U.S. Food and Drug Administration approved the first gene therapy treatment for cancer, giving hope to patients who have not benefited from more traditional drug therapies. It’s a treatment decades in the making, and some of the early stage work was done in the lab of David Kranz at the University of Illinois.

Kranz, the Phillip A. Sharp Professor of Biochemistry in the School of Molecular and Cellular Biology, has been involved in T-cell research since working as a postdoctoral researcher at the Massachusetts Institute of Technology, involved in early discoveries about how T-cells might be used to combat a host of diseases, including cancer. Prior to this, he trained as a graduate student at Illinois under Ed Voss, who at the time was the only immunologist on campus.

T-cells are involved in the body’s immune response, destroying foreign or damaged cells and viruses. In some cases, T-cells don’t recognize and attack like they’re supposed to. Kranz has spent decades modifying and improving the receptors on T-cells to help them better target diseases and pathogens, improving the body’s immune response.

“Immune therapies are the biggest class of new therapies for cancer by far over anything else,” he said.

Kranz’s early work at MIT included proof-of-concept work for using T-cells to fight diseases like cancer. He and colleagues now know that T-cells can be reprogrammed to fight cancer.

At Illinois, Kranz was involved in developing bi-specific antibodies. The proteins bind to T-cells on one end, and then attach to cancer cells on the other. The antibodies essentially act as guides for T-cells to find cancer cells and then do their natural jobs in destroying those cells.

“People constantly develop abnormal cells, and T-cells recognize and eliminate them. We never know it’s even happening. But with cancer, those T-cells don’t do their jobs,” said Kranz. “We have been looking for ways to harness T-cells to act against cancer, and bi-specific antibodies are one way we’ve done that successfully.”

There is currently one FDA-approved bi-specific antibody developed to treat lymphoma. Many others are in clinical trials.

Since the late 1990s, Kranz’s lab has also been working with T-cells for recently approved gene therapy treatments. The technique, called CAR (chimeric antigen receptor) or TCR (T-cell receptor) T-cell therapy, involves removing a patient’s T-cells, engineering the cells to express receptors so they will recognize cancer cells, and then putting them back into patients to attack those cancer cells.

“Now you’ve basically armed the patients with billions of T-cells that can recognize the cancer,” Kranz said.

The Kranz lab started working on ways to modify T-cell receptors, some of the basic work that has led to today’s cutting-edge treatments.

“We developed the methods that you could actually try to engineer and improve these receptors,” Kranz said. “We’ve received 17 patents, which include methods of engineering receptors as well as some of the receptors themselves.”

Many of the patients receive around a technique called “yeast display,” a technique for engineering proteins using the cell walls of yeast to single out antibodies. The technique allowed researchers to create millions of mutated antibodies within days, and then use high-throughput screening to select the best candidates.

Kranz and K. Dane Wittrup (now at MIT), who had been a professor in chemical engineering at Illinois, founded a company called BioDisplay Technologies in 1998. The company used yeast display to develop better antibodies or other proteins such as T-cell receptors. The company was acquired by Abbott Laboratories in 2001.

In 2008, Kranz again founded a biotechnology company called ImmuVen. ImmuVen opened in EnterpriseWorks, initially focusing on the development of vaccines against cancers. Vaccines are often thought of as a preventative measure against a disease, but the goal of the work is to use them as active therapies.

An overarching goal of these types of therapeutic approaches is to generate memory T-cells in cancer patients. Typically, these cells develop after an immune response to infectious agents, and they kick into action if the pathogen is reintroduced. Children who contract chicken pox, for example, have memory cells that play a role in keeping them from getting the illness again.

Kranz believes T-cells can do the same thing with cancer.

“We want to boost the patient’s own T-cells in the body, activating enough of them to ‘seek and destroy’ the cancer and then control some of the T-cells into long-lasting memory cells,” Kranz said. “If you have memory cells and the cancer comes back, a patient would have the T-cells that can eliminate the cancer.”

Kranz is working to identify the best cancer antigens to target with potential vaccines. He is now part of the Anticancer Discovery from Pits to People theme at Illinois’ Carl R. Woese Institute for Genomic Biology. Like many scientists whose work touches on cancer, Kranz wasn’t originally focused on the disease. Instead, he was fascinated with immunology and the ability to use the body’s natural defenses to treat or cure diseases and lessen or eliminate severe side effects such as those experienced by patients receiving chemotherapy.

“The promise of using immunology to fight cancer was clear in the 1980s. You have the potential to let the immune system go in and recognize only the cancer cells and not the healthy cells, diminishing those side-effects,” said Kranz.

Over the years, Kranz studied basic molecular immunology and applied his research to autoimmune diseases but shifted focus to cancer because he saw the field can have positive outcomes for patients and families, including his own.

