IGB NEWS

Upcoming Events
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Happenings at IGB
Image Of The Month
Research News
Department Announcements

Volume 15 Number 3

UPCOMING EVENTS

IGB Seminar - GEGC
Extending enzyme lifespan to increase net carbon fixation
April 19, 2022, 12:00 p.m.
Join via Zoom

Andrew Hanson, PhD
University of Florida;
Professor of Horticultural Sciences

IGB Lunchbox Series
Tortillas y tacos: food for your gut and your brain
April 20, 2022, 12:00 p.m.
Join via Zoom

Margarita Teran MD, PhD
Assistant Dean And Program Leader
Integrated Health Disparities, University of Illinois Extension, ACES

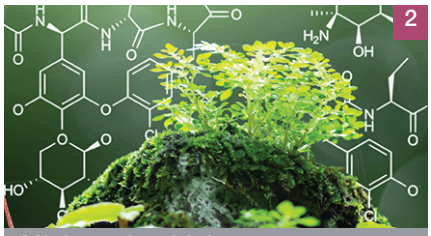
Lunch with the Core
Introduction to Abberior Minflux and Sample Prep
April 27, 2022, 12:00 p.m.
In-person in 612 or Join via Zoom

Kingsley Boateng,
Senior Research Specialist, IGB

IGB Seminar -MME
Understanding and Predicting Perturbations To Diverse Microbiomes
May 3, 2022, 12:00 p.m.
Join via Zoom

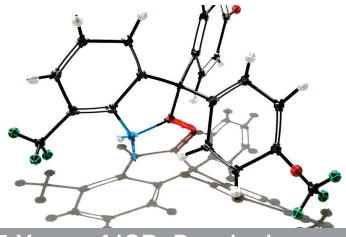
Gautam Dantas, PhD
Washington University; Professor of Pathology & Immunology, Biomedical Engineering, and Molecular Microbiology

FEATURED NEWS



Mining microbial genomes to discover natural products

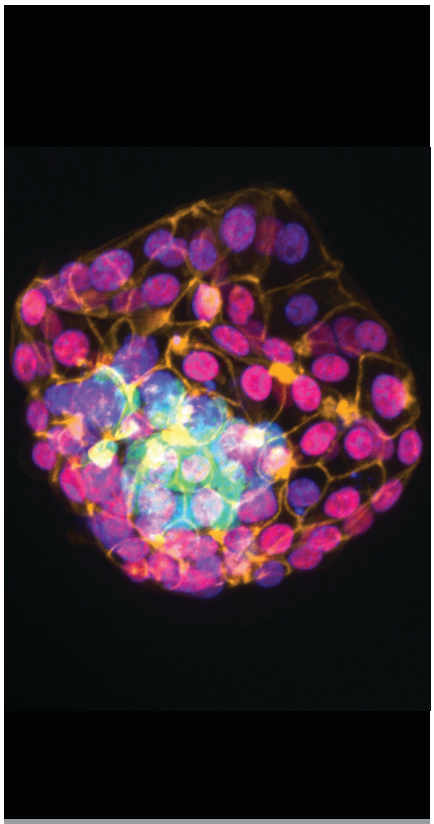
Liver metastases in breast cancer patients, low-carb diets



