Scientists fish for new epilepsy model and reel in potential drug

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Wild-type and larval zebrafish carrying a mutation in the Scn1a gene (mimicking a severe form of pediatric epilepsy) were used for drug screening. Credit: Dr. Baraban, University of California, San Francisco.

According to new research on epilepsy, zebrafish have certainly earned their stripes. Results of a study in *Nature Communications* suggest that zebrafish carrying a specific mutation may help researchers discover treatments for Dravet syndrome (DS), a severe form of pediatric epilepsy that results in drug-resistant seizures and developmental delays.

Scott C. Baraban, Ph.D., and his colleagues at the University of California, San Francisco (UCSF), carefully assessed whether the mutated zebrafish could serve as a model for DS, and then developed a new screening method to quickly identify potential treatments for DS using these fish. This study was supported by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National

Institutes of Health and builds on pioneering epilepsy zebrafish models first described by the Baraban laboratory in 2005.

Dravet syndrome is commonly caused by a mutation in the Scn1a gene, which encodes for Nav1.1, a specific sodium ion channel found in the brain. Sodium ion channels are critical for communication between brain cells and proper brain functioning.

The researchers found that the zebrafish that were engineered to have the Scn1a mutation that causes DS in humans exhibited some of the same characteristics, such as spontaneous seizures, commonly seen in children with DS. Unprovoked seizure activity in the mutant fish resulted in hyperactivity and whole-body convulsions associated with very fast swimming. These types of behaviors are not seen in normal healthy zebrafish.

"We were also surprised at how similar the mutant zebrafish drug profile was to that of Dravet patients," said Dr. Baraban. "Antiepileptic drugs shown to have some benefits in patients (such as benzodiazepines or stiripentol) also exhibited some antiepileptic activity in these mutants. Conversely, many of the antiepileptic drugs that do not reduce seizures in these patients showed no effect in the mutant zebrafish."

In this study, the researchers developed a fast and automated drug screen to quickly test the effectiveness of various compounds in mutant zebrafish. The researchers tracked behavior and measured brain activity in the mutant zebrafish to determine if the compounds had an impact on seizures.

"Scn1a mutants seize often, so it is relatively easy to monitor their seizure behavior at baseline and then again after a drug application," said Dr. Baraban. "Using zebrafish placed individually in a 96-part petri dish we can accurately quantify this seizure behavior. In this way, we can test

almost 100 fish at one time and quickly determine whether a drug candidate has any effect on these spontaneous seizures."

In the first such application of this approach, UCSF researchers screened 320 compounds and found that clemizole was most effective in inhibiting seizure activity. Clemizole is approved by the U.S. Food and Drug Administration and has a safe toxicology profile. "This finding was completely unexpected. Based on what is currently known about clemizole, we did not predict that it would have antiepileptic effects," said Dr. Baraban.

These findings suggest that Scn1a mutant zebrafish may serve as a good model of DS and that the drug screen may be effective in quickly identifying novel therapies for epilepsy.

Dr. Baraban also noted that someday these experiments can be "personalized," by looking at mutated zebrafish that use genetic information from individual patients.

This research was funded by the Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) program at NIH that supports innovative research with the potential for big impact in biomedical science.

"The goal of the EUREKA program is to provide a means to test high-risk ideas to see if they are worth pursuing further. These kinds of ideas often come from left field and are very creative. Since they are so unique, however, there may not be any existing preliminary data to support the hypothesis or demonstrate feasibility. EUREKA grants provide an opportunity to gather this information," said Brandy Fureman, Ph.D., program director at NINDS.

This particular study was chosen in response to a request by NINDS to

help spur novel research on epilepsy. "This research was selected for a EUREKA grant because it proposed a well-designed, inventive model of genetic epilepsy that could accelerate the pace of drug-screening for this devastating form of pediatric epilepsy" said Dr. Fureman.

Dr. Fureman noted that these findings not only describe a novel model of Dravet syndrome, but the positive results with an unexpected FDA-approved drug may lead to new therapeutic avenues. "There is more work to be done, but I am very pleased to see these initial results. These kinds of new directions are exactly what we hoped to stimulate with the EUREKA program," she said.

More information: Scott C. Baraban et al. "Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment," *Nature Communications*, September 3, 2013, DOI: 10.1038/ncomms3410

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