“As a disease, the need for cancer therapies is so significant that we decided to focus more on it,” Kranz said. “In immunology, we just happened to be working on things that you could immediately see would have an impact on cancer.”
Enormous strides in fighting breast cancer have been made over the last few decades, with drugs that target estrogen production having been made or approved. The survival rates have improved. “This is the way of cancer,” says Shapiro. “It only very rarely can be eradicated with a single drug. The normal thing in cancer is that typically the tumors become resistant so you have to come up with different sequential treatments.”

Shapiro began his independent research career interested in the basic mechanism of how hormones work. As his work and the work of others began to illustrate how much estrogen affected cancer cells, he shifted his focus to cancer. “Like many others, Shapiro has lost close family members, including his mother, to cancer.”

Cancer research is a crowded field. Shapiro has always been willing to seek out novel ways to look at and attack cancer. Recently that has involved screening tens of thousands of small molecules, not unlike looking for a needle in a haystack. “About six years ago, I realized that there were 200,000 papers on estrogen and in order to discover something fundamentally different we’d have to try a new approach,” he says. With the help of colleagues experienced in using the high-throughput screening facility, Shapiro’s group screened 150,000 small molecules.

“Instead of looking at small molecules whose actions we could explain with current knowledge, we’d actually study the small molecules whose actions we could not explain, with a view to identifying entirely new ways estrogen works,” he says. “It turned out, happily for us, that the most effective molecule out of the 150,000 we screened worked in this exciting new way and led us to a new pathway of estrogen action in cancer.”

Left: Data-derived computer generated model of the binding of the preclinical anticancer drug, BHPI, to its binding site near one end of the estrogen receptor (ER). BHPI binds to ER at a different site than estrogen, tamoxifen and other antiestrogens (model by Mara Livezey). BHPI fits tightly into a binding cavity on the surface of ER. Unlike tamoxifen, BHPI kills breast cancer cells by acting through ER to induce lethal hyperactivation of a normally protective stress response pathway.

BHPI was the only effective compound from the screen that works through the unfolded protein response (UPR) pathway. The UPR is a protective pathway and is turned on by stress, such as an unfolded or misfolded protein. Cancer cells use this same pathway to protect themselves from being killed by toxic anticancer drugs. If the protective pathway becomes overwhelmed, i.e. more unfolded proteins than it can handle, it reverts to a very high level, triggering a self-destruct process in the cells. Shapiro’s lab showed that estrogen bound to ER induces a moderate and protective activation of the UPR pathway in breast and ovarian cancer cells.

“BHPI hijacks this pathway and works through ER to throw the UPR pathway into overdrive, converting it from protective to lethal,” says Shapiro.

BHPI works even better in cancer cells resistant to anticancer drugs, because the UPR pathway is already turned on as part of the way cancer cells block the toxic action of anticancer drugs. This means that when BHPI turns the UPR up even more, those cells will tip over into the cell death pathway faster than in cells that are not under stress. Because the UPR is typically turned off in normal cells, when BHPI turns it on, it does not tip the UPR activation into the lethal range. This makes healthy cells are not affected, says Shapiro.

BHPI also works by shutting down proteins that cells use to pump foreign compounds out of the cell. One way cancer cells become resistant to anticancer drugs is by using these pumps, called multidrug resistance pumps, to pump anticancer drugs out of the cells. Despite years of effort, drugs that directly block the action of the pumps have failed clinical trials. BHPI targets the multidrug resistance pump in a different way. One of BHPI’s actions is to open up a compartment within the cell that stores calcium. When the cell becomes flooded with calcium, protein pumps snap into action, pumping the calcium back into the storage reservoir. But because the calcium continues to leak back into the body of the cell, the protein pumps burn through all the cells’ energy. Since the multidrug resistance pump also needs energy to work, it basically runs out of gas, spurring the cells to a stop.

Shapiro’s lab, in partnership with Nelson’s lab, used a mouse ovarian cancer model that is highly resistant to other drugs. They showed that not only did BHPI survive the multidrug resistance pump, it enabled the original drug to work again, since it was no longer getting pumped out of the cancer cells.

Yet another way cancer outwits anticancer drugs is by mutating ER. One-third of metastatic breast cancers have mutated estrogen receptors, these changes are associated with resistance to drugs. So in another project, Shapiro used CRISPR gene-editing technology to replace the normal ER with each of the two most common mutations found in metastatic cancer. His team also tagged the cancer cells with the gene from fireflies that enables them to light up. Using state-of-the-art imaging equipment, this allowed the researchers to see, or image, the tumors inside the mice. In a small study, they found that BHPI was exceptionally effective.

BHPI and its cancer fighting potential is only one of the most exciting findings in Shapiro’s long and successful career. The trick now is to continue down the road to clinical trials. Those efforts include collaborating with chemistry professor Paul Hergenrether, whose team is engineering new small molecules that might work even more effectively than BHPI.

There are still many complicated and expensive steps ahead, but Shapiro is undaunted. Together with his colleagues, both in MCB and across campus, Shapiro will continue to match wits with cancer.

For decades, MCB and the University of Illinois have been at the forefront of understanding the role of estrogen and the estrogen receptor (ER) in causing breast cancer. This is essential work: Breast cancer is the most commonly diagnosed cancer in women, affecting roughly one in eight women in the US alone.