15 Years of IGB: Developing new drugs to battle cancer

On the Grid: Happenings at IGB

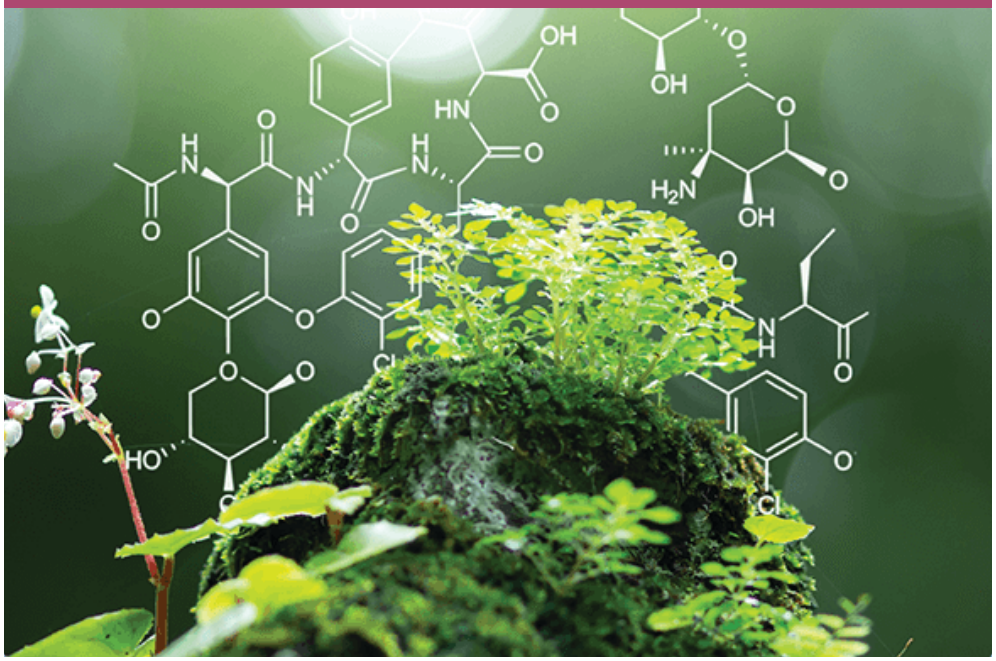
IMAGE OF THE MONTH



The image is of immunofluorescent staining of a hatched mouse blastocyst in control. DAPI-nuclear stain; phalloidin- F-actin; Cy3- inner cell mass (ICM); Cdx2- trophectoderm (TE). The image was taken using the Confocal-Zeiss LSM 880 airyscan microscope and comes courtesy of Nastasia Lai and Dr. Romana Nowak, Animal Sciences Lab.

IGB News

Share your news with the IGB. Send ideas on stories, articles, and features to *nvasi@illinois.edu*.



Mining microbial genomes
to discover natural products

The world around us contains many chemicals that are useful for medicines, crop protection, and animal health. These chemicals—known as natural products—have typically been discovered by sheer luck. Unsurprisingly, traditional techniques often find the same products, like antibiotics, repeatedly thus creating a need for new technologies. To address this growing demand, William Metcalf (MMG leader), a professor of microbiology, co-founded the company MicroMGx in 2015.

"A large number of antibiotics, herbicides, pesticides, and animal health medicines are derived from natural products. However, the biggest issue is rediscovery of the same compounds over and over again," Metcalf said. Along with Neil Kelleher, a professor at Northwestern University, Metcalf had been working on the idea of a new discovery platform for a long time. The project got a boost when James Doroghazi, who was a postdoctoral fellow at the IGB, did much of the early work. The company grew out of a proof-of-concept award at the IGB in 2012.

Together with Kelleher and Regan Thomson, also a professor at Northwestern University, Metcalf co-founded the company Microbial Pharmaceuticals. Later the name was changed to MicroMGx, an acronym for microbial metabologenomics. The company's first employee was Anthony Goering, who discovered the first novel compound using MicroMGx's technology platform.

"MicroMGx is working to lower the barriers for accessing natural products," Goering said. "Once we do that, it will greatly expand how we can use natural products to make a difference."

MicroMGx combines information from two sources: genes that are involved in the biosynthesis of natural products, and mass spectrometry data that show what molecules are produced by microorganisms. "We can pick out which molecules are valuable and have activities that are useful to human beings. At the same time, we can link those molecules to the genes that are responsible for their production. This allows us to enhance the production or make derivatives that may have different activities," Metcalf said.

"The platform was built to work with any bacteria. We work with soil bacteria that we've obtained from friends and family from around the country. So far, we've isolated 3500 unique bacteria for analysis with our platform, and have already published seven papers, each of which has a novel natural product," said Jack Kloeber, the CEO of MicroMGx. The company's scientists have also worked with fungi and have isolated 200 of them so far. "We have only scratched the surface of what valuable chemicals we can discover from these microbes," Kloeber said.

The company's platform can potentially discover hundreds of natural products that may be useful for different applications, increasing their ability to collaborate with other companies. MicroMGx currently partners with Corteva, an agricultural chemical company, and Elanco, a pharmaceutical company that produces medicines for animal health. The company has also recently been chosen as one of 6 finalists in the UPL-Radicle Challenge, out of 160 qualified entrants. The mission is to scale up innovative agricultural technologies with a focus on soil health, crop resilience, and reducing agriculture's carbon footprint.

"Because our platform's potential is too big for one company to do all the product development, we will create a stream of new molecules and collaborate with many companies," Kloeber said. "It's exciting because this small company could change the speed and cost of discovery in multiple life science industries. Very few pharmaceutical companies are looking at natural products right now. By giving them access to all the ones we find, we have a chance to place many useful products on the market."

