Colleen Niswender, PhD – Vanderbilt University

1) What prompted you to begin a career in research?
    a. I earned my undergraduate degree in pharmacy at the University of Toledo in Ohio, my home state. I found that, while I enjoyed my coursework immensely, traditional pharmacy work in either a hospital or drug store setting was not my passion. During my undergraduate training, I performed a clerkship rotation at the Northwest Ohio Developmental Center, a facility for individuals with severe developmental disabilities. I found their medical care, which involved a highly integrated team of doctors, nurses, social workers, and pharmacists, to be very unique and interesting, and I became very interested in their pharmacotherapy. I also had a pharmacology teacher who recognized my potential for research, and am forever grateful to her for taking me into her lab and serving as a mentor and role model. Under her guidance, I applied to the pharmacology department at Vanderbilt and completed my PhD, and I have continued my interest in questions at the interface of neuroscience, developmental disorders, and pharmacology.

2) Provide a brief outline of your training and the work you have conducted that has led to this proposal.
    a. My earliest training at the University of Toledo examined the activity of novel anticonvulsants in a rodent model of epilepsy. During graduate school at Vanderbilt, I worked in the lab of Dr. Ronald Emeson studying a process called RNA editing, which results in changes in the amino acid sequence of various proteins. We found that editing patterns in a receptor that responds to serotonin were distinct in depressed patients who had committed suicide compared to patients with other psychiatric disorders, such as schizophrenia. After postdoctoral work at the University of Washington in mouse genetics, I returned to Vanderbilt in 2004 and joined what is now the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD). During my first years with the group, I developed the hypothesis that one of the targets we were studying, metabotropic glutamate receptor 7 (mGlu7), might be involved in either the manifestation or treatment of Rett syndrome based on its cellular expression, functional activity, and potential epigenetic gene regulation. While interesting, at that time, other work responsibilities prevented me from focusing on Rett. However, after participating in a grant review focused on a different disorder, I shared a taxi ride to the airport with another investigator. During our conversation, she remarked, “You know, if I had to do it all over again, I would dedicate my life to working on a disease that affects children.” This conversation greatly moved me, and I returned to Nashville, wrote my first grant to rettsyndrome.org (the IRSF), and it was funded. After securing additional grants, we have been able to grow our “Vanderbilt Team MeCP2” group to include several students and postdoctoral fellows, and have also interfaced closely with Vanderbilt clinicians such as Dr. Sarika Peters. The work funded by the current grant focuses on the therapeutic potential of a new receptor of interest to the VCNDD, and some of our initial data suggest that this target might be a new candidate for drug development in Rett as well as *MECP2* Duplication syndrome. The VCNDD is a highly integrated group of chemists, pharmacologists, and drug discovery scientists working to “de-risk” development of novel therapeutics for disorders that are underrepresented within the portfolio of large pharmaceutical companies, and our goal is to provide the seed data and rationale to encourage a company to invest in rare disorders, such as Rett and *MECP2* Duplication syndrome.

3) What is the single most rewarding aspect of conducting Rett syndrome research?
    a. Meeting with the families and patients, most definitely. I feel such gratitude for the openness of families when we interface at meetings or host them in our labs at Vanderbilt. “Real world” exposure tremendously helps us, as scientists, both refine our scientific questions and well as give us an appreciation for the day-to-day lives of Rett and

MECP2 Duplication syndrome patients and their caregivers. Additionally, the families are always so appreciative that we would dedicate even a portion of our scientific life to help develop new treatments for their children and loved ones, and that feedback is very heartening to me.

4) Identify a potential positive outcome of the research you are conducting that is specific to this proposal. (i.e. Does this project target a specific symptom of Rett syndrome?)
    a. The current proposal will look at deficits in synaptic plasticity in mice under- (Rett syndrome model) or over- (MECP2 Duplication syndrome model) expressing a glutamate receptor called metabotropic glutamate receptor 3, or mGlu3. We have found reciprocal changes in mGlu3 expression in mice modeling Rett and Duplication syndrome and hypothesize that small molecules we are developing at Vanderbilt may impact symptoms in those mice, particularly in the cognitive domain. It is anticipated that these studies could someday lead to treatments that might impact the ability of patients with these disorders to better communicate with others around them.

5) If you could pick any one symptom of Rett syndrome to prevent or to provide relief for, what would it be?

    a. I actually ask this question of every Rett or Duplication family we meet with and the answer is different for each of them depending upon the most prominent symptoms of the affected individual in their lives. I do think seizure treatment is an area that would be important to impact, as well as improving motor effects and apneas. The subject of our first rettsyndrome.org grant, mGlu7, is showing tremendous progress in these areas in preclinical models, which makes us very excited to continue our drug development efforts for that target. I hope that the studies stemming from the current grant around mGlu3 will interface with our previous work, particularly in cognitive endpoints, which we anticipate could eventually allow for affected individuals to more easily communicate.

b.

6) What other disease(s) does your research focus on?
    a. At the VCNDD, we are committed to the study of a number of neurological or psychiatric diseases that are considered too risky by pharmaceutical companies. This includes orphan diseases like Rett and *MECP2* Duplication, but also other disorders ranging from Parkinson's disease, Huntington's disease, dystonia, depression, schizophrenia, and Alzheimer's disease. The VCNDD has recently filed and been granted Investigational New Drug status for one of our compounds for an Alzheimer's program and, excitingly, we began human dosing in July. Now that we have moved completely through the drug discovery process to the point of clinical trials for one target, we feel we are in a good position to translate this to other Vanderbilt-developed compounds and new indications. Rett and Duplication syndromes are considered "nascent" programs within the Center, and we are working to lay the groundwork for full drug discovery programs based on our basic science findings and validation studies. This rettsyndrome.org grant will provide crucial data that will allow us to more deeply explore the value of mGlu3 modulation in models of both of these disorders.

7) Besides your role as principal investigator on this project and as a Rett syndrome investigator, what other roles do you currently hold that are specific to the field of Rett syndrome research? (i.e. NIH Grant Reviewer, Rettsyndrome.org Grant Reviewer, member of specific Board or Panel, etc.)
    a. I have reviewed grants for the past several years for Autism Speaks. I am also an Investigator within the Vanderbilt Kennedy Center. The Center is focused on the study of and interventions for intellectual and developmental disabilities. Investigator status within the Center allows me to present to wide audiences, including the lay public, as well as interface with other scientists and clinicians focused on neurodevelopmental disorders.

8) Provide any other interesting information about yourself or your work that you would like the Rett syndrome community to know about you. (You might consider hobbies, etc. or anything else that is unique to you and/or your research)

    My main scientific mottos are:
    1) "Do as many experiments as you can every day because only one needs to work to keep you coming back."
    2) "No idea is too crazy. You have my buy-in to try anything once."

    On a personal note, I have been married to my husband, Kevin, for 20 years. He is an MD/PhD physician-scientist at Vanderbilt. We have two children, Aidan (16) and Molly (13), who keep us very busy. We love living in Nashville and consider ourselves lucky to be part of such a vibrant and fun city. Interesting fun fact: I have two brothers and three sisters. My name and the names of my sisters and my mother all rhyme. Can you guess them? ☺