Summer 2019

CIVITAN INTERNATIONAL RESEARCH CENTER

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THIS EDITION

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Summer Program in Neuroscience (SPIN)

We are very proud of all the 2019 SPIN students for their successful completion of the program.

Top row, from left:
Vicky Yanouskiy (Georgetown University) – Cowell Lab; Rosaria Rae (North Central College) Gray Lab; Tori King (University of Alabama at Tuscaloosa) Wang Lab; Miguel Duran (Troy University) Meador-Woodruff Lab; Katherine English (University of Evansville) Shacka Lab

Bottom row, from left:
Janna Jernigan (University of Georgia) Wadiche Lab; Natalie Remiszewski (Bay Path University) Roberts Lab; Hannah Martin (Agnes Scott College) Pozzo-Miller Lab; Angela Barattini (University of Louisiana at Lafayette) Volpicelli-Daly Lab; Emily Parrish (La Salle University) Lubin Lab

Researchers Spotlight

UAB research identifies drug to help Duchenne muscular dystrophy symptoms

Matthew Alexander, Ph.D.

Researchers from the University of Alabama at Birmingham have identified a novel drug, KPT-350, that has proven effective in blocking and ameliorating symptoms of Duchenne muscular dystrophy in zebrafish and mouse models. The findings were recently published in Molecular Therapy, the journal of the American Society of Gene and Cell Therapy.

The important findings found that KPT-350 improved the overall skeletal muscle quality, increased locomotive activity and slowed the disease progression in DMD animal models, which has promising hopes for future DMD treatments. The findings also demonstrated that KPT-350 promotes a specific type of pro-regenerative macrophage population of cells that exists in the dystrophic skeletal muscles.

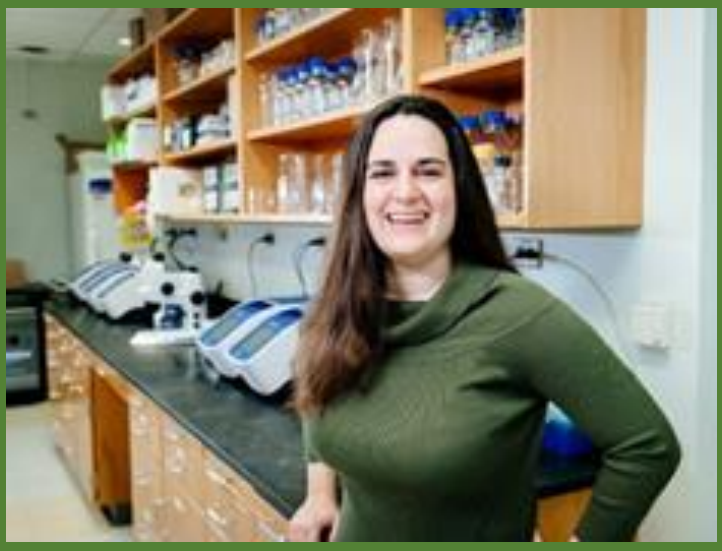
DMD is a genetic disorder characterized by progressive muscle degeneration and weakness. It is caused by the absence of dystrophin, a protein that helps keep muscle cells intact. The disease primarily affects boys and presents symptoms in early childhood.

“This type of translational science is tremendously valuable in helping us get closer to developing these drugs to make it to the patients with this disorder as fast as possible,” said Matthew Alexander, Ph.D., lead author of the study and assistant professor of Pediatric Neurology and Genetics in the University of Alabama at Birmingham Department of Pediatrics and Children’s of Alabama. “This is also an exciting time for the field as exon-skipping and gene therapy drugs for neuromuscular disorders are being evaluated in clinical trials, and some are even being given to patients in our community.”

The same class of drugs – SINE compounds – have been proven effective and tolerable in children with leukemia and other cancer types. Alexander hopes that KPT-350 will make it into a clinical phase 1 safety trial in boys with DMD in the future.

Additionally, Alexander is further expanding his research into the effects of KPT-350 on DMD hearts and lungs —which are also affected by the disease, and where more research is needed. His lab is also currently studying molecular mapping of the pathways in muscle affected by KPT-350.

DIY neuroscience tools help Thyme break new ground in schizophrenia research



Summer Thyme in her lab, where she and her team are putting the finishing touches on the behavior boxes she uses to study human genes in zebrafish. "There is a good flow between the patient work and basic biology [at UAB]," she said. "In some places, hospitals are really separate from the science. Here it's much more integrated."

(Top) The initial five of 12 behavior boxes that Thyme has specially designed for her research. (Bottom) High-speed cameras on each box record behavior at 285 frames per second. Each camera has its own dedicated computer to process all that data.

Working with some 25,000 larvae from the 132 zebrafish mutants, Thyme assessed their brain activity, brain structure and behavior. This included frequency of movement, features of movement (such as velocity and distance traveled) and preferred location in their wells, as well as each fish's reaction to weak and strong noises and flashes of light.

The zebrafish do not have schizophrenia, Thyme said, but they offer a rapid, low-cost way "to understand what the function of a gene actually is." Other studies have shown that the vast majority of scientific research is conducted on only 10% of human genes, so there are many important genes left to study.

Patients with schizophrenia tend to have deficits in prepulse inhibition — when a loud, startling sound is preceded by a non-startling stimulus, study subjects tend to have a milder reaction, but subjects with schizophrenia do not.

Zebrafish with mutations in the several schizophrenia-associated genes displayed decreased prepulse inhibition in response to startling events. Thyme also discovered that loss of genes with unrelated functions led to similar zebrafish phenotypes, indicating they could contribute to the same underlying disease mechanisms.

Thyme's research pointed to more than 30 genes that warrant further study. The transcription factor ZNF536, for example, is involved in the development of neurons in the cerebellum and forebrain, including forebrain neuron types implicated in social behavior and stress.

'Good flow'

Now at UAB, Thyme will focus on the most promising genes revealed in her earlier study, "trying to further understand their function," she said. Her work is supported by a K99/R00 Pathway to Independence award from the National Institutes of Health. "Understanding the molecular, cellular, developmental and behavioral processes regulated by schizophrenia-associated genes will provide the foundation to understand the causes of schizophrenia and develop new diagnostics and therapies," Thyme wrote in her grant abstract.

Thyme was recruited to UAB by neurobiology Chair Craig Powell, M.D., Ph.D., who also is the director of UAB's Civitan International Research Center. "We had worked together in the past, and he invited me to come down to check out the department," Thyme said. "I was really impressed. There is a good flow

between the patient work and basic biology. In some places, hospitals are really separate from the science. Here it's much more integrated."
The ease of creating mutations with CRISPR and rapid results from drug screens make zebrafish an ideal counterpart to human precision medicine studies. "I've been going to lots of meetings with the Precision Medicine Institute, talking about the genetic mutations they have identified in patients," Thyme said.

UAB opened a zebrafish research facility in 2011; some 15,000 of the fish, which are related to the minnow, are housed in tanks similar to home aquariums. In 2017, UAB hosted the Aquatic Models of Human Disease Society international meeting. Investigators across campus are using zebrafish as models for human disease. For example, Matthew Alexander, Ph.D., an assistant professor in the Division of Pediatric Neurology, is using zebrafish models of muscular dystrophies to find new drug therapies, Thyme said. "This is a good place to do the work I do."

Video Highlights

https://www.uab.edu/medicine/circ/test

For updates on the
Civitan International Research Center
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To schedule a private tour of the
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