MCB expertise began with the late Jack Nelson and Kannanganattu and Supriya Praasanth, who have been here for a while, and others like Erik Livezey. Nelson and Kannanganattu and Supriya Praasanth, who are relative new comers.

MCB has been a major center for hormones and hormone action, especially as it relates to cancer, for many years,” says David Shapiro, inaugural Eugene E. Howe Scholar in Biochemistry. “It only very rarely can be eradicated with a single drug. The normal thing in cancer is that typically the tumors become resistant so you have to come up with different sequential treatments.”

Medical students, co-discoverer of the estrogen receptor, the protein that estrogen must bind to in order to work. These days MCB faculty studying estrogen and ER include people like Milan Bajic and Renata Kuzdra-Debenham, who have been here for a while, and others like Erik Livezey and Supriya Praasanth who are relative newcomers.

Dr. David J. Shapiro, Professor of Biochemistry. Photo by L. Brian Stauffer

by Deb-Armstrong

MOTHER

SCHOOL OF MOLECULAR AND CELLULAR BIOLOGY

MCB

David Shapiro Lab

Employing the Help of the BHPI Molecule to Boost Anti-Cancer Drug Treatments
K.V. Prasanth Lab Discovers Cancer Connections with MALAT1

Kannanganattu V. Prasanth was a graduate student in India a little over 20 years ago when he was told that no one was interested in long non-coding RNAs (lncRNAs). Some of the professors also lamented that there was little future for studying the function of the so-called “unimportant and junk RNAs.” But he wasn’t discouraged. “Maybe it was my young age, but I wanted to do something that was outside the box,” said Prasanth, a University of Illinois MCB professor of cell and developmental biology. Today, not only is he still doing research on lncRNAs, but many other people have jumped on the bandwagon. “The field of lncRNA is really hot,” he said. “It’s like a puzzle,” Prasanth said. “MALAT1 is involved in all subtypes of breast cancer, he adds, but their lab is focused on triple negative breast cancer (TNBC), which is one of the most aggressive forms of breast cancer. Presently, the only option to treat TNBC is through chemotherapy, but the disease becomes resistant to chemo over time, so treatments are limited right now.” That’s why research to understand the biology of molecules such as MALAT1 in TNBC is crucial in order to develop new-generation drugs. LncRNA, such as MALAT1, is longer than 200 nucleotides, and it was once considered unimportant. Prasanth says, because biology was a protein-centric world 20 years ago. The central dogma of molecular biology says that genetic information flows from DNA to RNA to make proteins, which all of the heavy lifting in cells. LncRNA upended this dogma because it does not code for proteins and yet it still performs numerous vital functions in a cell. Back in 1995, researchers were aware of only a few lncRNAs, but today they have identified over 20,000, and they have pinpointed the function of several hundred of them.

Rising to the Challenge

Super resolution imaging of a human fibroblast nucleus reveals ordered assembly of oncogenic MALAT1 lncRNA (red), SR splicing protein (blue) and the pre-mRNA splicing U2 snRNA (green) in nuclear speckle sub-nuclear domains.

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Prasanth pointed out. “You always need to be challenged.”

We’re now trying to identify those oncogenic genes whose splicing is regulated by the MALAT1-SR protein axis.

MALAT1 seems to be involved in all subtypes of breast cancer, he adds, but their lab is focused on triple negative breast cancer (TNBC), which is one of the most aggressive forms of breast cancer. Presently, the only option to treat TNBC is through chemotherapy, but the disease becomes resistant to chemo over time, so treatments are limited right now. That’s why research to understand the biology of molecules such as MALAT1 in TNBC is crucial in order to develop new-generation drugs. LncRNA, such as MALAT1, is longer than 200 nucleotides, and it was once considered unimportant. Prasanth says, because biology was a protein-centric world 20 years ago. The central dogma of molecular biology says that genetic information flows from DNA to RNA to make proteins, which all of the heavy lifting in cells. LncRNA upended this dogma because it does not code for proteins and yet it still performs numerous vital functions in a cell. Back in 1995, researchers were aware of only a few lncRNAs, but today they have identified over 20,000, and they have pinpointed the function of several hundred of them.

Prasanth started his work on MALAT1 in 2005 while in Spector’s lab at Cold Spring Harbor, but with his mentor’s blessing he brought this research to the U of I when he and his wife came to Urbana as MCB professors in 2007. Today, Prasanth and Supriya have labs side-by-side in the Chemical and Life Sciences Building, and their students work together as one unit, even though each lab pursues its own unique projects. As Supriya and Prasanth continue to collaborate extensively on several ongoing research projects, they also challenge each other. “That’s the way science works,” Prasanth pointed out. “You always need to be challenged.”

“MALAT1 is present in normal cells, operating under normal conditions, so cancer cells might be exploiting this to their own benefit.”

