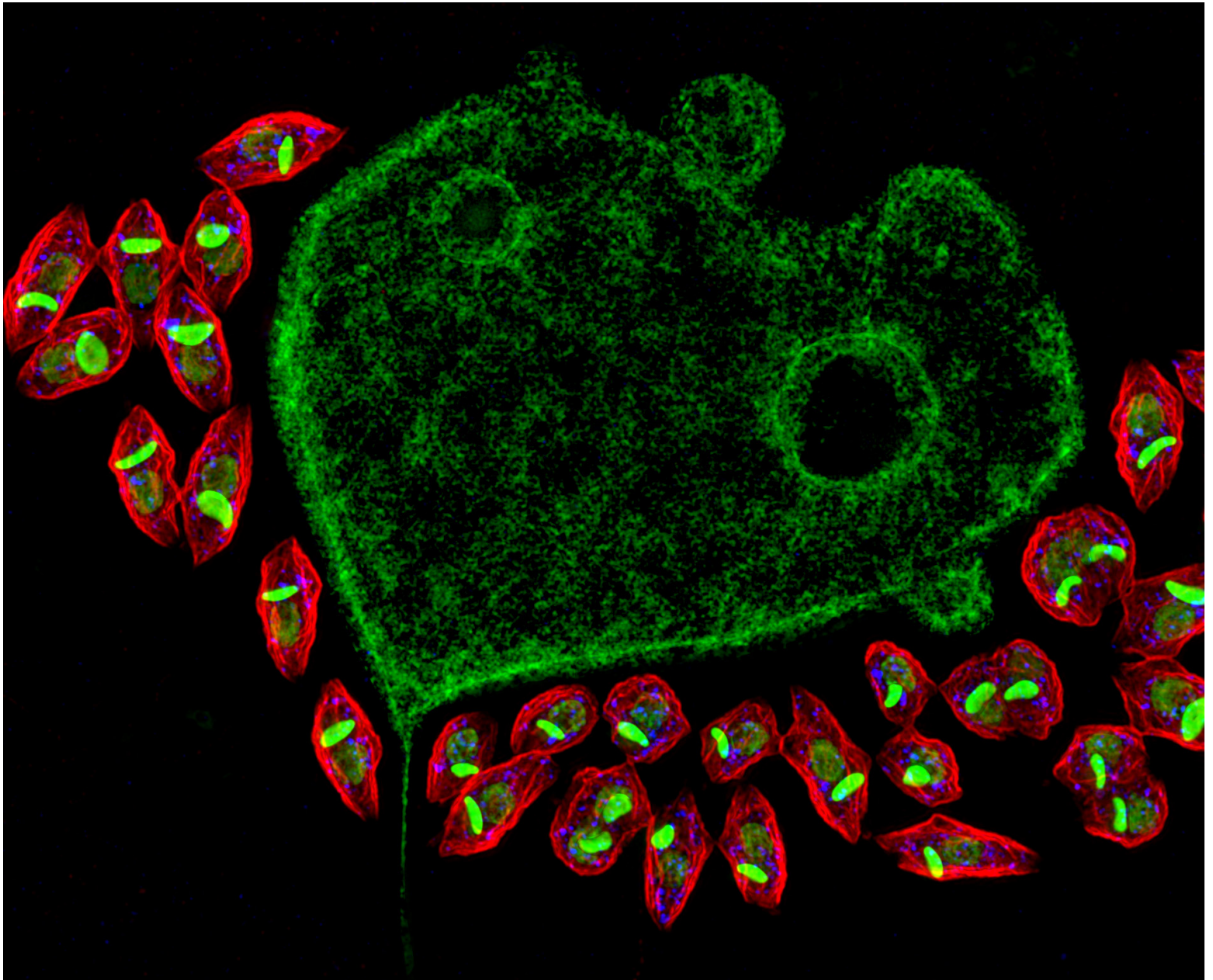




# Center for Tropical & Emerging Global Diseases

## UNIVERSITY OF GEORGIA



*Global Health Through Research*

## From the Director's Desk

It is spring in Athens and that is always an exciting time for the Center for Tropical and Emerging Global Diseases! We always look forward to our annual signature event, the Molecular Parasitology & Vector Biology Symposium. This year will mark the 28th edition of the meeting that brings together students, staff, postdocs, and research scientists from around the southeastern US to focus on the neglected tropical diseases caused by eukaryotic pathogens. This year the symposium will be held on April 26th at the Georgia Center for Continuing Education and will feature talks by students and postdocs from CTEGD and visitors from other universities. In particular, we are excited that Dr. Patricia Johnson, Professor of Microbiology, Immunology & Molecular Genetics at UCLA will present the Keynote Address. Dr. Johnson's research focuses on the molecular and cellular biology of *Trichomonas vaginalis*, the cause of the most prevalent, non-viral, sexually transmitted infection worldwide. Please make plans to join us in Athens for the symposium.



As you will see in this edition of the CTEGD Newsletter, we have an exciting array of published studies, significant awards, and new grant funding that demonstrate the culture of excellence and scientific productivity by our center's faculty, staff and students. In addition to multiple awards and recognitions for faculty and their research teams, I'm particularly proud of the spotlight focused on our pre-doctoral and post-doctoral trainees in this edition of the newsletter. Each of these trainees has exciting projects that they lead under the direction of our world-class faculty. Importantly, the CTEGD provides the robust scientific environment that is the venue for training this next generation of leaders in the fight against neglected tropical diseases caused by parasites.

We also have exciting news that our two core activities, the Biomedical Microscopy Core and the Cytometry Shared Resource Laboratory, are adding new instruments and capabilities that will support CTEGD as well as the broader UGA scientific community. We will highlight these new additions in our next newsletter once the instruments are installed. We thank Provost Pamela Whitten and Vice President for Research David Lee for supporting these core facilities with the new instrumentation.

Last but not least I want to thank the donors that provided support for CTEGD activities. All donations, no matter how small or large, help the CTEGD to achieve our mission of "Global Health Through Research."

**Our Mission:** To pursue cutting edge research on tropical and emerging diseases, train students in this field and effectively tackle global diseases of poverty.

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### Cover image description:

*A super resolution image of Trypanosoma cruzi stained for acetylated tubulin (red), DNA (green) and H<sup>+</sup> pyrophosphatase (acidocalcisomes, blue). Image by Kandasamy, Biomedical Microscopy Core. Sample courtesy of Melissa Storey, Docampo Laboratory.*





## Researchers battle neglected diseases around the globe

by Leigh Beeson

Photo by Andrew Tucker

**A UGA center takes on a public health problem that includes more than a dozen diseases of poverty.**

Lymphatic filariasis. Schistosomiasis. Cryptosporidiosis. They're some of the world's most widespread parasitic diseases, but many people have never heard of them.

Those who live in Western nations are lucky—these diseases don't really have to be on their radar. But for more than 2 billion people across the globe, the risk of contracting a disfiguring or potentially deadly parasitic disease is constant.

UGA's Center for Tropical and Emerging Global Diseases (CTEGD) is aiming to change that.

Founded 20 years ago by Regents Professor of Cellular Biology Rick Tarleton, CTEGD consolidates UGA's extensive, campus-wide tropical disease knowledge and drug discovery expertise into an interdisciplinary research unit that focuses on finding solutions for parasitic diseases. The center has garnered more than \$135 million in research funding, and its 25 faculty, spanning eight departments across four colleges and schools, focus on more than a dozen diseases commonly associated with poverty.

Parasite-caused illnesses ravage developing nations across Africa, Asia, and Latin America, especially in areas already afflicted by inadequate housing, poor sanitation and unsafe water supplies, and stagnant or failing economies. In addition to a significant death toll, neglected disease means billions of dollars in lost productivity—the kind of economic hit that can upheave governments.

"These diseases cause poverty. Poverty breeds unrest. Unrest breeds political difficulties," says Daniel Colley, professor of microbiology and the center's former director. "If you can provide people with good health, you can take away a tremendous amount of angst in people's lives."

But governments often don't have the ability or the resources to fix the problem. And, while several pharmaceutical companies donate existing drugs for some neglected diseases, there's little incentive for pharmaceutical companies to develop new treatments for many of them, says Kojo Mensa-Wilmot, head of the Department of Cellular Biology and CTEGD member.

"If a large pharmaceutical company goes to its shareholders and tells them it's going to invest \$300 million to find a drug to treat a disease for people who have it but cannot pay for medication, no

board member will vote for that project, and I cannot blame them," he says. "That's why we need people in academic institutions who are going to spend their time to try and help prevent or mitigate these very important global diseases."

With infectious disease expert and cellular biologist Dennis Kyle now at the helm, the center's diverse group of scientists, which includes entomologists, food safety researchers, geneticists, and more, are united in their commitment to vanquishing global diseases of poverty while training the next generation of scientists.

"It is a point of pride for UGA that we have this world-class assembly of scientists working on parasitic and neglected tropical diseases," says David Lee, vice president for research. "Their work is so impressive and impactful because it is multidimensional, encompassing numerous disciplines from molecular and cellular biology to immunology and vaccinology, and extending from laboratory-based investigations to field work in Africa, South America, and elsewhere."

For Kyle, Georgia Research Alliance Eminent Scholar in Antiparasitic Drug Discovery, the scope of the problem really hit home when he moved to Thailand in the early 1990s.

