DIY neuroscience tools help Thyme break new ground in schizophrenia research

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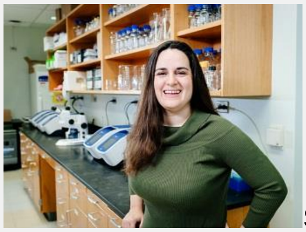

Summer Thyme in her lab, where she and her team are putting the finishing touches on the behavior boxes she uses to study human genes in zebrafish. "There is a good flow between the patient work and basic biology [at UAB]," she said. "In some places, hospitals are really separate from the science. Here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

Keeping an eye on thousands of baby zebrafish is no simple task. So Summer Thyme, Ph.D., an assistant professor in the **Department of Neurobiology**, built a black box to get the job done.

It is, literally, a black box, maybe four feet high, that was shaped by a local laser cutting company according to Thyme's design. At the top is an opening for a high-speed camera; underneath are slots for rows of 96-well microplates, with tiny zebrafish embryos in each one.

The camera records zebrafish behavior, which is surprisingly complex. Zebrafish are nothing if not precocious. "They have a beating heart in only 30 hours, and in the early stages they are transparent," Thyme explained. "You can see all the brain cells up until a couple of weeks." In adulthood zebrafish are roughly one-and-a-half inches long and can lay up to 500 eggs every week. Crucially, they share some 70 percent of their genes with humans, unlike other "high-throughput" animal models such as fruit flies and worms, where the overlap is on the order of 30 percent.

High-speed analysis

These traits have made zebrafish increasingly popular among scientists. Thyme uses them to study neuropsychiatric diseases, such as schizophrenia, with the long-term goal of creating new therapies. Using CRISPR gene-editing technology, she can turn genes on or off in zebrafish brains and study the results. But this is no job for the naked eye. The video cameras in Thyme's boxes capture images at 285 frames per second. Thyme also designed the software that makes sense of all those images, turning them into useful data. “There are commercial boxes and commercial software available,” she said. “But it’s much cheaper if you do it yourself. And you can set them up exactly the way you want them.”

In April, while she was still at Harvard University, Thyme was the lead author on a **paper in the journal Cell** that broke new ground in the study of schizophrenia. The researchers focused on 132 genes associated with schizophrenia in large-scale human studies and examined the results when they mutated these genes in zebrafish.

(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.

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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.”

The Research, Innovation and Economic Development pillar of **Forging the Future**, UAB's strategic plan, states that the institution will "create an environment and opportunities that facilitate collaboration and foster innovation." Summer Thyme's research exemplifies that goal.