“MALAT1 is present in normal cells, operating under normal conditions, so cancer cells might be exploiting this to their own benefit.”

by Doug Peterson

Dr. K.V. Prasanth, Professor of Cell and Developmental Biology

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Taking a Deep Look at Protein Structures that Contribute to Cancer

by Stephanie Adams

Thirteen years ago, when Lin-Feng Chen joined the Department of Biochemistry, he had his sights set on a specific protein that could both contribute to the growth of cancer and be a major factor in boosting the body’s immune system.

“The protein in question was NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells), a kind of ‘master controller’ of innate and adaptive immune response, and cell survival,” explains Chen.

In healthy cells, it spends most of its life in the cell’s cytoplasm, quietly awaiting orders to assist the immune system. In response to viral and bacterial infection, NF-kappaB moves into the nucleus and triggers the expression of many genes that help to fight against infection. After eliminating the pathogens, NF-kappaB returns to the cytoplasm, awaiting the next order. However, NF-kappaB can work against the body’s best interests, too. Sustained nuclear NF-kappaB is associated with a variety of inflammatory diseases and cancers.

“It’s exciting findings. This is very translational research,” Dr. Chen’s postdoctoral work at the Gladstone Institute of Virology and Immunology at University of California at San Francisco focused on the post-translational regulation of NF-kappaB in immunity and cancer. What chemical modifications were needed to make NF-kappaB dormant, until needed, in healthy cells and run amok in diseased cells?

That work identified acetylation, a chemical tag that can be added to lysine, of NF-kappaB that dictates the transcriptional outcome of NF-kappaB. So the major question when Dr. Chen started his lab at the University of Illinois was to find out how the modification of lysines affected the activity of NF-kappaB.

Binding of bromodomain 2 of BRD4 to acetylated lysine of NF-kappaB

At that time there were some clues that the acetylated lysine can control the protein’s activity through a signaling partnership with a bromodomain, a pocket-like structure, that can accommodate acetylated lysine and change the properties of the proteins.

“We started to look for bromodomains that might recognize the acetylated lysine of NF-kappaB and proteins that contain such a domain could be working with NF-kappaB,” said Chen. In 2009, Chen’s group identified bromodomain-containing protein 4 (BRD4) as a co-activator of NF-kappaB, specifically recognizing the acetylated lysine of NF-kappaB via its bromodomains.

“This discovery launched a decade of work in Chen’s lab focusing on BRD4’s role in inflammation and cancer. BRD4 belongs to a class of molecules that can recognize specific chemical tags on other proteins to spur the marked proteins to perform various tasks. Chemical tag ‘readers’ such as BRD4 are important players in the field of epigenetics, which focuses on how specific genes are regulated.

“Epigenetics, there are writers, there are readers, and there are erasers. BRD4 is the reader,” Chen said. The writers and erasers add or remove tags to or from proteins, without changing the underlying sequence of the gene that codes for them. Drugs targeting epigenetic regulators have emerged as novel therapies in cancer treatment, and a number of small-molecule inhibitors against epigenetic regulators have already been developed for cancer therapy.

Exploiting the role of BRD4 in cancer, Chen’s group found that BRD4 prevents the degradation of nuclear NF-kappaB by binding to acetylated NF-kappaB, and contributing to the sustained presence of NF-kappaB in the nucleus of cancer cells. They also found that a small molecule, JQ1, which blocks the interaction between BRD4 and NF-kappaB, reduced proliferation of cancer cells and suppressed the activity of cancer cells to form tumors. “These findings opened exciting possibilities for translational research. The interaction between BRD4 and NF-kappaB could be a target for therapies to stop the spread of cancer or inflammatory disease,” said Chen.

Chen’s lab recently discovered that there was a higher expression of BRD4 in gastric cancer cells and in gastric cancer patient samples. They identified an enzyme, PIN1, the expression of which was highly correlated to BRD4 in gastric cancer cells and regulated the tumor-promoting activity of BRD4 in gastric cancer cells. They also found that BRD4 promoted gastric cancer cell proliferation by preventing the cell senescence.

Chen’s latest research is delving even deeper into the physiological role of BRD4 in cancer and inflammation. A recent paper in Oncogene demonstrated that removing BRD4 from specific mouse tissues compromised the mice’s innate immunity to find against bacterial infection and tumor. With these tissue specific BRD4-deficient mice, they tried to determine the contribution of BRD4 in inflammatory diseases and inflammation-associated cancer. Various inhibitors targeting BRD4 are undergoing clinical trials for the treatment of cancer and inflammatory diseases. ‘Our studies will provide new insights for developing therapies targeting BRD4,’ said Chen. ‘This is very translational research.’
Exploring RNA’s Binding Role in Liver Disease and Cancer

Auiinash Kalsotra wasn’t originally interested in studying cancer. In fact, he wasn’t looking to study any particular disease at all.

Kalsotra wanted to know how the complex machinery of our bodies takes the codes embedded in our DNA and turns them into healthy organ tissues, specifically heart and liver. In other words, he wanted to know how how things worked — not why they break or how to fix them.