"I saw people suffering and dying of malaria," Kyle says. "Most don't realize how many people are affected by parasitic diseases like malaria, and the effort to try to eliminate those diseases is just not what it should be."

### Children very vulnerable

People infected with malaria present with symptoms similar to many viral illnesses: fever, chills, and headaches. The difference is that, left untreated, malaria intensifies after the first 24 hours, ultimately leading to respiratory distress and multi-organ failure. There are more than 200 million clinical cases of malaria every year, with almost half a million people dying from the disease. Of those, three out of four are children.

"It sounds like a great decrease from the 2 to 3 million people who died annually from malaria in past decades, but it still means that basically one child under the age of 5 is dying every minute," Kyle says. "We still have lot of people who are suffering, and we have to come up with better drugs to fight the disease."

In partnership with the Bill & Melinda Gates Foundation and Medicines for Malaria Venture, Kyle developed a drug-testing device in his lab and is using it to test thousands of potential treatments in

the hopes of finding the next wonder drug. But it's an uphill battle, as the disease quickly grows resistant to the drugs intended to vanquish it.

"The malaria parasite has adapted to infect us, yet we have to fight it off somehow," Kyle says. "Resistance is a big problem, and that's one of the reasons we study it. We've identified new ways the parasite avoids the current drugs on the market, and we're building on that knowledge to create better drug candidates going forward."

What's going on at the University of Georgia? That's the question Distinguished Research Professor of Genetics Jessica Kissinger hears at parasitic disease conferences across the nation.

"CTEGD put Georgia on the map for tropical disease research," says Kissinger, who was one of the first faculty to be recruited by the center. "Researchers and graduate students want to come to Georgia because we have CTEGD."

Kissinger is a principal investigator on a National Institutes of Health-funded project known as EuPathDB, short for Bioinformatics Resource Center for Eukaryotic Pathogens. The online resource consolidates genomic information from thousands of datasets on more than 280 disease-causing organisms, enabling researchers to look up others' lab results to test hypotheses rather than having to do basic, preliminary experiments themselves. This saves both time and resources. The database, which attracts about 50,000 users per month from countries across the globe, has revolutionized how research on parasites is conducted.

"It's taken for granted if you want to plan a trip that there are lots of online databases you can use, and within seconds, you can find flights from competing companies, what seats are free, and hotel and rental car information," says Kissinger, director of UGA's Institute of Bioinformatics. "They've made your life easier by linking together diverse things. Our EuPathDB database is basically the Expedia or Trivago for research on an important class of human pathogens."

It wasn't Briana Flaherty's PhD '15 first trip abroad when she went with Colley's research group to Kenya. It wasn't even her first trip to a developing nation. But it was the first time she spoke with people who had experienced firsthand the effects of living in areas where the threat of infection with any number of parasitic diseases was constant.

"Tropical diseases are so prevalent in Kenya that it's almost like the common cold." — Briana Flaherty

A doctoral candidate in CTEGD member David Peterson's malaria lab at the time, Flaherty worked with Colley's team to explore the effects of worm-transmitted parasites on immune responses to standard vaccinations.

"Tropical diseases are so prevalent in Kenya that it's almost like the common cold," says Flaherty, now a postdoctoral fellow at the Centers for Disease Control and Prevention. "Everyone has had one, and everyone knows someone whose life has been taken by one. It's why the work of CTEGD is so important."

Colley's work in Kenya is part of a larger global collaboration he founded almost 10 years ago called SCORE, short for Schistosomiasis Consortium for Operational Research and Evaluation. Funded by a grant from the Gates Foundation, SCORE's mission is to control and eventually eliminate schistosomiasis, a disease caused

by worms that leads to anemia and stunted growth and affects at least 240 million people. Another 700 million people are at risk of contracting the parasite, making schistosomiasis one of the major parasitic diseases in the world.

It's not particularly deadly, at least not when compared to malaria, but the adult worms live inside people's veins, laying eggs that ultimately embed and can cause severe damage to surrounding tissues.

"Schistosomiasis contributes to anemia, wasting, and stunting in childhood," Colley says. "Tropical diseases like schistosomiasis keep children from going to school to learn. They keep people from getting good jobs."

"These are important diseases that are vastly understudied. CTEGD is turning that around."

(first appeared in the Spring 2018 issue of Georgia Magazine.)



### Trainee Spotlight on Ruby Harrison

NIH T32 trainee Ruby Harrison is a co-advised by Drs. Michael Strand and Mark Brown in the UGA Department of Entomology. She received a Bachelor's of Science in Entomology from the University of Wisconsin-Madison in 2012 and lived in Madison an additional two years working with mosquitoes as a research assistant. Before coming to UGA to begin her doctoral studies, she spent a year in Gabon, Africa, working as a tropical ecology field technician.

Ruby studies mosquito-microbiome interactions. Currently, she is investigating the influence of the gut microbiome on mosquito reproductive processes. She also plans to begin exploring the role of the mosquito microbiome in deterring pathogen infection in the very near future.

"I chose this research focus because I was inspired by the research of a former graduate student of Dr. Strand's, Dr. Kerri Coon. Kerri pioneered fascinating work on the influence of the microbiota on development in mosquitoes in the immature (larval) stage," said Ruby. "I saw an opportunity to extend her work, to observe if the same bacterial signal essential to larval development is recapitulated in any way in the adult stage."

More broadly, she sees insect-microbe interactions as a promising field which may offer new solutions for mosquito population control and reduction of pathogen transmission.

Ultimately, Ruby hopes to build a career as a vector biologist. For the capstone experience provided by the NIH T32 Training Grant, she is interested in returning to francophone West or Central Africa to work with mosquitoes in the field.

"I am truly grateful to receive the T32 pre-doctoral training fellowship, which presents me the opportunity to interact more closely with the CTEGD, opens doors for possible collaboration, and will help me to pursue my research goals," said Ruby.





## NIH awards UGA researchers \$2.6 million to fight African sleeping sickness

by Alan Flurry

Photo by Andrew Davis Tucker

The National Institutes of Health has awarded \$2.6 million to University of Georgia researchers to develop new drugs to treat human African Trypanosomiasis, also known as African sleeping sickness.

African Trypanosomiasis, commonly known as HAT, is caused by a single-celled parasite called *Trypanosoma brucei*, which is transmitted to humans through the bite of a blood-sucking insect called a tsetse fly.

Following a bite, the parasite multiplies in subcutaneous tissues and eventually crosses the blood-brain barrier to infect the central nervous system, causing changes in behavior, confusion, poor coordination and sleep disturbances. Without adequate treatment, the infection is almost invariably fatal.

Rural populations in sub-Saharan Africa that depend on agriculture, fishing, hunting and animal husbandry are most likely to be exposed to the tsetse fly bites, according to the World Health Organization, which has led sustained control efforts to reduce the number of new cases.

"There are immense challenges in understanding trypanosome biology because a significant number of their genes are not found

in humans or yeasts, which are more intensely studied," said Kojo Mensa-Wilmot, professor in the department of cellular biology in the Franklin College of Arts and Sciences whose team was awarded the NIH grant. "Using chemical biology tools to identify disease-relevant genes in the parasite, we discovered a small-molecule that prevents duplication of the nucleus in a trypanosome, and arrests proliferation of the parasite."

"Our goal is to translate this basic science finding into the design of drugs to treat HAT," he said. Using an animal model for the disease, the UGA-led team administered a drug that cured HAT in mice.

"HAT is a disease of poverty, so there is little incentive, understandably, for large pharmaceutical industries to be heavily invested. Two compounds are currently in clinical trial, but the pipeline for new anti-trypanosome drugs needs to be bolstered," said Mensa-Wilmot, who leads a UGA Chemical Biology Group and is a member of the Center for Tropical and Emerging Global Diseases.

Collaborators in the UGA-led consortium are Andrei Pural of Cleveland BioLabs Inc. and Michael Pollastri, department of chemistry and chemical biology at Northeastern University.



**Dennis Kyle**, GRA Eminent Scholar in Antiparasitic Drug Discovery and Director of The Center for Tropical and Emerging Global Diseases, was awarded Medicines for Malaria Venture (MMV) Project of the Year 2016 jointly with two other drug discovery research teams. The award recognizes his team's impressive progress in developing new assay platforms to test compounds for activity against the dormant liver stages of malaria. These new assays are making it possible to screen and identify novel compounds that could prevent relapse and protect against *Plasmodium vivax* and *Plasmodium ovale* malaria.

"There is a huge unmet medical need for new medicines to stop the debilitating relapse of *P. vivax* malaria," said Dr. David Reddy, MMV's CEO. "Each episode keeps a child or adult from school or work for at least 3 days. This places a huge burden on countries and communities that can afford it least. These three research teams have made impressive strides towards helping meet this unmet need and are deserving recipients of MMV's Project of the Year 2016."

