CURE MDS ASKS COMMUNITY TO TAKE ACTION TO SUPPORT EFFORTS CRITICAL TO ADVANCING CLINICAL TRIALS

The collaboration between the Rett Syndrome Research Trust (RSRT) and Cure MDS (formerly 401 Project) has resulted in the funding of seven research projects, numerous scientific breakthroughs, pre-clinical trials, and most importantly, three potentially curative therapeutic approaches. These approaches include work of the Huda Zoghbi lab at Baylor College of Medicine on antisense oligonucleotide drug therapy (ASO), Anastasia Khvorova's project at the University of Massachusetts Medical School that is developing a system to reduce levels of the MeCP2 protein via small interfering RNA, and Ronald Cohn's research at The Hospital for Sick Children in Toronto focusing on a genome editing approach that removes the duplicated gene.

Before clinical trials in each of these approaches can be pursued, five very important steps now need to be accomplished:

1. Develop a clinical severity scale (CSS) to use as a measurement tool to objectively assess response to treatment (funding source is identified).

2. Deep phenotyping of MDS individuals to characterize the disease better and explore the differences in MDS and Rett that can help to prevent over- or under-treatment of MDS.

3. Genetic studies to guide dosing of medications at individual level (personalized medicine, i.e. each individual requires different dosing/redosing).

4. Develop biomarkers that will help indicate the level of MECP2 in patients (funding source is identified).

5. Expand a patient registry and cohort through an online portal (funding source is identified).

A team of researchers and experts at Texas Children's Hospital (TCH) Rett Center is making significant progress on all five of these next steps. The goal is to enable the implementation of human clinical trials with the greatest possible efficacy and safety. Support is needed for two projects at the Rett Center:

1. Deep phenotyping of MDS individuals to unravel the natural progression and characteristics of MDS, and understand the subtle differences to Rett syndrome.

2. Accelerate the genetic studies to understand each individual's genetic structure and role for those genetic structures in medication dosing. Dr. Davut Pehlivan (a geneticist and neurologist) is leading these efforts at TCH Rett Center. MDS individuals can participate in genetic studies remotely from their home town.

This vital work is set to begin in July and will have a cost of $125,000 in its first year. Action and support from the MDS community are urgently needed to make these efforts possible. Families can take action in several ways:

- Start your own Facebook fundraising campaign **https://www.facebook.com/fund/401project/**
- Donate directly here **https://reverserett.org/donate/** Please check the box that says "This is for the Duplication Syndrome Fund."
- Start a crowdfunding campaign on RSRT's platform **www.RettGive.org**.
- Reach out to your networks in other ways, such as an email or a letter.

To get started with any method of fundraising, please contact Tim Freeman, RSRT's Chief Development Officer, at tim@rsrt.org.

You can learn more about the TCH efforts by watching a recording of the webinar that was held on 17 June. Hosted by RSRT and CURE MDS, the webinar was led by two key members of the TCH team, Dr. Davut Pehlivan and Dr. Bernhard Suter.
https://youtu.be/qA45OdIB4AY

Background

MECP2 Duplication Syndrome (MDS) is caused by duplications in the Xq28 region of the X chromosome spanning the MECP2 gene. It is clinically complex and variable but the most prevalent clinical features include low tone, severe developmental delay, epilepsy, gastrointestinal problems and frequent infections.

The mission of **CURE MDS** (www.curemds.org) is to bring together affected families from around the world to raise and contribute the funds needed to support curative strategic research efforts for MDS.

In 2008 the Rett Syndrome Research Trust launched with a laser focus on curing Rett Syndrome. Rett Syndrome and MDS are interrelated because both disorders are linked to a gene called MECP2. Rett Syndrome results from random mutations or deletions in that gene, whereas MDS symptoms arise when the same gene is erroneously duplicated. The symptoms of both disorders have some overlap, and the target culprit gene that researchers need to focus on is the same.

In 2010, RSRT agreed to a request made by parents of MDS children to also drive research efforts for a cure for MDS, leveraging RSRT's infrastructure, deep knowledge base and global scientific networks. Following its rigorous scientific peer review process, RSRT awarded funding to its first MDS-focused project: Is MECP2 Duplication Syndrome Reversible? from the lab of Dr Huda Zoghbi, Baylor College of Medicine, Houston Texas.

Remarkably, not only did Dr. Zoghbi show that indeed MDS is reversible but she offered up a strategy to accomplish this in the clinic, Antisense Oligonucleotide Therapy. The results were published in "Nature" November 2015. Additional projects funded by RSRT at the University of Massachusetts Medical School and The Hospital for Sick Children in Toronto have also resulted in potentially curative approaches.