“There’s a molecular logic to how cells are put together, how something becomes a nerve or muscle cell,” Kalsotra said. “Once these cell features have formed, how do they mature and give rise to a functioning adult tissue that carries out a particular function?”

But as often happens, scientists start on one path and eventually find themselves pulled onto others. In this case, Kalsotra’s search for a deeper understanding of cellular mechanisms has led to significant findings that show linkages between liver diseases and cancer and may improve our understanding of the origins of these diseases.

Kalsotra’s research has focused on RNA, the workhorse cousin of DNA, which makes up the genetic instructions for living things. RNA is often viewed as important for messenger and other functions, taking DNA’s code and transporting it to and carrying out functions in cells. It’s often taken a back seat to DNA in terms of significance.

In particular, Kalsotra is intrigued by the fact that one gene can give rise to multiple types of RNA. In this case, Kalsotra’s search for a deeper understanding of cellular mechanisms has led to significant findings that show linkages between liver diseases and cancer and may improve our understanding of the origins of these diseases.

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Kalsotra knew that RNA binding proteins played a role in the formation of mRNA, so his lab started knocking out these proteins from mouse livers to study their functions. In liver cells, mice that lost certain RNA binding proteins started displaying signs of fatty liver disease. The condition is common among people who abuse alcohol, but also affects more than 100 million people in the U.S. and more than a quarter of people in the non-developed world as non-alcoholic fatty liver disease.

“One-third of people with non-alcoholic fatty liver disease get an aggressive form of the disease,” Kalsotra said. “In addition to having fat in their livers, they’re going to have a lot of inflammation, scarring and liver cell death.”

The mice eventually developed liver cancer. It got Kalsotra’s lab looking for connections between genes and non-alcoholic fatty liver disease. Analysis revealed that the genes that ranked highest as likely contributing to the disease are associated with RNA splicing.

“Our goal in knocking out these genes was to understand how these cells mature and how RNA splicing plays a role in tissue development,” Kalsotra said. “Instead, what we saw was a very specific disease that seems to match a human phenotype.”

Kalsotra collaborated with the Carle Hospital to analyze biopsy samples of patients with non-alcoholic fatty liver disease. Each patient showed a striking decrease in RNA binding proteins.

The findings raise more questions, such as whether the loss of RNA binding proteins leads to the liver disease and cancer. It’s possible that loss of RNA binding proteins could be a biomarker for fatty liver disease and cancer. Or maybe the opposite is true, that loss of the binding proteins is a result of the liver diseases.

Kalsotra also wants to know if and how the cancer profiles in mice match with humans, who tend to get cancer after fatty liver diseases. And whether there are mutations in genes from birth that lead to liver disease and cancer, or whether there are environmental triggers, such as diet, that are involved.

In addition, the Kalsotra Lab is looking at how the transition from the body making fetal cells to making adult cells might play a role in cancer formation. Fetal cells rapidly proliferate, much like cancer cells. But at some point, the body switches to making adult cells — a few years after birth in humans and a few weeks in mice.

“Maybe one day, if we understand how normal cells work, we can understand what goes wrong in a cancer cell that makes it divide uncontrollably and not listen to the rest of the organ that is telling it to stop growing.”

Kalsotra collaborated with the Carle Hospital to analyze biopsy samples of patients with non-alcoholic fatty liver disease. Each patient showed a striking decrease in RNA binding proteins.

The Kalsotra Lab has discovered that deletion of a splicing factor results in spontaneous development of nonalcoholic Steatohepatitis (NASH) in mice revealing an unexpected link between splicing deregulation and fat metabolism in the liver.
High cholesterol levels have been associated with breast cancer spreading to other sites in the body, but doctors and researchers don’t know the cause for the link. A new study by University of Illinois researchers found that the culprit is a byproduct of cholesterol metabolism that acts on specific immune cells so that they facilitate the cancer’s spread instead of stopping it.

The study, published in the journal *Nature Communications*, identifies new potential drug targets that could inhibit the creation or actions of the dangerous cholesterol byproduct, a molecule called 27HC.

“Breast cancer impacts roughly 1 in 8 women. We’ve developed fairly good strategies for the initial treatment of the disease, but many women will experience metastatic breast cancer, when the breast cancer has spread to other organs, and at that point we really don’t have effective therapies. We want to find what drives that process and whether we can target that with drugs,” said Erik Nelson, a professor of molecular and integrative physiology who led the study.

Nelson’s group fed mice with breast cancer tumors a diet high in cholesterol. The researchers confirmed that high levels of cholesterol increased tumor growth and metastasis, and that mice treated with cholesterol-lowering drugs called statins had less metastasis. Then they went further, specifically inhibiting the enzyme that makes 27HC during cholesterol metabolism.

“By inhibiting the enzyme that makes 27HC, we found a suppressor effect on breast cancer metastasis. This suggests that a drug treatment targeting this enzyme could be an effective therapeutic,” said Amy Baek, a postdoctoral researcher at Illinois and the first author of the paper.