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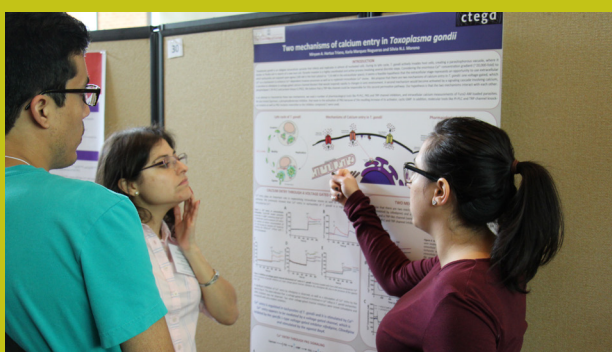
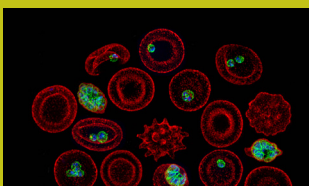
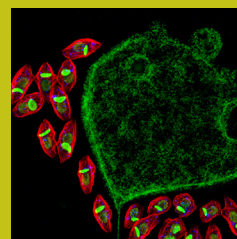
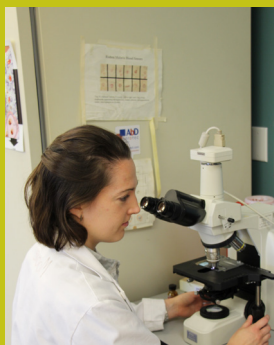
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The Georgia Center, University of Georgia, Athens, GA



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- 12 Talks from top graduate students & senior researchers
- Keynote Address by Patricia Johnson, UCLA

The Molecular Parasitology & Vector Biology Symposium is a day-long interactive conference on parasites and host/parasite interactions. This regional symposium routinely draws 150+ attendees from many departments at UGA and colleagues from other institutions in the southeast.

This year's symposium will include talks and poster presentations from graduate students, postdoctoral fellows and leading researchers and concludes with a keynote address by Patricia J. Johnson, UCLA Molecular Biology Institute.

This event is free but registration is required. For more information visit:

<https://ctegd.uga.edu/events/symposium>

**Abstracts Due:**  
**Friday, April 6, 2018**



**Center for Tropical & Emerging Global Diseases**  
**UNIVERSITY OF GEORGIA**





## UGA researchers receive NSF grant to study hormone regulation in mosquitoes

by Donna Huber

Mosquitoes transmit diseases such as Zika virus, dengue, and malaria to people and other vertebrates worldwide. In a newly funded National Science Foundation (NSF) project, Michael Strand and Mark Brown, both professors in the Department of Entomology and members of the Center for Tropical and Emerging Global Diseases, hope to gain new insights into how hormones coordinate immune responses with reproduction.

The immune and reproductive systems of all animals, including mosquitoes, require large amounts of energy but how these energetic demands are regulated at the molecular level are poorly understood. How immune defenses are regulated relative to other functions like reproduction is of long-standing interest and the main goal of this project is to answer this question.

Mosquitoes provide an interesting system for addressing these issues because almost all species must feed on blood from a vertebrate host, such as humans or another animal, to reproduce. However, blood feeding exposes mosquitoes to microorganisms that cause disease in mosquitoes, the vertebrate hosts mosquitoes feed upon, or both. Background studies by Strand and Brown have shown that certain hormones co-regulate reproduction and immune defense.

“What we hope to characterize in this project are the biochemical

pathways these hormones interact with, and how these pathways affect the ability of mosquitoes to defend themselves from infection,” said Strand. “We also will learn whether these pathways function similarly or dissimilarly between species.”

The fundamental questions about reproduction and immunity that this project is designed to answer apply not only to mosquitoes but to all animals. “The information we generate will also potentially provide information that can be applied toward reducing mosquito reproduction and transmission of pathogens that cause human disease,” said Strand.

NSF requires grant recipients to engage in activities that have broader impacts that enhance STEM education and improve science literacy in the general public. “The public at-large generally knows that mosquitoes can transmit human diseases, but people often do not understand how disease transmission occurs or why some mosquito species are disease vectors but most are not,” said Strand. In conjunction with Georgia 4-H and the Cooperative Extension Program at UGA, teaching materials for middle and high school students will be developed that explain disease transmission, the mosquito life cycle, and strategies for controlling vector populations.

National Science Foundation Award #1656236 “Endocrine regulation of immunity and reproduction in mosquitoes”



### Trainee Spotlight on Evgeniy Potapenko

Evgeniy Potapenko, a post-doctoral trainee in Roberto Docampo’s laboratory, is from Kyiv, Ukraine. He obtained his MD from Bogomolets National Medical University (Kyiv) in 1997. Then he proceeded to earn a Ph.D. from Bogomoletz Institute of Physiology (Kyiv) in 2004. Later he conducted postdoctoral training in Europe at the

University of Goettingen and the University of Birmingham and also in the USA at Augusta University before coming to the University of Georgia. Evgeniy is a recipient of the Center’s NIH funded T32 Training Grant for Interdisciplinary Parasitology, Vector Biology, and Emerging Diseases.

Generally, Evgeniy is interested in mechanisms of transmembrane transport and their role in parasite homeostasis. His current project goal is to characterize how the IP3R function modulated within the *Trypanosoma brucei*, the parasite that causes African Sleeping

Sickness, acidocalcisomes where it resides and how deregulation of this process can contribute to cell death. This research topic addresses poorly studied mechanisms of parasite physiology and has the potential importance of discovering new methods of patient treatment.

Each T32 trainee is provided with the opportunity to complete a capstone experience at the end of their fellowship. This experience often involves an extended visit to a collaborator’s laboratory to learn new techniques or to an endemic country to see how their research connects to actions being taken in the field.

“I hope to expand my expertise in both electrophysiology and cellular biology approaches, which will allow me to conduct independent research,” said Evgeniy.

Fellowships like the T32 training grant provide important opportunities to trainees. “T32 is a unique possibility to prepare me for an independent research career,” said Evgeniy. “It gives great tools to achieve this goal.”



### Trainee Spotlight on Molly Bunkofse

NIH T32 trainee Molly Bunkofse, a Ph.D. student in Rick Tarleton's laboratory, is originally from Illinois and I obtained my BA in Biology from a small, liberal arts college called Augustana, which is located in Rock Island, IL.

Molly's project focuses on the host CD8+ T cell response that is generated against flagellar proteins from the parasite *Trypanosoma cruzi* and exploring how these responses might be enhanced.

"I chose this research focus because I have always been interested in the host immune response to pathogens and especially pathogens that are able to escape the immune response and persist, such as the case in *T. cruzi* infection."

Each T32 trainee is provided with the opportunity to complete a capstone experience at the end of their fellowship. This experience allows for an extended visit to a collaborator's laboratory or travel to a scientific meeting where they present their research and interact with colleagues.

"For my capstone experience, I'd like to work in South America where Chagas disease is endemic, perhaps with one of our collaborators that works with human patients infected with *T. cruzi*."

"I think that the T32 fellowship will provide me with new opportunities to develop my research and skills as a scientist. The experiences and training will enable me to become a well-rounded scientist that can think critically and logically approach a question/problem."

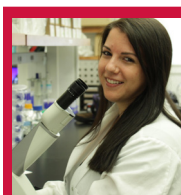
Molly hopes to continue her research in a government laboratory after graduation.

### Biomedical Microscopy Core

The Biomedical Microscopy (BMC) provides access to confocal, deconvolution, super resolution and other optical microscope systems that are useful for multicolor imaging of live and fixed cells and tissue samples, and high-content screening.

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### Trainee Spotlight on Beatrice Colon

Beatrice Colon, an Illinois native, is a Ph.D. trainee in Dennis Kyle's laboratory. She holds a Bachelor of Science degree from the University of Illinois at Urbana-Champaign and a Master of Science degree from the University of South Florida (USF). She began her Ph.D. at USF as well.

Beatrice moved to the University of Georgia in January 2017 with the Kyle Lab.

"I decided to transfer universities because of the excellent infectious disease department," said Beatrice.

"My favorite thing about the CTEGD is the openness for collaborations; the center is also very focused on training a new generation of scientists."

Beatrice is currently working on a drug discovery project for the brain-eating amoeba, *Naegleria fowleri*. The disease was the major factor that drew her to the project. Primary amoebic meningoencephalitis is nearly always fatal and affects young healthy children. Moreover, there is not an effective drug treatment for people that do get infected with the amoeba.

In her short time at UGA, Beatrice has won first place for a poster presentation at the graduate student and postdoc symposium. She was also selected for the Biology of Parasitism course at Woods Hole, MA this past summer.

"This course was definitely a career-changing experience – I was able to work with a variety of infectious diseases and learn techniques that were not available for the parasite I work on."

Beatrice is interested in staying in drug discovery for infectious diseases and currently looking at positions in both academia and industry.



### CTEGD receives award from Georgia Bio

The Center for Tropical & Emerging Global Diseases received a Community Award, presented to those whose contributions to Georgia's life sciences community are worthy of special recognition. Directed by Dennis Kyle, CTEGD is one of the largest international centers of research focused on diseases of poverty common to undeveloped and poor regions of the world. CTEGD researchers work on diseases that afflict hundreds of millions of people around the globe, including malaria, schistosomiasis, African sleeping sickness, Chagas disease, cryptosporidiosis, toxoplasmosis, leishmaniasis and filariasis.





## Pathway to a cure: Roberto Docampo targets lethal parasites

by Leigh Beeson

### Chagas disease and African sleeping sickness kill more than 10,000 people every year in Latin America and Africa.

Millions are currently living with the potentially deadly diseases, and tens of millions more are at risk of being infected.

With numbers like those, you'd expect more people to be paying attention. But neither Chagas nor sleeping sickness receives much press.

Roberto Docampo wants to change that.

