CTNNB1 Connect & Cure
Contact: Lauren Cochran
lauren@curectnnb1.org
www.curectnnb1.org

CTNNB1 Connect & Cure Lead Researcher, Dr. Michele Jacob, Awarded NIH Grant for Gene Replacement Therapy

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Chatham, NJ – CTNNB1 Connect & Cure Board Members are delighted to share the great news that lead researcher, Dr. Michele Jacob, Professor of Neuroscience at Tufts University, was recently awarded an NIH grant to conduct proof-of-concept studies of the therapeutic efficacy and safety of gene replacement therapy in CTNNB1 syndrome models. The studies are using two preclinical models of *CTNNB1* heterozygosity, an *in vivo* mouse line and human muscle cells derived from pluripotent stem cells (iPSCs). The lab is using newly developed, next-generation muscle tropic adeno-associated viral vectors (AAVs) to express CTNNB1/β-catenin in the heterozygote models. They will test whether gene replacement therapy will significantly normalize β-catenin levels and muscle phenotypes relevant to this syndrome.

This new next generation AAV vector displays greater potency, muscle selectivity and a more favorable safety profile, compared to earlier generation AAVs. Preliminary studies show that the gene therapy treatment increases β-catenin protein levels in both mouse skeletal muscle *in vivo* and human muscle cells *in vitro*. Dr. Jacob will test the effectiveness for remedying phenotypes, safety, and long-term maintenance of benefits achievable with a single gene therapy treatment. Findings will provide critical insights into viral gene therapy as a potential treatment strategy that may provide significant benefits to children with CTNNB1 syndrome. The grant award is $275,000 over 2 years in direct funding to the lab.

The new Gene Therapy Program complements existing research into small molecule therapeutics. In addition to one extremely effective small molecule discovered by the Jacob Lab in collaboration with MIT, both in vivo and in vitro, the lab is also testing new drugs that are modified to have superior brain penetrance and potency. Together as a non-profit and research lab, we are actively seeking a pharmaceutical partner for this promising treatment.

A novel RNA based therapy rounds out Dr. Jacob's treatment strategy, in collaboration with John's Hopkins, that is already giving promising preliminary results in human cell studies. The research goal is to identify the most effective and safest treatment strategy to advance to clinical trials.

The Jacob lab is expanding their preclinical models to include iPSCs created by the Simon's Foundation from blood samples donated by de-identified CTNNB1 syndrome individuals to Simon's Searchlight. To date, Simons has generated 5 different iPSC lines carrying distinct *CTNNB1* gene mutations. The patient derived cells have passed all quality control tests and will be available shortly. They will be used in assessments of all ongoing treatment strategies in the Jacob lab. This work will provide essential insights into the effectiveness for correcting phenotypes caused by the various CTNNB1 mutations found in individuals with this syndrome.

CTNNB1 Connect & Cure has issued over $390,000 in research grants since its inception in 2019 to Jacobs Lab at Tufts and most recently Boston Children's Hospital. As our lead CTNNB1 researcher, Dr. Jacob's has received nearly $600,000 in government funding (as direct costs) for her promising work on CTNNB1 syndrome treatments.