The researchers also saw unusual activity among specific immune cells—certain types of neutrophils and T-cells—at metastatic sites high in 27HC.

“Normally, your body’s immune system has the capacity to attack cancer,” Nelson said, “but we found that 27HC works on immune cells to fool them into thinking the cancer is fine. It’s hijacking the immune system to help the cancer spread.”

Because 27HC acts through the immune system, and not on the breast cancer itself, the researchers believe their findings have broad applicability for solid tumors. They performed experiments looking at colon cancer, lung cancer, melanoma and pancreatic cancer, and found that 27HC increased metastasis for all the tumor types, suggesting that a treatment targeting 27HC could be effective across multiple cancer types.

The researchers are working to further understand the pathway by which 27HC affects the immune cells. With clinical partners at Carle Foundation Hospital in Urbana, the team is working to establish whether 27HC has the same pathway in human patients as in mice.

“We hope to develop small-molecule drugs to inhibit 27HC,” Nelson said. “In the meantime, there are good cholesterol-lowering drugs available on the market: statins. Cancer patients at risk for high cholesterol might want to talk to their doctors about it.”

Nelson also is affiliated with the Cancer Center, the division of nutritional sciences, and the Carl R. Woese Institute for Genomic Biology at Illinois. The National Institutes of Health and the Susan G. Komen Foundation supported this work.
Robert Gaynes, a distinguished doctor known for his effective teaching and mentorship of medical students, has been chosen as a 2017 Illini Comeback Guest by the University of Illinois Alumni Association.

Robert P. Gaynes (BS,’75, biology-honors), professor of medicine and infectious diseases at Emory University, professor of epidemiology at the Rollins School of Public Health, and an attending physician at the Atlanta Veterans Medical Center, said that it’s a thrill to be coming back to campus. “There were a couple decisions I made as an undergraduate student at the University of Illinois that reflect back on as being quite influential in my life,” Gaynes said.

After receiving his degree from Illinois, Gaynes went on to receive his medical degree from the University of Chicago Pritzker School of Medicine. Since then, Gaynes has served as a consultant to the World Health Organization and the Joint Commission on Accreditation of Healthcare Organizations, earned induction into the Academy of Medical Educators for his teaching and mentorship of medical students, and hosted the Centers for Disease Control and Prevention’s (CDC) Morbidity & Mortality Weekly Report podcast.

Gaynes said majoring in the Honors Biology Program gave him a solid academic background in the field, as well as an opportunity to work closely with others. As an undergraduate, Gaynes and 13 other students spent an entire three semesters taking courses together under the guidance of one professor. “We all got to know each other quite well. We learned basic biology and learned critical thinking,” Gaynes said. “It really was collaborative science. Medicine today is a team sport — you really work with a variety of allies and medical professionals. That collaborative approach is something I got out of Honors Biology.”

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Team Discovers How Bacteria Exploit a Chink in the Body’s Armor

by Staph Adam

Scientists have discovered how a unique bacterial enzyme can blunt the body’s key weapons in its fight against infection. Researchers at the University of Illinois at Urbana-Champaign and Newcastle University in the U.K. are investigating how infectious microbes can survive attacks by the body’s immune system. By better understanding the bacteria’s defenses, new strategies can be developed to cure infections that are currently resistant to treatments, the researchers said.

The study, reported in the journal PLOS Pathogens, focused on the bacterium Staphylococcus aureus, which is found on approximately half of the population. While it usually safely coexists with healthy individuals, S. aureus has the ability to infect nearly the entire body, in its most pathogenic form, the bacterium is the so-called “superbug” methicillin-resistant S. aureus, or MRSA.

The human body uses a diverse array of weapons to fight off bacteria like S. aureus. “Our immune system is very effective and protects the majority of microbes we encounter from causing infections,” said U. of I. microbiology professor Thomas Kehl-Fie, who led the study with Kevin Yuritzi Garcia, a graduate student in Kehl-Fie’s lab, Dr. Stephanie Ceman (cell and developmental biology), Dr. Auinash Kalsotra, (biochemistry), Dr. Geena Skariah (Ceman lab), and Joseph Seimetz (Kalsotra lab). “But pathogens such as S. aureus have developed ways to subvert the immune response.”

S. aureus can overcome one of the body’s key defenses, nutritional immunity, which prevents bacteria from obtaining critical nutrients. It starves S. aureus of a nutrient, a metal needed by the bacterial enzyme superoxide dismutase, or SOD. This enzyme functions as a shield, the body’s second punch, with nutritional immunity weakening the bacteria’s shields, enabling the oxidative burst to kill the bacterium. S. aureus is particularly adept at causing devastating infections. Differing from other closely related species, S. aureus possesses two SOD enzymes. The team discovered that the second SOD enhances the ability of S. aureus to resist nutritional immunity and cause disease.