"In some areas, you have 50 to 60 percent of people who are infected with Chagas disease," says Docampo, the Georgia Research Alliance Eminent Scholar in Cellular Biology. This obscenely high disease burden strains developing nations' resources by reducing the available workforce and complicates even the most routine medical procedures by making it almost impossible to ensure a parasite-free blood supply for surgeries and transfusion.

The inadequate housing that frequently dots the landscapes of impoverished nations makes the task of eradicating the bugs much more difficult.

"The insects that carry the parasite invade houses, so it's practically impossible to eliminate the disease," Docampo explains. "The only way to do it is by improving housing, which would prevent the bugs from getting inside," something that may not be possible in the nations where the diseases are most prevalent. Instead, Docampo is working to find new targets and tools that could eliminate the trypanosome parasites that cause both Chagas and sleeping sickness.

Most cases of Chagas disease occur in Latin America, where infected kissing bugs, also known as assassin or vampire bugs, bite people or animals and transfer the parasite into their bloodstreams. African sleeping sickness is contracted through the bite of a tsetse fly.

### DOCAMPO'S ORGANELLE

University of Georgia's Roberto Docampo and his team discovered an organelle that is necessary for the survival of the trypanosomes, making it a potential target for drugs. The team is now investigating medical interventions that could destroy the parasite by singling out the organelle.

Working with colleagues in the university's Center for Tropical and Emerging Global Diseases, Docampo discovered a specialized structure, or organelle, inside the trypanosome parasites.

Proteins within this structure proved to be responsible for the parasite's growth and replication, making ideal targets for fighting the disease.

"These parasites are separated by millions of years of evolution from humans, and it is theoretically possible to target these organelles for chemotherapy," Docampo says. "The idea is always to find pathways that are different in the parasite than in the host in order to find targets for vaccines, drugs or diagnostics."

Experiments proved the organelle may be the key to successfully battling the trypanosome: Once the proteins were disabled, the parasite couldn't reproduce or cause disease in its host.

Docampo is now looking for ways to specifically target those proteins with medications. His lab has already shown that the parasites that cause Chagas are vulnerable to specific antifungal agents, and he is continuing to search for new targets that could eliminate the threat trypanosomes pose to both humans and animals.

"These are fundamental discoveries about cellular function and life," Docampo says. "We will continue to investigate these structures and pathways in the hope of finding new therapies to treat these diseases that affect so many people."

first appeared on [Great Commitments](#)



An international team of researchers which includes **Jessica Kissinger** launches the Clinical Epidemiology Database, an open-access online resource. Read the full story at [Medical Xpress](#).



## The cure for malaria could be in your backyard

by Donna Huber

Malaria is a mosquito-borne disease that has a disproportionate effect in poor and underdeveloped countries without access to western medicine. According to the [WHO's World Malaria Report](#), there were 212 million new cases of malaria worldwide in 2015 and an estimated 429,000 deaths.

Malaria is caused by the *Plasmodium* parasite. *Plasmodium falciparum* is the deadliest of the species infecting humans, causing 50% of all malaria cases. Unfortunately, it has become resistant to current drug treatment.

Belen Cassera and her laboratory group at the University of Georgia have been identifying possible compounds for new antimalarial medication from natural plant sources.

Malaria has long been treated with plant-based medicine. Quinine, which comes from the bark of a cinchona tree, was first isolated as an antimalarial compound in the 1800s, though there is evidence that bark extracts have been used to treat malaria since the 1600s. The cinchona tree is native to Peru.

Quinine was the treatment of choice until the 1940s when other drugs, with fewer side effects, replaced it. One of those drugs was chloroquine, which was discovered in 1934. Following World War II, chloroquine became the preferred treatment for malaria and was prominent in mass drug administration programs of the 1950s. This wide-spread use, in part, led to chloroquine resistant strains of *P. falciparum*.

The rise of chloroquine-resistance led to the discovery of several potential synthetic alternatives. However, in 1972 Chinese scientists isolated artemisinin from *Artemisia annua*, commonly known as sweet wormwood. It is native to Asia but has been naturalized in several regions including North America. It has been the main treatment of malaria in south-east Asia. However, in recent years artemisinin resistance has also emerged. (Source: [History of Anti-malarials](#))

Cassera in collaboration with David Kingston at Virginia Tech and Michael Goetz and Jason Clement from the Natural Product Discovery Institute (NPDI) has a grant from the National Center for Complementary and Integrative Health ([R01 AT008088](#)) to study plants in the NPDI Repository to identify new antimalarial compounds.

In this project, they are concentrating on plants that have not been studied for their anti-malarial properties. Also, they are looking at

plants that indigenous people have used to treat the various symptoms associated with malaria.

So far over 28,000 extracts have been screened and the team has identified over 100 compounds with anti-malarial activity.

In recently published findings, the group has reported the discovery of anti-malarial compounds in *Malleastrum* sp., *Crinum firmifolium*, and *Magnolia grandiflora*. The first two are plants found in Madagascar, but the last one is better known as the southern magnolia and can be found in backyards throughout the southeastern United States.

From the southern magnolia extracts, the Cassera and Kingston labs identified two new compounds with anti-malarial activity. It was also discovered that it contained six compounds that have been identified in other plants as possible malaria drug compounds. An online version of the study is available: <https://doi.org/10.1002/cbdv.201700209>

Extracts from *Crinum* species, which are in the amaryllis family, have been used traditionally to treat ailments including fever, pain management, swelling, sores and wounds, cancer, and malaria. Following success in isolating new anti-malarial compounds from an extract of *Crinum erubescens* L. F. ex Aiton, they turned to *C. firmifolium*, which was already in their International Cooperative Biodiversity Group collection. Extracts yielded 4 known compounds and three new compounds with possible anti-malarial activity. It was observed that the potency of several of the compounds against the drug-resistant strain of *P. falciparum* was approximately the same as their potency against the drug-sensitive strain. An online version of the study is available: <https://doi.org/10.1016/j.bmc.2017.06.017> An extract of the wood from a species of *Malleastrum* in the mahogany family was found to have moderate antimalarial activity against a drug-resistant strain of *P. falciparum*. The genus *Malleastrum* (Baill.) J.-F. Leroy is endemic to Madagascar and comprises 20 currently accepted species. However, there appear to be at least four previously unidentified species. The plant material in this study is almost certainly from one of the species that is still waiting to be named and described. An online version of the study is available: <https://doi.org/10.1002/cbdv.201700331>

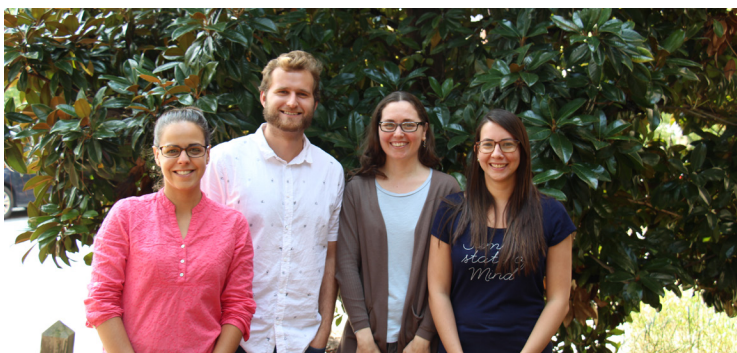
"We have identified some really promising compounds," said Belen Cassera. "A few could be ready for pre-clinical studies in a few years."



In addition to testing for anti-malarial activity, the Cassera lab is also looking at the mechanism of action – how the compound works. This is an important step in drug discovery; because once it is understood how the compound works a synthetic analog could be synthesized and manufactured at a cheaper cost and in a safer form.

Each compound they have identified has several molecules associated with it. In their current state, some of these compounds have too high of a toxicity to be considered for potential drug treatment. Therefore, it is important to strip the compound down to only those molecules that have potent antimalarial responses and hopefully they can remove the molecules associated with toxicity. Once this has been accomplished, then matching synthetic molecules can be created in the lab and scaled up for mass production.

Being able to create these synthetic molecules is a necessary step in the drug discovery process. Natural material can be costly to collect or not available in abundance. While the southern magnolia seems to be abundant in the yards of Georgia, its natural range only stretches from coastal North Carolina south to central Florida, and then west to eastern Texas and Oklahoma. In addition, due to environmental differences, many times compounds isolated from a plant from one part of the world cannot be found in the same plant grown in another which reinforces the need to focus on active compounds that can be resynthesized in the lab.



The Natural Products Research Team at UGA

With the appearance of drug resistant strains of the malaria parasite to all current medications, it is imperative new treatments be discovered. Since plant-based and traditional medicine have yielded a number of drugs historically it is likely that the next treatment option will again come from a plant source. There are countless numbers of plants that have yet to be studied for their anti-malarial uses. Belen Cassera and her team just might find the cure for malaria in your backyard.



**Patrick Lammie**, CTEGD member and adjunct faculty in the Department of Cellular Biology, was awarded the Donald Mackay Medal during the American Society for Tropical Medicine and Hygiene's (ASTMH) annual meeting in Baltimore, MD.

The Donald Mackay Medal recognizes outstanding work in tropical health, especially relating to improvements in the health of rural or urban workers in the tropics. In a long-standing partnership with the Royal Society of Tropical Medicine and Hygiene (RSTMH), the Donald Mackay Medal is awarded in odd years by ASTMH and in even years by RSTMH.

