Nicholas Katsanis, PhD - Duke University

Using zebrafish to screen potential drugs for use in Rett syndrome.

The Research

Dr. Katsanis will study the effects of MeCP2 using a zebrafish animal model, with the goal of developing a new, faster method to screen compounds or drugs for potential use in Rett syndrome. This work is currently done using a mouse model. Zebrafish have been successfully used to screen drugs for use in other diseases. Dr. Katsanis will use zebrafish with a mutation in the *mecp2* gene to test the effect of *mecp2* mutation on target genes and test the effects of compounds on the zebrafish. Dr. Katsanis's work is a first of its kind and paving the way for faster, more efficient progress in finding treatments for Rett syndrome. Click here to read more about his research.

The Hope

Developing a method to screen drugs in Zebrafish could accelerate our Scout Program's drug screening capacity from 8-10 compounds per year in the mouse model to hundreds per year in zebrafish at a fraction of the cost. The *mecp2* mutant zebrafish can be produced on a much larger scale than *mecp2* mutant mice. In short, we can make many more *mecp2* mutant zebrafish much more quickly and at a much lower cost than *mecp2* mutant mice. Dr. Katsanis aims to demonstrate that zebrafish models can accelerate the pace of screening beyond what is attainable with any other animal model. The hope is that this study will develop a more rapid and efficient screening process.

The Answers to your Questions

Why zebrafish?

Zebrafish have high similarity to many aspects of human anatomy and physiology. In the field of genetics, the zebrafish is an excellent test subject and is used in many labs to replace or to supplement higher vertebrate models, such as rats and mice, due to cost savings and time efficiency. The zebrafish is a special animal model to researchers because its' body is transparent. Scientists can introduce mutations that include fluorescent proteins which allow the mutation to be monitored by the "glow". Scientists use zebrafish to study the genetic/phenotype connections associated with human disorders.

How does a zebrafish exhibit Rett-like symptoms?

Like humans, the zebrafish genome has a copy of the human gene, and its *mecp2* gene can be mutated. While motor skills like hand wringing in Rett syndrome cannot be modeled in zebrafish, they do show motor defects in their swimming as early as 3 days old. We can also assess how loss of MeCP2 function affects neuronal activity, plasticity, and neural development in zebrafish. We can see dysfunction in specific neurons that are similar to those seen in Rett syndrome.

What is the cost of a zebrafish with a mecp2 gene mutation compared to a mouse?

Fractional. The biggest "savings" though is in the ability to generate very large numbers, which enable us to do studies that are simply not tenable in the mouse. Also, having a non-mammalian model is useful for animal welfare issues as well.

How does using zebrafish accelerate the screening process?

It is incredibly difficult and time-consuming to test candidate drugs in mice and you cannot test more than a handful. The zebrafish model allows us to test hundreds to thousands of candidate drugs. It also allows us to look at the whole organism and can help us study things such as metabolic effects and toxicity.

What is the most exciting aspect of this project and its possible results?

We are excited to demonstrate that this method can efficiently and rapidly increase the pace of drug discovery in Rett syndrome. We hope to use the zebrafish method along with the mouse and cell work currently being done to contribute to both drug discovery and drug validation.

What is the timeline of your work?

We are deeply grateful to receive two years of exploratory support from Rettsyndrome.org, during which time we hope to have the model validated. After that point, we should be able to move to a high throughput drug screening quickly.

The Researcher

Dr. Katsanis is Director of the Center for Human Disease Modeling at Duke University, a Professor in the Departments of Cell Biology and Pediatrics, and is the Chief Scientific Officer and Founder of drug discovery company Rescindo Therapuetics whose primary focus is on rare genetic disorders. The Center aims to facilitate collaboration across disciplines and to develop physiologically relevant tools to study variation found in human patient genomes. As part of that effort, Dr. Katsanis leads the Taskforce for Neonatal Genomics. This multidisciplinary group of physicians and basic scientists strives to synthesize genomic and biological data for the faster diagnosis, improved/focused clinical care, and potential therapeutic paradigms, for infants and neonates with genetic conditions.

View Dr. Katsanis' full scientific abstract here.