“This realization was both exciting and perplexing, as both SODs were thought to utilize manganese and therefore should be inactivated by manganese starvation,” Kehl-Fie said. “The most prevalent family of SODs, to which both of the S. aureus enzymes belong, has long been thought to come in two varieties: those that are dependent on manganese for function and those that use iron. In light of their findings, the team tested whether the second staphylococcal SOD was dependent on iron. To their surprise, they discovered that the enzyme was able to use either metal. While the existence of these cambialistic SODs, capable of using both iron and manganese, was proposed decades ago, the existence of this type of enzyme was largely dismissed as a quirk of chemistry, unimportant in real biological systems. The team’s findings dispel this notion, demonstrating that cambialistic SODs critically contribute to infection.”

“We found that, when starved of manganese by the body, the S. aureus activated the cambialistic SOD with iron instead of manganese, ensuring its critical bacterial defensive barrier was maintained,” said Yuritzi Garcia, senior graduate student and a lead author on the study. “By learning how S. aureus’s defenses work we are able to better understand the inner workings of this human pathogen,” she said.

The cambialistic SOD plays a key role in this bacterium’s ability to evade the immune defense,” Waldron said “Importantly, we suspect similar enzymes may be present in other pathogenic bacteria. Therefore, it could be possible to target this system with drugs for future antibacterial therapies.”

The emergence and spread of antibiotic-resistant bacteria, such as MRSA, make such infections increasingly difficult, if not impossible, to treat.

This has prompted leading health organizations, such as the Centers for Disease Control and Prevention and the World Health Organization, to issue an urgent call for new approaches to combat the threat of antibiotic resistance. 

A study led by Dr. Geena Skariah, a recent Neuroscience graduate of the Ceman lab in Cell and Developmental Biology, and current postdoctoral researcher at the University of Michigan, revealed the importance of the protein Mov10 (Moloney leukemia virus 10) in neurological development in animals. The findings were published in BMC Biology.

The study began with an idea from fellow graduate student in the Ceman lab, Mini Kim. “Why don’t you look at the brain over time and see what happens with the protein Mov10?” she asked.

It was a novel question because Mov10 has been characterized only in cell lines as an RNA helicase and as a regulator of retrotransposons,” said Dr. Stephanie Ceman. “No one was really looking at its effect on the brain.”

Sharak was intrigued. She walked over to the lab of Dr. Auinash Kalsotra, a biochemist who, along with Dr. Ceman, focuses on RNA biology. Skariah knew that the Kalsotra lab was working on cytosolic poly(A)-binding protein 1 (PABPC1) in the livers and hearts of mice and asked if they would be willing to share resources.

“We both share the interest in how RNA brings things together and makes the cells and tissues in our bodies work,” said Dr. Kalsotra.

From the resources available in the Kalsotra lab, Skariah was able to test post-mortem brains of mice at different points in their development and measure the level of Mov10. “We saw that Mov10 goes up during development and goes back down in the adult,” said Skariah. “That was my first piece of real data.”

No one had ever looked at Mov10’s role in the development of the brain, and this was a completely new finding. “That finding started off this whole project,” said Skariah.

Mov10 was thought to be unimportant to brain function because there are usually low levels of it found in adult brain. “I didn’t think they were going to see anything. I didn’t say not to do it, but I did say it was not going to work,” admitted Dr. Ceman, with a laugh.

But Skariah was able to convince Dr. Ceman with the impact of her first results. “That’s great!” Ceman said. “Now test it in different sexes and with different strains.”

“Every single day Over and over and over!” quipped Dr. Kalsotra.

The initial finding opened the door to a cascade of questions. Why is this protein going up in early development? What is it is doing in the brain?

“What’s fun about this,” said Ceman, “it’s the biggest discovery project I have been part of in a long time.” Every time they did an experiment in this project, they had no idea what they were going to find. Further experiments showed that reduced levels of the protein resulted in behavioral changes that suggested neurological impairment. They were seeing several defects in the cells, but where were they coming from? To address this question, they moved to a neurobiologist cell line (Neuro2A), on which they could use CRISPR-Cas9 to remove both copies of Mov10. Then they examined the effect of Mov10 loss on total RNA levels and on the ability to grow a neurite, Ceman explained.

“They sequenced the cellular RNA millions of times at the Carver Biotech Center on campus and obtained a huge amount of data. showing a lot of differences in the RNA levels,” Skariah explained. “We all started to talk about what to make of it and delve into the data.”

The Ceman and Kalsotra labs have run an RNA journal club that meets every week, and through this club, Skariah learned that Joseph Seimetz, in the Kalsotra lab, could help with the bioinformatics on this project.

“There is a list of gene candidates, and you can’t test every one because there are thousands of them,” said Skariah.

“Bioinformatics is so powerful because you can pick important ones and remove them from the cell.”

“The Ceman lab basically did all the work,” said Seimetz. “It was perfect timing. We had started to build our own bioinformatics pipelines for analyzing “Big Data,” so we combined it with our work.”

“Joe developed the graphs that were so important for the paper,” said Skariah. “We could move from a point of taking out genes to a point where we see a phenotype, we remove it and see how the genes change and how they function.”

There is a lot more research that can come from this data. Their next step is to see what happens when Mov10 is removed from the brain. The lab is continuing to look at how the reduction of Mov10 changes the neurons.