## Trainee Spotlight on Catherine Smith



Catherine Smith is a Ph.D. trainee in Julie Moore's laboratory. She is originally from Rochester, New York and received her B.S. from Haverford College in Pennsylvania before coming to the University of Georgia. Catherine is a second-year recipient of the Center's NIH T32 Training Grant for Interdisciplinary Parasitology, Vector Biology, and Emerging Diseases.

Catherine is studying the role of syncytiotrophoblastic autophagy in the pathogenesis of placental malaria.

Placental malaria is a severe manifestation of *Plasmodium falciparum* infection that impacts pregnant women and causes poor birth outcomes, including pregnancy loss and low birth weight.

The placenta acts as the connection between a mother and her fetus. Within the placenta, a fetal tissue, the syncytiotrophoblast, acts as the interface between the maternal and fetal blood supplies. During maternal malaria infection, *P. falciparum*-infected red blood cells adhere to the syncytiotrophoblast.

"The response of the syncytiotrophoblast to maternal malaria infection is not completely understood," said Catherine. "I hypothesize that the trophoblast performs autophagy, a self-eating mechanism that allows cells to recycle damaged proteins and organelles, to offset the stress caused by maternal malaria infection."

While working to characterize the role of syncytiotrophoblastic autophagy in placental malaria pathogenesis, she observed that mice bred and reared in different facilities exhibited differences in susceptibility to malaria infection regardless of pregnancy status. This difference in susceptibility can be attributed to differences in the composition of the gut microbiota. The immunological mechanisms driving this difference in susceptibility have yet to be defined. The Moore Lab plans to explore the immunological mechanisms underlying this gut microbiota-dependent difference in susceptibility to malaria infection in pregnant and virgin mice.

Catherine chose to study placental malaria because she was interested in exploring host-pathogen interactions and the basic cellular biology of the placenta. In addition, she chose to join Dr. Moore's laboratory because she was interested in contributing to a field of research with the potential to improve the lives of women and infants around the world.

Each T32 fellow is provided with the opportunity to complete a capstone experience. Catherine plans to travel to a collaborator's laboratory in the United States where she will complete specialized experiments that cannot be performed at The University of Georgia.

"The T32 fellowship has enhanced my training by allowing me to focus on my research," said Catherine. "As part of my capstone experience, I plan to spend some time in a collaborator's lab, which will allow me to form relationships with scientists at other institutions, learn new techniques, and perform experiments that will strengthen my research project."

After completing her training, Catherine plans to pursue a career in parasitology research in either an academic or an industrial setting.

# CTEGD-Janssen Visiting Scholars Program

Through the generous support of Janssen Research and Development

## **The Center for Tropical & Emerging Global Diseases at The University of Georgia**

is pleased to announce competitive visiting scholar positions in the area of Chagas Disease for highly qualified investigators from Latin America.

- Selected Post-doctoral Scholars will receive round-trip travel support, 12-months salary, and health insurance benefits.
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See complete program details at: <https://ctegd.uga.edu/scholars/>

Email us with questions at [ctegd-scholars@uga.edu](mailto:ctegd-scholars@uga.edu)



**Center for Tropical &  
Emerging Global Diseases**  
**UNIVERSITY OF GEORGIA**

*Global Health Through Research*







## A double hit strategy may provide better treatment for toxoplasmosis

by Donna Huber

Silvia Moreno and her research team at the University of Georgia's Center for Tropical and Emerging Global Diseases and Department of Cellular Biology provided evidence that it is possible to develop a drug combination that acts synergistically by inhibiting host and parasite enzymes in a recently published article in *Antimicrobial Agents and Chemotherapy*.

Toxoplasmosis is caused by the pervasive intracellular Apicomplexan parasite *Toxoplasma gondii*. The parasite is found throughout the world and can infect humans and a number of animal species. In the U.S., people may contract it by consuming undercooked meats, especially pork, lamb, venison, or through contact with contaminated cat feces.

Human infections are usually asymptomatic but the parasite can persist in the form of tissue cysts. It has been estimated that 30–50% of the global population may be chronically infected with *Toxoplasma*. The immune system of a healthy individual can control the infection, but it can reactivate when there is immunosuppression due to organ transplant, cancer chemotherapy, or in people infected with HIV.

Toxoplasmosis is especially dangerous to the unborn fetus when the mother becomes infected during pregnancy as it can result in miscarriage or stillbirth. Surviving infants can suffer from visual, hearing, motor, cognitive, and other problems.

Some strains of *T. gondii* can cause severe ocular disease in people with a healthy immune system. Current drug therapies do not prevent disease progression that leads to blindness in ocular toxoplasmosis patients.

Toxoplasmosis represents a serious public health problem and no preventative or therapeutic vaccine is available for humans.

Drugs presently used against toxoplasmosis do not eradicate chronic infection and as many as half of treated patients do not respond to the therapy. Additionally, a large number of people have an allergic reaction to the current treatment option. Furthermore, some of the current drugs have recently become very expensive.

There is a need for safe and effective treatment.

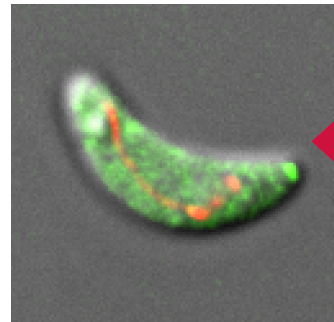
Moreno and her team study the isoprenoid pathway to identify new drug targets. Isoprenoids are lipid compounds with many important functions. One particular step in this pathway has been identified as essential in *T. gondii*. A drug targeting this pathway could kill the

parasite.

Moreno's group proposes a double hit strategy of combining inhibitors of host and parasite pathways as a novel approach against toxoplasmosis. They have found a synergistic effect by combining new and potent sulfur-containing bisphosphonates, as well as other commercially available bisphosphonates, with several statins against a lethal infection of *T. gondii* using a virulence mouse model.

Bisphosphonates are widely used for the treatment of bone disorders. Previous studies by Moreno and her colleagues have shown that bisphosphonates inhibit the growth of a variety of protozoan parasites like *T. gondii*. There are a number of commercially available bisphosphonate drugs.

Statins are a class of drugs typically prescribed to lower cholesterol. They work by blocking a particular enzyme known as 3-hydroxy-methylglutaryl-coenzyme A reductase. As with the bisphosphonates, there are already a number of commercially available statins.



A *Toxoplasma gondii* parasite with cytosolic Green fluorescent protein and the mitochondrial red fluorescent marker.

Bisphosphonates alone have been very effective when treating a lethal infection of *T. gondii* in mice. However, Moreno's team found that combining bisphosphonates with the statin atorvastatin (Lipitor) was almost 3 times more effective under similar conditions of infection and treatment. Additionally, they found very low doses of both drugs could be used for treatment, which would significantly decrease the potential for adverse side effects.

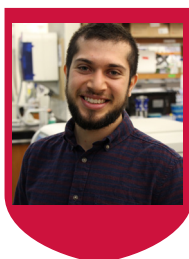
This double hit strategy may be the key to effective treatment because the parasite not only makes its own isoprenoids, but it can also import them from the host. The ability to manipulate the host cell for its own benefit poses a challenge for drug development against toxoplasmosis. Therefore, inhibiting the host from producing this material along with inhibiting the parasite's ability to create isoprenoids is an interesting and novel strategy for drug develop-

ment.

This study demonstrates that early treatment is key to the cure of infection with a particular strain of *T. gondii* for acute infection. Since current treatments often fail to cure chronic infection Moreno and her group will next test this combination strategy in an established chronic infection mouse model.

Furthermore, Moreno predicts that this double-hit strategy of inhibiting both host and parasite pathways will work for other intracellular Apicomplexan parasites, such as the malaria-causing *Plasmodium* parasite. Additional studies will be needed to test this hypothesis.

An online version of this study is available: Li Z-H, Li C, Szajnman SH, Rodriguez JB, Moreno SNJ. 2017. Synergistic activity between statins and bisphosphonates against acute experimental toxoplasmosis. *Antimicrob Agents Chemother* 61:e02628-16. <https://doi.org/10.1128/AAC.02628-16>



### Trainee Spotlight on Manuel Fierro

Manuel Fierro is a pre-doctoral trainee in Vasant Muralidharan's Laboratory. He is originally from Ecuador. His family moved to the US when he was 9 years old, and he has lived in Georgia ever since. Manuel received his Bachelor of Science degree in Cellular Biology from the University of

Georgia in 2014. He is a recipient of the Center's NIH funded T32 Training Grant for Interdisciplinary Parasitology, Vector Biology, and Emerging Diseases.

Manuel's project deals with understanding how calcium is regulated in the endoplasmic reticulum of *Plasmodium falciparum*, the parasite that causes malaria.

"My undergraduate training was in Dr. Silvia Moreno's lab studying calcium signaling in *Toxoplasma gondii* and I wanted to answer the same type of questions in *Plasmodium*," said Manuel.

For his capstone experience, Manuel hopes to go to Ecuador. "My home country of Ecuador is approaching elimination of malaria," said Manuel, "and I would like to work with some of the researchers in the field there who track populations of infected mosquitoes as well as monitor cases of infection in humans."

The T32 training grant allows trainees a number of opportunities that will help them achieve their goals. "I truly enjoy working in a lab, but it is not the same as experiencing what diseases are like in the real world," said Manuel. "This fellowship will help me expand my understanding of malaria by giving me the opportunity to see it in a different setting."