"I love this work and I would do it solely for the science," Metcalf said. "But I love the idea that doing what you love can lead to the discovery of something that could help people. This science has the potential to solve big problems for society and that makes it all the more gratifying,"

The other members of MicroMGx include Rajmony Pannu, Gini Besant, Jason Pillai, Andrew Sutter, Jennifer Kelleher, and Jayaram Pazhanikumar. Pannu is an angel investor who also serves as one of the Directors. He brings pharmaceutical and entrepreneurial expertise to the company's decision making. ■

Written by Ananya Sen. Photo courtesy MicroMGx.

Treatment of liver metastases
in breast cancer patients improved by low-carb diets

A new study by Zeynep Madak-Erdogan (CGD/EIRH/GSP), pictured above, Associate Professor of Food Science and Human Nutrition and Cancer Center at Illinois Education Program Leader, and her team have found a new mechanism of endocrine resistance in breast cancers metastasized to the liver.

The study, published in *Molecular Cancer Research*, a journal of the American Association for Cancer Research, found that liver metastases rely on increased amounts of glucose, revealing the possibility of a dietary intervention to reduce tumor burden and increase treatment efficacy.

Approximately one-third of breast cancer patients will later present with metastatic disease, which commonly occurs in the bones, lung, and liver. Patients with liver metastases are often resistant to endocrine treatment and suffer from a reduced quality of life and poor survival rates. The unique nature of the liver tissue environment, with its high nutrient and lower oxygen composition, may be providing metastatic tumors with an advantage over other tissue.

The study began by observing differences in the breast cancer patient population and found that patients with liver metastases typically did not respond to the standard of care endocrine therapy, Fulvestrant, very well. The team of researchers, including fellow Cancer Center at Illinois researchers Professor of Molecular and Integrative Physiology Benita Katzenellenbogen (CGD) and Professor of Biochemistry David Shapiro, and graduate students Qianying Zuo, Ayca Mogol, and Ashlie Santaliz Casiano, who confirmed these findings in animal and cell line models, and set out to understand the drivers behind this resistance.

"We examined tumor metabolism, the function of the estrogen receptor, which is an important driver of resistance. We found that the tumors had an increased reliance on glucose, so we provided the animals with diets of varying carbohydrate levels," Madak-Erdogan said.

The researchers discovered that liver metastases decreased with carbohydrate levels and low-level carbohydrate diets restored the efficacy of Fulvestrant in reducing metastatic tumor burden in mice.

"Following the clinical observation, we used our metastasis models to uncover vulnerabilities in the tumor in terms of metabolic pathways to show proof-of-concept. And we found that we can indeed inhibit glucose metabolism to restore the efficacy of these endocrine treatments," Madak-Erdogan said.

As a cancer progresses, the tumor cells require new building blocks to divide and survive in different environments. These processes require extra generated energy, taking glucose and storing it as glycogen for the cell to use in times of stress, such as during treatment.

The study also found indicators of special survival mechanisms that become activated during these times of stress. Madak-Erdogan intends to pursue these findings in future research to determine the role of these regulatory pathways.

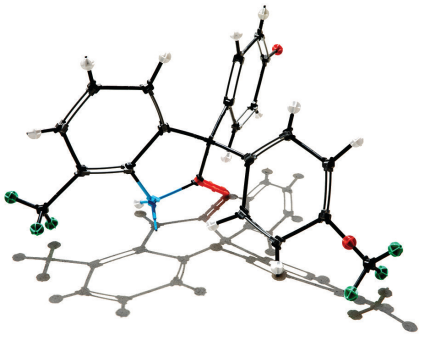
Other possible avenues of future research include studies of the effects of increased glucose utilization on epigenetic differences in metastases and the impact of combination endocrine and dietary therapy in a model with a fully functional immune system.

"We are so excited about the possibilities, especially in terms of the dietary intervention, where there are not as many regulatory steps. Low-carb diets can easily be tested in the clinic, and one of our near-future goals is to get this to clinical trials," Madak-Erdogan said. "Small molecular inhibitors are very effective and specific, but there is so much time needed to get through testing and trials, and they can be very costly for patients. But, an effective dietary intervention can be implemented by the patient, and without requiring travel to a medical center."

This research was supported by grants from the University of Illinois, Cancer Center at Illinois, and National Institute of Food and Agriculture.

The paper "Targeting metabolic adaptations in the breast cancer-liver metastatic niche using dietary approaches to improve endocrine therapy efficacy" is available online. ■

Written and photo by CCIL Communications Team.



This small molecule, ErSO, eradicates breast cancers in mice by targeting a pathway that protects cancer cells, one of two drugs from the ACPP theme moving to clinical trials for brain and breast cancer.

