Colleen Niswender, PhD and Rocco Gogiliotti, PhD, Vanderbilt University

Recipient of a $150,000 Rettsyndrome.org Basic Research Award for this work

"Tailoring gene replacement therapy for MECP2-related disorders"


MECP2 - human gene MeCP2 - human protein *Mecp2 - mouse gene*

The Research

Drs. Niswender and Gogliotti are leading research to address one of the most important challenges of gene therapy - gene dosage. The *MECP2* gene controls how much MeCP2 protein is made in the body. When there is a mutation in the *MECP2* gene, protein levels and protein function are affected, causing many of the symptoms associated with Rett syndrome and similar disorders. However, across the spectrum of Rett patients, there are a number of patient-relevant mutations that may not induce equivalent impact on MeCP2 levels or function.

One of the difficulties with gene therapy is determining how much of the gene needs to be delivered to patients to obtain the correct level of the MeCP2 protein. Too little protein may not improve symptoms and too much protein can lead to symptoms of *MECP2* Duplication Syndrome. Drs. Niswender and Gogliotti are working to evaluate the effectiveness of gene therapy for different *MECP2* mutations and also testing whether increasing MeCP2 levels on top of specific point mutations may put some patients at increased risk for *MECP2* Duplication-like symptoms. Click here to read more about their research.

The Hope

Determining the correct dosing levels for effective gene therapy across a range of Rett models is an important next step in development of this therapeutic strategy. Drs. Niswender and Gogliotti will be able to conduct these delicate studies on mice that have mutations that mirror human mutations. This will allow them to study the effects of gene dosage and function, and the effects of expressing normal MECP2 protein in the presence of several different patient-relevant mutations.

The Answers to your Questions

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

One important result from this work will be an understanding of the predicted efficacy and safety of MeCP2-replacement strategies across a range of mutations. We believe that developing an understanding of how disease-relevant mutations impact these factors will be complimentary to existing datasets in knockout mice, and will provide answers to questions that are critical to advancing gene therapy into Rett syndrome patients.

Why is this work important to helping my child?

Gene therapy trials are, excitingly, becoming a reality for Rett syndrome patients. A comprehensive understanding how this approach affects mice mimicking each patient populations will help develop a rational approach for these first trials, and allow for the rapid translation of early results across the spectrum of Rett syndrome patients.

Is there any way for families to help with your project? Enrolling, completing a questionnaire etc.?

Participation the Rett syndrome Natural History Study is one important way that families can help with our research. As we advance new therapeutics into clinical trials, we need to ensure that we are able to examine and quantify outcome measures to test if a drug candidate or therapeutic approach like gene therapy is working. The more we can understand about Rett syndrome patients across a whole spectrum of mutations, the better we can plan for a clinical trial. For example, perhaps patients with one mutation exhibit more severe symptoms in a specific disease domain, like apneas or seizures, than patients with a different mutation. This will assist in interpreting data in eventual trials, where one patient may respond better than another.

What are you looking for/measuring/trying to solve in simple terms?

This particular grant is asking the following questions relevant to gene therapy: 1) will increasing MeCP2 expression work equally in the context of specific mutations, and 2) are some patients at elevated risk for *MECP2* Duplication-like side effects based on their unique mutation.

Does the knowledge gained help treat Rett or cure Rett?

Gene therapy, if successful, is predicted to be a curative strategy for Rett syndrome. The more information we can obtain about potential responsiveness or safety of gene therapy based on specific mutations, the better we can plan for expanded trials if warranted by early data.

The Researchers

Dr. Colleen Niswender is a Professor of Pharmacology and Director of Molecular Pharmacology at the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) in Nashville, TN. She has established a research program around the therapeutic potential of metabotropic glutamate and muscarinic receptors in Rett syndrome and MeCP2-related disorders. VCNDD's "Team MeCP2" is focused on the study of MeCP2-related disorders with a goal toward new therapeutics development for these and other neurodevelopmental and psychiatric disorders. Excitingly, the VCNDD has now advanced a compound into a clinical trial; this compound is designed to treat cognitive impairments in schizophrenia and Alzheimer's disease.

Dr. Rocco Gogliotti joined the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) in April of 2012 as a post-doctoral fellow and joined the Vanderbilt Department of Pharmacology as an Assistant Professor in October of 2017. Rocco's work in the VNCDD has focused on the syndromic forms of autism, such as Rett syndrome and MECP2-Duplication syndrome. Through a combination of genetic, behavioral and pharmacological methodologies, he seeks to better understand the disparities in nervous system function during health and disease, and to design novel intervention strategies to correct these deficits.