Manuel is currently considering a career in industry, but he is open to staying in academia.

### Thank you for your gift to CTEGD!

Baylee Bruton  
Thomas Chatman  
Christopher Fagot  
Elizabeth Forrester  
Andrew Graham



The University of Georgia has created the Drug Discovery Core laboratory, a campus-wide collaborative facility designed to hasten the development of therapeutic drugs for a number of major diseases.

A survey distributed to UGA researchers in 2016 identified chemical screening and toxicity profiling as the most critical needs for enhancing drug discovery research at UGA, and the DDC will address many of those needs for faculty working in infectious disease, regenerative medicine, cancer biology and other human health-focused disciplines.

Phase one of the new lab will allow for the curation, management and distribution of chemical libraries containing more than 50,000 compounds. The lab also will enable researchers to rapidly screen these chemical libraries in miniaturized models of various diseases using robotics and high-throughput signal detection. Finally, the lab will provide opportunities to identify potential toxicity of the compounds and determine if their chemical properties will allow them to be successfully delivered to patients. Additional capabilities, including pharmacokinetic characterization, genotoxicity and assay design, are under development.

"The most immediate outcome of the DDC lab will be to generate preliminary data from pilot chemical screens, which is necessary to secure large drug discovery grants from the National Institutes of Health to fund more advanced drug discovery research," said Shelley Hooks, interim director of the Center for Drug Discovery and associate professor of pharmaceutical and biomedical science. "The longer-term goals of the lab are to discover and develop new drug candidates and chemical probes, as well as enhance training of graduate students in biotechnology."

Creation of the DDC was initiated by Hooks in collaboration with Brian Cummings, director of the Interdisciplinary Toxicology Program and professor in the pharmaceutical and biomedical sciences department, and Scott Pegan, chair of the DDC steering committee and associate professor of pharmaceutical and biomedical sciences.

Sponsoring campus organizations include the College of Pharmacy, the College of Veterinary Medicine, the Office of Research, the **Center for Tropical and Emerging Diseases** and the Department of Cellular Biology.

The laboratory is located in Room 224 of the Wilson Building in the College of Pharmacy. For more information on capability, resources and access to the libraries and screening instruments, contact Pegan ([spegan@uga.edu](mailto:spegan@uga.edu)) or see [cdd.rx.uga.edu](http://cdd.rx.uga.edu).





## Assistant professor focuses research on environmental drivers of disease

by Beth Gavrilles

Photo by Dorothy Kozlowski

Courtney Murdock was well on her way to becoming a veterinarian; as a pre-vet student at the University of Michigan she majored in biology and volunteered at a small animal hospital. But then she spent the summer before her senior year working at the university's biological field station.

"I learned about general ecology and field mammalogy, and by the end of that summer, I knew I wanted to study ecology in graduate school," she said.

For her doctoral work, also at the University of Michigan, she researched avian blood parasites, becoming interested in the ecology of disease transmission. That led her to Penn State University where she spent five years as a postdoctoral research scholar studying the ecology of disease vectors, the living organisms that carry and transmit diseases.

Now Murdock has come full circle. In 2014 she joined the faculty at UGA as an assistant professor with a joint appointment in the Odum School of Ecology and the College of Veterinary Medicine infectious diseases department.

Murdock's research program is focused on the environmental drivers of disease transmission and the ecology of vector-borne diseases. She is particularly interested in two types of diseases that are transmitted by mosquitoes: human malaria and arboviruses, which include dengue and Zika.

She and her group combine lab and field experiments with computer modeling to generate predictions about disease spread and to evaluate disease control strategies in the context of changing environmental conditions.

As the recent outbreak of Zika demonstrated, the stakes are high. "Often mosquito interventions are the only way to mitigate these diseases," Murdock said, which is why understanding how variables like temperature, rainfall and land use affect mosquitoes' capacity for transmitting disease is so important.

Murdock's research interests inform her teaching, which includes an upper-level undergraduate/graduate course on the population biology of infectious diseases. A participating faculty member in the Infectious Disease Ecology Across Scales interdisciplinary doctoral training program, she also enjoys teaching general ecology for undergraduates.

"It broadens your thinking," she said. "And working with students with different skill sets and backgrounds has helped me become a better mentor."

Murdock's teaching goes beyond the classroom. She is currently developing an Athens-based outreach project to inform people about the risks—and how to mitigate them—of living with mosquitoes, and she recently taught a course on Zika for the UGA Osher Lifelong Learning Institute.

"People want to learn about these issues," she said. "They want to be engaged."

The kind of diversity she values in her students is something Murdock also appreciates about her faculty colleagues.

"The appeal of UGA was the joint position with the College of Veterinary Medicine and the Odum School, and having access to so many renowned colleagues with different expertise than mine," she said.

Murdock cited the Faculty of Infectious Diseases, the Center for Tropical and Emerging Global Diseases and the Center for the Ecology of Infectious Diseases as important resources that make UGA an ideal place for her to work.

"If you're curious, ecology is a good field," said Murdock. "It's theory driven: you make hypotheses and design experiments to test. There are a lot of major problems that can benefit from an ecological perspective and integration from other fields, like antibiotic resistance and urbanization. This is a great time, and a great place, to be an ecologist."

first appeared in Columns



**Dennis Kyle's** research program is featured on Bill & Melinda Gates Foundation's blog [Impatient Optimists](#).

Dennis was also featured as Red & Black's Scientist of the Week in January. [Read the article](#).



### Trainee Spotlight on Msano Mandalasi

Msano Mandalasi, a post-doctoral trainee in Chris West's laboratory, is originally from Malawi, (located in southeastern Africa) and obtained her bachelor's degree in Chemistry from the University of Malawi. After graduation, she worked briefly for the University of Malawi and then came to

the US to obtain a Master's degree in Chemistry. Later, she enrolled in a doctoral graduate program at the University of Maryland Eastern Shore where she graduated in 2012. She spent two years teaching undergraduate Chemistry before deciding to get back into research. She joined Dr. West's group while he was at the University of Oklahoma and moved with the lab to the University of Georgia.

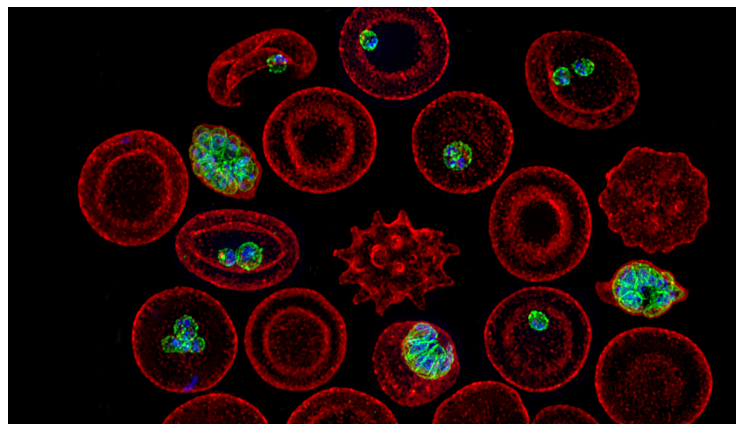
The focus of Msano's project is on the role of prolyl hydroxylation and glycosylation of E3 Ubiquitin ligase on *Toxoplasma* growth.

With a research background mostly in chemistry and biochemistry, her graduate research introduced her to some aspect of parasitology working on Schistosome glycobiology. However, she did not have a strong background in molecular biology prior to joining the West lab. This current project merges glycobiology and molecular biology and also extends some parasitology studies, thus giving her the opportunity to learn molecular biology and parasitology to complement her chemistry background. A combination of this expert knowledge will benefit her to address the research objectives on her *Toxoplasma* project.

Each T32 trainee is provided with the opportunity to complete a capstone experience at the end of their fellowship. This experience allows for an extended visit to a collaborator's laboratory or travel to a scientific meeting where they present their research and interact with colleagues. Msano plans to use her capstone experience to give oral presentations at scientific meetings, to publish some of the studies conducted within this time period, and interact with other trainees in the program.

"Through the funding provided by the T32 Training Grant, I will be able to address research questions that should lead to launching my own area of research," said Msano.

Msano hopes to run her own independent research program in academia one day.



### Researcher seeks to unlock secrets of malaria parasite

by Donna Huber

Image by Muthugapatti Kandasamy

Vasant Muralidharan and his research team at the University of Georgia's Center for Tropical and Emerging Global Diseases are making great strides in understanding how the malaria parasite hijacks red blood cells to cause disease but many of the parasite's strategies remain elusive. A new \$1.875 million grant from the National Institutes of Health will allow them to continue this research.

Malaria is a parasitic disease that infects nearly 220 million people and kills nearly half a million people every year. Almost all the deaths occur in young children and primarily in sub-Saharan Africa. The parasite *Plasmodium falciparum* invades human red blood cells which directly leads to malaria symptoms that include headaches, muscle pain, periodic fevers with shivering, severe anemia, trouble breathing, and kidney failure. The parasite can also cause the most severe forms of malaria, such as cerebral malaria which can lead to brain damage, coma and death, and placental malaria, which occurs in pregnancy and can be life-threatening to both the mother and fetus.