15 Years of IGB

Developing new drugs to battle cancer

Figuring out which drugs can help cure cancer is a laborious process, often requiring decades of careful research and multiple phases of clinical trials. To this end, the "Anticancer Discovery from Pets to People" research theme at the IGB has painstakingly worked on getting two drugs into clinical trials: PAC-1 and ErSO to treat brain and breast cancer respectively. PAC-1 is currently in phase I clinical trials in humans and has been granted orphan drug status by the U.S. Food and Drug Administration for the treatment of glioblastoma, a deadly brain cancer. ErSO has been licensed by the pharmaceutical company Bayer AG and is currently being tested for human clinical trials.

One of the first steps in drug design includes testing them on animals that serve as a proxy for humans. Although researchers tested ErSO in mice models, they used a different animal for PAC-1: dogs with certain naturally occurring cancers. According to Timothy Fan (ACPP/CGD), a professor of veterinary clinical medicine, dogs may be better than rodents in many cancer drug-testing models because the latter need to be implanted with human cancer cells to mimic specific types of tumors. Additionally, certain cancers in dogs are genetically similar to those in humans and respond to the same medications. Dogs are also more similar in size to humans and are, therefore, better models to test how well the drugs work on larger tumors.

Researchers discovered PAC-1's anti-cancer capabilities in 2006 in the Hergenrother lab. "One of the unusual features of this drug is that unlike most cancer drugs, PAC-1 gets into the brain. We wanted to embrace that and try to address the unmet clinical need of brain cancer," said Paul Hergenrother (ACPP leader/MMG), a professor of chemistry.

PAC-1 activates the cellular enzyme procaspase-3, which triggers a series of reactions that causes only cancer cells to self-destruct, sparing healthy cells. "Even though they have elevated levels of procaspase-3, cancer cells never turn the enzyme on. They keep growing and become tumors," Hergenrother said. "PAC-1 restores the enzyme activity and because it is elevated in cancer cells, it targets cancer cells over non-cancerous cells."

In 2013, a $4 million investment, informed by the trials in dogs, helped PAC-1 on the road to human clinical trials. In 2016, the same anonymous donor contributed $7 million to help the studies progress in the drug-approval pipeline. Moreover, the funding also helped many veterinary patients that would not have received treatments for their cancer. PAC-1 is still in clinical trials in dogs with osteosarcoma, the most common type of bone cancer.

Fan and his colleagues are also looking at PAC-1 in combination with radiation and in combination with temozolomide, a brain cancer drug used in humans and dogs. "One of PAC-1's greatest strengths is that it synergizes with other drugs, increasing the anti-cancer effects of many compounds that are out there," Fan said. The three dogs in the trial tolerated the combination treatment well and responded well to the therapy. Fan said that a much larger study will be needed to quantify how much PAC-1 contributed to the positive results.

Currently in the human trials, PAC-1 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. So far, there have been no significant side effects. The phase I trial will also determine if PAC-1 can be used safely with temozolomide. "We've been at this now for more than 10 years, and we're excited to be able to continue down this road," Hergenrother said. "It takes a lot of time, effort, and money to do human clinical trials. To expand access to PAC-1 from a dozen patients to, we hope, hundreds, is very exciting. That will allow us to get some definitive data on the drug."

The precursor to ErSO was first discovered in 2014 in the laboratories of Hergenrother and biochemistry professor David Shapiro. Although the original compound prevented breast cancer cells from growing, it did not rapidly kill them and had undesirable side effects. In 2021, the researchers discovered the small molecule ErSO that had powerful anticancer effects without side effects in mice. When they tested the drug in mice models of human estrogen-receptor-positive breast cancers and their metastases in the bone, brain, liver, and lungs, the drug killed 95-100% of the cancer cells and shrank large tumors to undetectable levels. The compound was also well tolerated in mice, rats, and dogs.

ErSO works by binding to the estrogen receptor, upregulating the anticipatory Unfolded Protein Response or a-UPR, which kills cancer cells. About 75% of breast cancers are estrogen-receptor positive, making ErSO a potent drug. "Since the process is estrogen-receptor dependent, ErSO doesn't touch the cells that lack the receptor, and it also doesn't affect healthy cells—whether or not they have an estrogen receptor," Hergenrother said.

Impressively, within a week of exposure to ErSO, advanced, human-derived breast cancers in mice shrank to undetectable levels. "Many of these breast cancers shrunk by more than 99% in just three days," Shapiro said. "ErSO is fast-acting and its effects on breast cancers in mice are large and dramatic."