“The findings were published in BMC Biology, and the paper has piqued significant interest, with nearly 5000 views in the last six months,” Seimetz said.

Seimetz’s work organizing the sizable amounts of data collected during the project is now shared in a public database that allows scientists around the world to work with and use the data.

“It’s like our data keep on giving,” Dr. Ceman said.”
Exploring the Effect of Liver Disease on the Heart

Infants and children with liver diseases are more likely to succumb to heart failure than to liver failure, and in fact, the heart’s health often improves after a liver transplant. New research from the Anakk lab, published in the journal Hepatology, demonstrates that excess bile acids in the liver cause metabolic change and stress in the heart. “That there is a connection between liver and heart disease has been known for hundreds of years,” said Dr. Sayee Anakk, assistant professor of Molecular and Integrative Physiology, whose lab studies the regulation of metabolic signaling in the liver. “That there is a connection between liver and heart disease has been known for hundreds of years,” said Dr. Sayee Anakk, assistant professor of Molecular and Integrative Physiology, whose lab studies the regulation of metabolic signaling in the liver. “That there is a connection between liver and heart disease has been known for hundreds of years,” said Dr. Sayee Anakk, assistant professor of Molecular and Integrative Physiology, whose lab studies the regulation of metabolic signaling in the liver. “Healthy hearts metabolize fat as its main energy source to pump blood,” said Mathur. “Whereas, a stressed heart exposed to high levels of bile acids, switches to glucose as its energy source, and this switch in fuel metabolism is seen during heart disease.” The researchers also discovered that increased bile acids suppressed a master regulator of mitochondrial function, Pgc1α, that is central for regulating fat breakdown. Thus, suppression of this key gene can result in reprogramming the substrate preference and heart failure. The researchers named this Bile acid mediated effect “Cholecardia.”

“Cholecardia”

“The discovery that excess bile acid affects heart metabolism was a big step forward, since this could allow us to identify potential treatment options,” said Anakk. Based on these findings, Ms. Mathur tested whether reducing bile acid levels would be sufficient to reduce the heart defect. They treated the mouse model with Cholestyramine, an FDA approved drug to treat high cholesterol that can remove bile acids from the blood, and found that these mice are lean and resistant to diet induced obesity. “To learn why the mice are lean we examined their caloric intake, activity and basal metabolism,” said Riessen. DKO mice ate the same amount of food as the mice, which became obese but they were more active and burnt more fat. Therefore we asked why are they more active?” said Akinrotimi. The answer was in skeletal muscle of these mice, which had more type I, or slow twitch fibers, with high oxidation capacity. “These mice were like marathon runners!” said Riessen.

DKO HFD

The team, with Dr. Moreshwar Desai, a pediatrician at Texas Children’s Hospital and first author with Bhoomika Mathur, undertook this study. “The curative potential is exciting, but we have many more questions for bile acid’s role in cardiac malfunctioning,” said Anakk.

Uncovering a Way to Fight Fatty Liver Disease

In a second paper, the Anakk lab explored the mechanism by which the liver can be protected from developing fatty liver disease. This work was also published in Hepatology and led by two former undergraduates of the MCB program, Odunemilade Akinrotimi (Demi) and Ryan Riessen along with another MCB alumnus, Phil Vanduyne. Using the same experimental mouse model with double knockout (DKO) of Farnesoid X Receptor (Fxr) and Small Heterodimer Partner (Ship), they found that these mice are lean and resistant to diet induced obesity. “To learn why the mice are lean we examined their caloric intake, activity and basal metabolism,” said Riessen. DKO mice ate the same amount of food as the mice, which became obese but they were more active and burnt more fat. “Therefore we asked why are they more active?” said Akinrotimi. The answer was in skeletal muscle of these mice, which had more type I, or slow twitch fibers, with high oxidation capacity. “These mice were like marathon runners!” said Riessen. Since the Anakk lab is focused on understanding liver diseases, they examined why the DKO mouse model did not develop fatty liver disease despite eating high fat containing food. It is typically thought that the receptor named Fxr (Farnesoid X Receptor) is crucial to control the amount of fat in the liver. Fxr functions by recruiting another receptor, Ship, to do its bidding. So when they found that really it was Ship that was important to causing fatty liver it was very surprising. “I didn’t believe it,” said Anakk. “I told them to do the experiment over and over again.” The study showed that Ship has a role of its own. The paper was highlighted in an editorial by Dr. Richard Green from Northwestern, who suggests that “Targeting Ship may be efficacious for drug development to treat fatty liver disease.”

Research is really exciting and takes a lot of hard work,” said Anakk. “But what makes this journey truly stimulating are the individuals who make it happen. I have been very fortunate to have wonderful undergraduate and graduate students in my laboratory who have made my job easy, and it is to them I owe my success.”

by Sayeepriyadarshini Anakk and Bhoomika Mathur

Dr. Sayeepriyadarshini Anakk and Bhoomika Mathur