Complete control of the infected red blood cell is required for parasites to grow and spread. The malaria parasite remodels the host cell by exporting hundreds of parasite proteins across numerous membranes that transform all aspects of infected red blood cells to suit its needs. The export of these proteins by *P. falciparum* to the host red blood cells is a unique parasite-driven process that is associated with many of the clinical manifestations of malaria, including death. The mechanisms which these proteins are exported are unknown.

"Exported proteins, many of them absolutely essential for the growth of the parasite, are recognized and sorted throughout the trafficking process by dedicated machinery that we have only now begun to understand," said Muralidharan, assistant professor in the department of cellular biology.

His lab hopes to reveal unique protein trafficking mechanisms of *P. falciparum* that may be targets for antimalarial drug development.

"We expect that this project will significantly advance our understanding of the protein export pathway in *P. falciparum* and how key decisions are made within the parasite that usher exported proteins to their site of action in the infected red blood cells," concluded Muralidharan.

National Institutes of Health Award R01 AI130139 "Elucidating the trafficking mechanisms of effector proteins to the *Plasmodium* infected red blood cell."



The Center for Tropical & Emerging Global Diseases, Dept. of Infectious Diseases, and Office of Research invite you to a reception honoring

**Dr. Julie Moore**

for her years of service to the University of Georgia.

Wednesday, May 9, 2018  
4:00 pm - 6:00 pm  
The Terrace Room, Garden Club  
State Botanical Garden





## An ancient bacterial protein complex in human malaria parasites is essential for parasite growth

by Donna Huber

Several species of *Plasmodium* parasites cause malaria in humans and results in nearly 450,000 deaths annually. The deadliest of these species is *Plasmodium falciparum*. Unfortunately, it is also drug resistance to many of the currently available treatments. Vasant Muralidharan, assistant professor in the department of cellular biology, and his research group at The Center for Tropical and Emerging Global Diseases at The University of Georgia reported on an essential protein in hopes of identifying new drug targets.

*Plasmodium* parasites contain an organelle known as the apicoplast that evolved via the endosymbiosis of a red alga. The apicoplast produces several essential metabolites required for parasite growth and survival. Therefore, drugs that target the apicoplast are clinically effective. However, there is still not a lot known about this organelle. Understanding the function, structure, and biogenesis of the apicoplast provides a gold mine of antimalarial drug targets.

Clp (Caseinolytic Proteases) are conserved prokaryotic proteins that serve a wide variety of biological functions in bacteria, the evolutionary ancestors of the apicoplast. Several Clp proteins have been reported to localize in the apicoplast of the parasite but their biological functions were unknown.

The research team used different genetic tools to conditionally inhibit the function of various apicoplast-Clp proteins. "It is similar to understanding the role of a single card in holding up a house of

cards by removing it from the structure," said Muralidharan.

Their data show that the Clp chaperone PfClpC is essential for parasite viability and that its inhibition resulted in morphological defects, and loss of the apicoplast. They also revealed that the chaperone activity is required to stabilize a Clp Protease, PfClpP, suggesting that, similar to bacteria and plants chloroplasts, these two proteins form a proteolytic complex. These data may be relevant to the function of bacterial and plant Clp complexes. "Our findings shed light on the biological roles of the apicoplast Clp Proteins and their involvement in apicoplast replication," said Dr. Anat Florentin, lead author on the study.

The role that bacterial Clp proteins play in cell division, stress response and ability to cause disease have placed them at the center of several drug discovery programs. The new understanding of Clp proteins in *Plasmodium* provides an avenue for drug development in malaria in which highly active antibacterial compounds can be repurposed as effective anti-malarial agents.

An online version of this study is available: A. Florentin, D.W. Cobb, J.D. Fishburn, M. J. Cipriano, P.S. Kim, M.A. Fierro, B. Striepen, V. Muralidharan. 2017. PfClpC is an essential Clp chaperone required for plastid integrity and Clp protease stability in *Plasmodium falciparum*. *Cell Reports* 21, 1 – 11. <https://doi.org/10.1016/j.celrep.2017.10.081>



### Visiting Scholar: Elvis Ofori Ameyaw

Elvis Ofori Ameyaw is a Fulbright Scholar visiting M. Belen Cassera's laboratory in the department of molecular biology and biochemistry. He is a senior lecturer, Head of the Department of Biomedical Sciences and the Vice-Dean of the School of Allied Health Sciences in the College of Health

and Allied Sciences at the University of Cape Coast in Ghana.

Dr. Ameyaw holds a B. Pharm and Ph.D. in Pharmacology. His research focuses on natural product drug discovery for infectious, in particular, malaria and Leishmania, and inflammatory diseases. At the University of Georgia, he is using in vitro techniques to screen some natural products isolates from plants that are traditionally used to treat malaria in Ghana.

"UGA is globally known for excellent research and education and my host scientist, Prof. M. Belen Cassera has created an envious and reputable niche in natural product research," said Dr. Ameyaw.

The availability of seminars and other opportunities to interact with leading scientists also factored into Dr. Ameyaw's decision to come to UGA.

"The research staff at UGA are very supportive and willing to share ideas," said Dr. Ameyaw.

Athens reminds him of the college town of Cape Coast where he resides and works in Ghana.

"The city makes me feel at home away from home."





## Trainee Spotlight on Kerri Miazowicz

Kerri Miazowicz is a 3rd year Ph.D. trainee in Courtney Murdock's laboratory. She grew up in southern Michigan where she received a B.S. in microbiology from Michigan State University in 2012. After graduation, she spent more than two years as a Postbaccalaureate IRTA Fellow at the Rocky Mountain Laboratories, NIH/NIAID in Montana with the Virus Ecology Unit within the Laboratory of Virology.

Kerri chose the University of Georgia for her graduate training because she wanted to conduct interdisciplinary research related to disease ecology and vector-borne disease transmission.

"UGA hosts many experts across several scientific disciplines allowing me to link molecular biology and individual level phenotypes to population-level dynamics," said Kerri. "UGA is also home to the Center for Tropical and Emerging Global Diseases and the Center for Ecology of Infectious Diseases (CEID), which both provide valuable research resources and expertise."

Kerri's research focuses on environmental drivers of mosquito-borne disease transmission. Mainly, understanding how the environment affects the mosquito vector and modeling the consequences of these interactions on transmission dynamics.

"My current project revolves around temperature effects on *Anopheles stephensi* [the primary mosquito that transmits malaria in Asia] trait performance (longevity, biting frequency, and population growth), and mathematically exploring the implications these effects have on transmission."

She will also investigate how *Plasmodium*, the parasite that causes malaria, exposure and infection modify these mosquito traits which are critical in transmission events.

"I find vector-borne diseases interesting due to the immense complexity that these systems contain," said Kerri. "I also find it interesting to think about 'scaling-up' the outcome of molecular interactions and individual phenotypes to the context of population-level dynamics."

Kerri has been able to conduct fieldwork within the Athens area to study how microclimate across an urban area can influence mosquito development along with adult mosquito traits which are important for mosquito-borne disease transmission.

"If I was able to travel for research purpose, it would be to India or

Africa, where malaria is endemic, to study local mosquito populations."

Kerri has received a number of awards recognizing her academic and research achievements. In 2009, she was named a 2008-2009 Regional Semifinalist for the Young Epidemiology Scholars (YES) Program. In 2010, Kerri was named a National Institutes of Health Undergraduate Scholar.

In 2014, she received an OITE Travel Award to attend the NIH Graduate and Professional School Fair, which allows NIH interns and postdocs to explore where the next step in their training will be.

Since coming to UGA, she has received an American Society of Virology Travel Award (2016) and a National Science Foundation Graduate Research Fellowship that funds 3 years of research training. In 2017, she received a travel award to attend the annual meeting of the Vector Behavior Ecology Research Coordination Network (VectorBITE RCN) at Imperial College in London.

While Kerri has a few more years of training at UGA, she hopes to continue conducting scientific research related to disease ecology and transmission dynamics in either an academic or government setting.



Schistosomiasis expert **Daniel Colley** is quoted in the Science article "Worms living in your veins? Seventeen volunteers said 'OK'" [Read the article.](#)





## Drug discoveries: Dennis Kyle uncovers drug resistance in malaria and brain-eating amoeba

by Leigh Beeson

### Roughly half a million people die every year from malaria.

It's a significant decrease from the millions who died from the disease each year a decade ago, but with three of every four malaria-related deaths being children under the age of 5, that's still one child dying every minute. And the parasite that causes the disease is growing resistant to drugs we have to battle it.

Dennis Kyle puts the problem in simple terms: "We have to come up with better compounds to fight the disease."

And that's just what he's doing.

Kyle serves as the director of the University of Georgia's Center for Tropical and Emerging Global Diseases, an interdisciplinary venture that focuses on tackling diseases that affect millions around the world. His area of expertise lies in developing new drugs and investigating drug resistance mechanisms to see why the drugs we have to combat certain diseases don't work or stop working.

Led by director Dennis Kyle, researchers in the University of Georgia's Center for Tropical & Emerging Global Diseases focus on a variety of neglected tropical diseases that devastate many of the world's poorest nations. Dennis Kyle studies malaria and brain-eating amoeba, among other maladies.

"Pretty much every drug that we come up with for malaria, within a few years of treating people with it, we get resistance," says Kyle, the Georgia Research Alliance Eminent Scholar in Antiparasitic Drug Discovery. He worked on the drug that is currently prescribed to people planning to visit Africa to protect them against the diseases and "saw the first case of resistance in the second person we treated."

