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## Cure RTD has awarded a \$16,680 grant to Dr. Manoj Menezes, MD and PhD, at The Children's Hospital at Westmead (CHW) in Sydney, Australia



*Dr. Manoj Menezes*

Cure RTD has awarded a \$16,680 grant to Dr. Manoj Menezes, MD and PhD, at The Children's Hospital at Westmead (CHW) in Sydney, Australia for the project "Riboflavin transporter deficiency *C. elegans* model: Characterization and response to flavin and antioxidant treatment."

While it is known that the riboflavin transporters RFVT2 and RFVT3 are responsible for the transport of riboflavin in the body, the exact mechanism by which riboflavin deficiency causes neuronal damage in riboflavin transporter deficiency (RTD) patients is not understood. Over the past few years it has become clear that riboflavin treatment merely slows the disease progression of RTD rather than completely halting disease progression in some patients. Hence, there is a great need to identify complementary, novel therapeutic strategies that can act synergistically with riboflavin treatment to halt RTD disease progression.

In a recently completed project funded by Cure RTD, Dr. Manoj Menezes and his team successfully developed the first animal model of RTD using *Caenorhabditis elegans* (roundworms). In that project three independent *C. elegans* models were generated carrying different mutations in the worm riboflavin transporter gene (*rtf-1*), which is the human equivalent to the *SLC52A2* gene causing RTD type 2. Initial investigations of this model demonstrated that these worms have similar neuronal degeneration as patients with RTD.



In this proposal, Dr. Manoj Menezes and his team will use these newly developed RTD *C. elegans* animal models to clarify the underlying mechanism of neuronal injury in RTD. Areas of investigation in this model will include neuronal and muscle morphology, tissue flavin levels, mitochondrial function, synaptic transmission, life span as well as motor and sensory behaviors. In addition, the RTD worm's response to various therapeutic treatments, including both riboflavin and various antioxidants, will also be investigated.

## **Meet Dr. Manoj Menezes**

Dr. Manoj Menezes is considered an international expert in the pathophysiology and therapy of RTD, having published several research papers describing its phenotype, pathophysiology and use of disease-modifying therapy. Dr. Manoj Menezes completed his MD in Paediatrics from MS University, Baroda, India and completed his PhD in inherited peripheral neuropathies including RTD from the University of Sydney. He is a Staff Specialist in Neurology and Neurogenetics at CHW and a Clinical Senior Lecturer at the CHW Clinical School at The University of Sydney. He is also Director of the Peripheral Neuropathy Management Clinic, CHW and co-team leader of the Neuropathy Group at the Kids Neuroscience Centre, Kids Research.

## **How will this project work?**

*Caenorhabditis elegans* (*C. elegans*) is one of the most widely used animal model systems to address questions in neurobiology. *C. elegans* possess a simple, but extremely well-defined nervous system that functions similarly to mammalian systems. In this project, the previously generated RTD *C. elegans* models will be studied both with and without various treatment interventions. This model will enable the study of neurons and other areas affected by RTD at different developmental stages and their response to novel treatment protocols.

## **What is the significance of this study?**

Findings from this study have the potential to significantly impact our understanding of how mutations in the SLC52A2 genes cause neuronal damage in individuals with RTD. This animal model may help identify novel pathways for therapeutic intervention, leading to the development of complementary novel therapeutic strategies that can act synergistically with riboflavin treatment to halt RTD disease progression. In addition, the response of the model to various novel treatments will provide valuable information that may lead to new treatment approaches to be trialed in RTD patients.

## **Cure RTD Research Funding**

This grant to Dr. Manoj Menezes is part of Cure RTD's Basic Research and Drug Discovery programs that we are currently announcing for our 2020-2021 grant cycle.

**Basic research** is the first step in our comprehensive research model. We fund basic research to investigate the biology and cause of RTD in order to identify the most effective treatment strategies.