

DEVELOPMENTAL BIOLOGY
PEDIATRICS

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PROJECT TITLE: Human Stem Cell Models of CHD and NDD

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Project Description

Over 97% of children with congenital heart defects (CHD) are expected to reach adulthood due to the success of modern surgical intervention. However, up to 50% of these patients will develop neurodevelopmental disorders (NDD) including autism spectrum disorder (ASD). The cause of this co-occurrence is unknown, however there are two major theories: 1) the heart defect leads to poor brain development and thus NDD/ASD is a secondary outcome or 2) there are mutations in DNA that cause both disorders. A collection of studies investigated the DNA sequence of thousands of patients with ASD or CHD have uncovered hundreds of mutations that appear to confer risk for these disorders compared to controls. Interestingly, many of the genes where mutations were found are shared between both patient populations suggesting that these genes may be causing both disorders. Unfortunately, a simple survey on the function of the genes do not provide clues on to how hundreds of mutations could be related and manifest into a disorder. We then wondered whether subsets of these genes could funnel into a common pathway of action. From our analysis, we identified a key developmental pathway that is shared between both patient populations and is critical for both heart and brain development. We posit that several mutations associated with ASD and CHD will converge onto this key pathway to disrupt both embryonic heart and brain development.

It is challenging to test these theories because during embryonic development, the heart and the brain do not develop independently and thus is challenging to disentangle cause and effect. Therefore, we opted to investigate major developmental pathways and a subclass of genes mutated in CHD and ASD using a human pluripotent stem cell (hPSC) developmental platform. hPSCs are cells that can be made into all the different cell types of the body and current technological advancement have uncovered methods to generate organ-like structures called "organoids". The differentiation of hPSCs into heart and brain organoids recapitulate several milestones of

organogenesis and include several developmentally accurate cell types and organization found in the developing organ. These organoids can be generated independently which will allow us to test whether mutations independently cause defects in the heart and brain. Importantly, organoid technology is not advanced enough to form a fully functional heart and brain but does provide insight into early human development which is largely unknown. Using these organoids, we will identify when and in which cell types utilize certain programs and pinpoint key pathways shared between the heart and brain. Secondly, we will perform a clinical-trial-in-a-dish where heart and brain organoids are generated from 28 ASD or ASD+CHD patient-associated mutations and assessed for the cellular composition as well divergence from shared pathways.

From this work, we expect to answer whether there are shared pathways between human heart and brain development, which patient associated mutations impact these shared pathways and whether CHD and ASD are caused by shared mutations independently. The results will lay the foundation of our research program on co-occurring disorders with ASD and provide insight into this highly complex disorder. As a new Assistant Professor in Pediatrics, I want the ability to help devise treatments or therapies for children with neurodevelopmental disorders. Expanding my basic research goals using hPSCs and organoid technology toward more translational goals will help fill an unmet need in the ASD research community. This award will advance my career in this space and solidify my collaborations with clinicians specializing in CHD and ASD. While there is no silver bullet in treatments for ASD, understanding the underlying framework for how organs develop and untangling the genetic diversity are first steps to identifying patient specific treatments. Our work could be incorporated into the Exceptional Family Member Program where service members would have access to resources describing current research and findings for those with children diagnosed with ASD. Finally, fundamentally, this is a basic science study and will unlikely impact patients and families directly, however as our research program progresses, we foresee the development of diagnostics and therapeutics within 5-8 years that will enable clinicians and families to adopt alternative treatment regimens based on the genetic makeup of the child.