In order to better protect travelers, that drug is now being used in combination with other medications, following the protocol set in place by researchers contending with drug-resistant tuberculosis.

An additional concern is that, in about half of the cases of malaria, the parasites enter the liver and become dormant, sitting for weeks, months, even years before being reawakened and thrusting their host into illness.

Working with the Gates Foundation and Medicines for Malaria Venture, Kyle developed a way to mimic the conditions in the liver for drug testing, and his lab is testing thousands of drug compounds to find new ones to serve as replacements for those that become

ineffective.

His lab is also testing compounds against brain-eating amoeba, or *Naegleria fowleri*, a deadly organism found in many of the South's freshwater lakes and rivers that travels up the nose and into the brain, where it destroys brain tissue. Infections are rare, but almost all cases are fatal.

"It's terrifying. It's the most pathogenic of any of the parasites we work on," Kyle says.

A more ubiquitous amoeba to worry about is the *Acanthamoeba*, which is frequently found in contact lens cases. This microorganism enters the eyeball through abrasions on the surface of the eye, causing intense pain and potentially blinding or impairing vision permanently. When growing conditions aren't ideal, the amoeba hardens and forms a cyst, which protects it and helps it survive until it can revert back to its amoebic form.

The compounds on the market now "probably overestimate" their efficacy in battling the microorganism, and most of them can't penetrate the surface of the cysts, says Kyle. But his lab is working on a solution that could eliminate the threat of *Acanthamoeba* to contact lens wearers by destroying the amoeba in both of its forms.

"All these parasites have adapted to infect us, and we have to fight them off somehow," Kyle says. "We have this misconception that they aren't something we have to worry about here in Georgia or the U.S., but it's amazing how many of them are here. With temperatures rising, we might have even more of them."

As the threat of emerging tropical infectious diseases continues to grow, it becomes more important than ever to face them head on. And Kyle and his lab are committed to doing just that.

First appeared on [Great Commitments](#)

"We have this misconception that tropical diseases aren't something we have to worry about here in Georgia or the U.S., but it's amazing how many of them are here."





## Researchers reveal key cause of treatment failure in Chagas Disease

by Donna Huber

Photo by Peter Frey

Researchers at the University of Georgia have discovered that dormancy of the parasite *Trypanosoma cruzi* prevents effective drug treatment for Chagas disease, which kills more than 50,000 people each year in Central and South America and is a growing threat in the United States and Europe.

The disease infects an estimated 6 million to 7 million people, according to the World Health Organization, although some scientists estimate the number could be as high as 20 million. Chagas disease causing irreparable damage to the heart and digestive system, and effective prevention and treatment methods are virtually nonexistent.

In a new study published in eLife, Rick Tarleton and his research team at the Center for Tropical and Emerging Global Diseases sought to determine why drug treatments such as benzimidazole frequently fail.

"Benzimidazole has been shown to be particularly effective in reducing parasite infection," said Tarleton, Regents' Professor in the department of cellular biology. "A single dose can eliminate nearly 90 percent of parasites within 48 hours, but we didn't know why it didn't kill 100 percent of the parasites."

For the first time, they show that a small proportion of *T. cruzi* parasites halt replication within 24 hours of invading the host cell. These dormant parasites are resistant to extended drug treatment and can resume replication after treatment ends, thus re-establishing a growing infection.

The researchers don't know why some of the parasites exhibit this behavior, but they are hopeful that future studies into this mechanism will shed more light on the way *T. cruzi* evades the host's immune response.

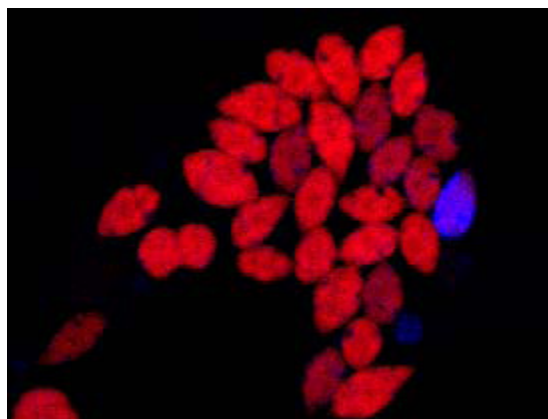
"This isn't drug resistance in the classical way we think of resis-

tance," said Tarleton. "The parasites aren't dormant because of the presence of the drug."

In fact, while treatment continued they saw some of the dormant parasites "wake up" and then become susceptible to the treatment. The team believes the key to effective treatment will be to catch the parasite as they resume replication, continuing medication until no parasites remain in the host.

"This discovery really offers a solution for current drugs to be used in a more effective way," said Tarleton. "A longer, less concentrated dosing schedule could lead to a cure."

An online version of the study is available: <https://elifesciences.org/articles/34039>



Proliferating *T. cruzi* amastigotes dilute the violet dye staining while non-replicating dormant parasite in the same host cell retains the violet signal.

### Fellowships for Trainees

Applications for the 2018 - 2019 NIH Trainee Fellowships are due by May 21, 2018.

Pre-doctoral and post-doctoral trainees interested in short term (6 weeks - 3 months) field experience at an international research site in October through April should submit their application for the CTEGD TIPS fellowship by August 1, 2018.

For more information: <https://ctegd.uga.edu/opportunities/funded-training>



## International collaborations recognized

The University of Georgia is one of eight universities nationwide to be recognized for its exemplary international programs and partnerships by NAFSA, a nonprofit association dedicated to international education.

The university's network of partnerships within the Brazilian state of Minas Gerais received **NAFSA's 2018 Senator Paul Simon Spotlight Award**, which is named after the late Illinois senator who was a strong advocate for international education and cross-cultural learning.

**Courtney Murdock**, assistant professor with a joint appointment in the Odum School of Ecology and the College of Veterinary Medicine and member of CTEGD, is working with Tiago Mendes from the Federal University of Viçosa to study how temperature impacts the spread of the Zika virus among disease-carrying mosquitos.

## Recently Funded Projects

**Roberto Docampo** and collaborators from the Woods Hole Oceanographic Institute, MIT, and Harvard University were awarded a grant from the Gordon and Betty Moore Foundation to support preliminary research on stable transfections and the use of the CRISPR/Cas9 technique in marine protists.

Ph.D. trainee **Catherine Smith** received an American Association of Immunology Travel for Techniques Award in order to go to University of Texas Medical Branch in Galveston to learn about advanced microscopy and deep tissue imaging.

**Courtney Murdock** received a 1 year grant from Ceva Sante Animale to assess a heartworm product.

**Ynes Ortega** received a grant from the Florida Department of Health for strengthening the capacity of the Integrated Food Safety Centers of Excellence.

**Rick Tarleton** received a grant from Tres Canto Open Lab Foundation for Chagas AcylAminoBenzothiazol lead optimization.

A list of published scholarly articles by CTEGD laboratories is available online:  
<http://ctegd.uga.edu/publications>



## Trainee Spotlight on Karla Márquez Nogueras

NIH T32 Trainee Karla M. Márquez Nogueras is in her 4th year of graduate training in Silvia Moreno's laboratory. Before entering the Ph.D. program at UGA, she taught for a semester at Turabo University in Puerto Rico, teaching undergraduate courses like Introduction to Microbiology and

Human Anatomy. She has a Bachelor's degree in Industrial Microbiology and a Master's in Science where she focused on generating renewable energy systems using methane generated by anaerobic microbial communities.

Karla's project focuses on calcium signaling in *Toxoplasma gondii*. Calcium is a universal signal molecule and very little is known about calcium signaling in *T. gondii*, even considering that all steps of the parasite's lytic cycle are regulated by calcium. Calcium is highly regulated by *Toxoplasma*, specially upon exit from host cells and the surrounding calcium changes from very low levels inside the host cell to the high concentration found in the extracellular environment. In order to shed light into the mechanisms involved and to discover the molecules involved they are studying two key aspects: the calcium channels that could be responsible for calcium entry into the cytosol and the calcium binding proteins that could regulate them.

"When I first entered grad school my research goals were different," said Karla. "During my rotation in Dr. Moreno's lab, I became fascinated by the biology of *Toxoplasma* and by how little is known about calcium signaling in *T. gondii*. As a scientist, I became very curious and interested in finding more about these signaling pathways and I decided to change my research focus."

Each T32 trainee is provided with the opportunity to complete a capstone experience at the end of their fellowship. This experience allows for an extended visit to a collaborator's laboratory or travel to a scientific meeting where they present their research and interact with colleagues.

"I was invited to the University of Puerto Rico to present my research project and discuss graduate and fellowship opportunities available at UGA. I would be presenting at an undergraduate event organized by the University."

In addition, she would like to visit the laboratory of Dr. Ivana Kuo at Northwestern University to study the function of two TRP channels that Karla is characterizing. Dr. Kuo uses lipid layers and regular patch-clamp to characterize intracellular and plasma membrane channels. Using this system Karla hopes to understand the physiology of these channels that are important for calcium signaling in *T. gondii*.

"The fellowship will provide me with the necessary experience and opportunities for me to develop the skills to become a better scientist."

Karla would like to go back to Puerto Rico and establish her own research lab. She would like to have the opportunity to train and give students the same opportunities that were given to her during her Ph.D. training.

"All the skills gained throughout this two years will prepare me for my ultimate goal which is to have my own research lab."