In the past 250 years, researchers have made several discoveries that have helped in the battle against cancer, a disease that has been afflicting humanity for thousands of years. Unfortunately, patients with metastatic estrogen-receptor-positive breast cancers or glioblastoma eventually succumb to the disease, even with treatment. Although PAC-1 and ErSO may not be the silver bullet we are looking for, the studies so far have all pointed to a favorable outcome. Hopefully, as we learn more about these drugs, we will get closer to finding better weapons that can help us treat cancer. ■

Written by Ananya Sen. Photo by L. Brian Stauffer.

ON THE GRID
HAPPENINGS AT THE IGB

AWARDS

ALISON BELL

Alison Bell, Professor of Evolution, Ecology, and Behavior (GNDP leader) received the Quest Award from the Animal Behavior Society (ABS) in recognition of outstanding seminal contributions in animal behavior.

MAY BERENBAUM

May Berenbaum, Professor and Head of Entomology (GEGC/IGOH) was named to the President's Committee on the National Medal of Science, a committee of scientists and engineers appointed by POTUS to evaluate nominees for the Award.

ROHIT BHARGAVA

Rohit Bhargava, Founder Professor in Bioengineering (CGD), was selected as the winner of the 2022 New York/New Jersey Society for Applied Spectroscopy Gold Medal Award, which recognizes outstanding contributions to the field of Applied Spectroscopy.

CALL FOR APPLICANTS

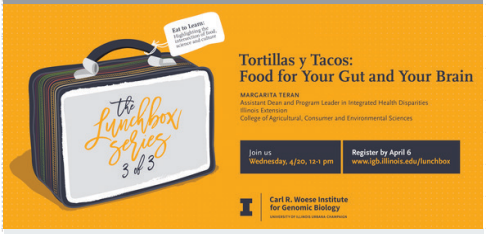
KLEINMUNTZ CENTER YOUNG INNOVATOR PROGRAM

The Catherine and Don Kleinmuntz Center for Genomics in Business and Society and Carl R. Woese Institute for Genomic Biology are excited to offer the Young Innovator Program (YIP) for the second year.

The ten-week summer course is designed for trainees to practice using skills necessary to become innovative leaders and bring science to society. The trainees will learn about the process of innovation, protecting intellectual property, and how to develop their discoveries beyond the laboratory. Upon completion of the program, all participants will earn a certificate. Additionally, winners of the idea competition, held at the end of the program, will be awarded between $5,000 to $20,000 to develop their projects over one year.

To learn more about how to apply, please visit: https://www.igb.illinois.edu/KCYIP.

EVENT



LUNCHBOX SERIES LECTURE

Our series where we highlight the intersection of food, science, and culture will see the final lecture this semester, noon on April 20th on Zoom, with "Tortillas y tacos: food for your gut and your brain" from Margarita Teran, MD, PhD, Assistant Dean And Program Leader, Integrated Health Disparities, ACES. Join us on Zoom!

SYMPOSIUM

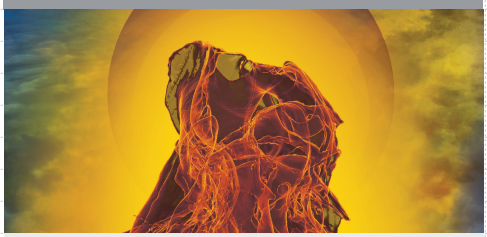
IGB FELLOWS SYMPOSIUM

IGB FELLOWS SYMPOSIUM REGISTRATION NOW OPEN

Learn about IGB research, hear about current issues in the life sciences, and network with other students at the annual Fellows Symposium! Register for free to attend and present a poster at our in-person poster session. Lunch is provided.

Register at fellows.igb.illinois.edu.

EVENT



ART OF SCIENCE 12.0

Join us for the Art of Science 12.0 at Cafeteria & Company in Urbana. Opening night on May 6th from 4:00pm to 8:00pm, and an additional showing on May 7th from 10:00am to 4:00pm.

Sponsored by the IGB, BodyWork Associates, and the Catherine and Don Kleinmuntz Center for Genomics in Business and Society

Cafeteria & Company
208 W. Main Street, Urbana

RECENT PUBLICATIONS

Please include your connection to the IGB in your author byline when submitting publications, as it will greatly help track potential newsworthy items and increase the possibility of coverage.

Iyer, R. R., Sorrells, J. E., Yang, L., Chaney, E. J., Spillman, D. R., Tibble, B. E., Renteria, C. A., Tu, H., Žurauskas, M., Marjanovic, M., & Boppart, S. A. (2022). Label-free metabolic and structural profiling of dynamic biological samples using multimodal optical microscopy with sensorless adaptive optics. *Scientific reports*, 12(1), [3438]. https://doi.org/10.1038/s41598-022-06926-w

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ILLINOIS

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