The MECP2 Duplication Syndrome (MDS) is caused by a genetic error that results in a duplication of a section of the X chromosome that includes the MECP2 gene. Having two MECP2 genes leads to overproduction of the MeCP2 protein. Efforts to dramatically address the symptoms of MDS will require bringing the levels of the MeCP2 protein back to normal.

In 2011 the Rett Syndrome Research Trust (RSRT) was asked by the MDS family community to create the MECP2 Duplication Syndrome Fund (MDS Fund) and to manage research efforts on its behalf. In so doing the MDS community benefits from the infrastructure and staff already in place at RSRT as well as decades of experience with the MECP2 research field. 100% of every dollar donated to the MDS Fund directly supports research for MDS.

As of July 2019 the MDS Fund has raised a total of $3,281,147.
Efforts aimed at addressing the root cause of MDS, too much MeCP2 protein, offer the best chances of dramatically improving symptoms of the disorder. Whether a full cure can be developed, and if so for what ages, remains to be seen. Our goal however is a cure.

Currently efforts are underway in the lab of Huda Zoghbi, MD at Baylor College of Medicine to address MDS with either an antisense oligonucleotide approach (ASO) as well as a small molecule drug approach. As is often the case in science there are numerous potential strategies to achieve the same goal of lowering MeCP2. Since it is impossible \textit{a priori} to know which strategy will ultimately be the one that works the best, it is in the interest of patients and their families that all strategies be implemented in parallel. This will lead to a diversified portfolio of potential therapeutics and increase the chances of success.

Below we propose priority interventions that have the potential to be curative for MDS. The interventions fall into three basic categories:

1. RNA strategies that destroy excess MECP2 RNA
2. Gene editing to remove duplicated region
3. Disruption of the MECP2/NCOR interaction

Funding from the MDS Fund would enable the pre-clinical work to be done, meaning basic testing of the principles and proof that the concepts work in cells, mice, or other models of the disorder.

For those projects that generate encouraging data we would then seek industry partners. These biotechnology or pharmaceutical companies would then take on, at their own expense, the experiments and work involved to develop and commercialize therapeutics for MDS individuals.

But in order to get to that stage we first need to fund the proof of concept projects below. For each project listed we have elite scientists ready to be recruited once funding is in place.

We would like to initiate the prioritized projects below as soon as funding allows. Funding of Priority Project 1 and 2 would require a total of $1.3 million. Once these projects are funded we will turn our attention to Projects 3 and 4.

Although Rett Syndrome has more awareness, more families, and more money, the fact is that reducing protein levels for MDS is technologically easier than boosting protein levels for Rett. In that respect MDS should be easier to cure/treat than Rett Syndrome.
PRIORITY PROJECT 1:

Gene editing approach to remove duplicated region

$500,000 3 Years

This is an exciting “one and done” therapeutic strategy that uses CRISPR technology to remove the duplicated region in MDS restoring normal dosage of the MECP2 gene. An enzyme called Cas9 guides molecular scissors to the exact location on the DNA that needs to be spliced out.

A mouse model that would allow testing of this strategy has already been developed. Upon full characterization of the mouse model editing in vivo can commence.

Having a vector or other delivery method that efficiently spreads throughout the brain will be key. Research already being funded by RSRT for Rett can be fully leveraged for MDS.

A proposal from an accomplished researcher at an elite institution has already been submitted to RSRT and is currently moving through the peer review process.
PRIORITY PROJECT 1:
Gene Aditing Approach
PRIORITY PROJECT 1:
Gene Editing Approach

MOLECULAR SCISSORS

CAS9

MECP2  IRAK1  MECP2  IRAK1
PRIORITY PROJECT 1:
Gene Editing Approach

MECP2

IRAK1

MECP2

IRAK1
PRIORITY PROJECT 1:
Gene Aditing Approach

MECP2  IRAK1
Knockdown of MECP2 by siRNA

PRIORITY PROJECT 2:

$500,000 2 Years (siRNA)
$310,000 2 Years (Delivery Platform)

RNA is the intermediary step by which genes (DNA) make protein.

In MDS there is too much MECP2 RNA.
Knockdown of MECP2 (siRNA)

Strategies to destroy excess MECP2 RNA include Dr. Zoghbi’s ASO approach. Another approach we would like to pursue in parallel uses small interfering RNA (siRNA) to destroy the MECP2 RNA. As the name suggests these RNA molecules interfere with the translation of proteins by binding to and promoting the degradation of RNA. siRNA can be synthesized in a lab to target any desired RNA. The siRNA guides molecular scissors directly to the MECP2 RNA and the scissors then destroy the RNA.
PRIORITY PROJECT 2:
Knockdown of MECP2 (siRNA)
Knockdown of MECP2 (siRNA)
Knockdown of MECP2 (siRNA)

This project would leverage a new delivery technology that would make ongoing treatment less invasive and likely less frequent.

We have a commitment from a scientist who is a world expert with this type of chemistry to pursue this approach if we have funding.

The leader in ASO technology is a biotech company called Ionis who is already working collaboratively with Dr. Zoghbi. The leader in siRNA technology is a company called Alnylam. Both companies have ASO and siRNA products on the market. In so doing they have paved the drug development pathway and have dramatically reduced risk for other diseases following in the same pathway. Furthermore both companies are interested in brain diseases.

With the ASO project well underway with MDS Funds we feel it’s of utmost importance to launch the siRNA project.

Disruption of the MECP2/NCoR Interaction

In order for MECP2 to function properly it needs to bind to a partner protein called NCoR. Since the root cause of MDS is too much MECP2 it stands to reason that disabling the function of MECP2 by blocking its ability to bind to NCoR could be a viable therapeutic strategy. Priority Projects 3 and 4 take this approach.
PRIORITY PROJECT 3:

Small Molecule Drug Treatment

$750,00 3 Years

Find a drug that can inhibit the MECP2/NCoR interaction. The drugs could be created by chemists or obtained through access to a large library of existing molecules through a collaboration with a pharmaceutical company. Researchers would perform an experiment called a screen, where they would test as many molecules as they had access to for the ability to reduce MeCP2 function. Once the top molecules were identified, they would further be characterized to make sure they didn’t make the cells sick and that they were able to keep MeCP2 away from its binding partners. They would then be tested in MDS mice for safety and efficacy. The best molecule would then proceed along the drug development process.

One advantage of a small molecule drug treatment is that the effects are temporary and allow changes in dose to modulate the response up or down. A treatment like this would need to be repeatedly given to patients on a regular schedule like other oral or injected medications.
PRIORITY PROJECT 3:
Small Molecule Drug Treatment

DRUG

MECP2

NCOR
PRIORITY PROJECT 3:
Small Molecule Drug Treatment

MECP2

NCOR
PRIORITY PROJECT 4:

Small Peptide Decoy Drug Treatment

$750,00 3 Years

This project proposes to develop a small peptide that can bind to the NCoR protein and behave as an MECP2 mimic or decoy. It would prevent existing MECP2 from interacting with its partners and thereby inactivate MeCP2/NCoR function. A peptide has already been identified. Its structure would be optimized and ways to deliver it to the brain would be developed.

These strategies will also need to be administered on an ongoing basis allowing for dose escalation, titration and optimization.
Drug Discovery Process

1. Basic Genomic Research
   - Research on orphan receptors, ligands, disease-related genes and orphan enzymes

2. Identification of target Molecules
   - Functional Analysis of genes

3. Discovery of seed lead compounds
   - High-throughput screening
   - Combinatorial chemistry

4. Scrutiny of drug candidates
   - Estimation of drug efficacy
   - Safety evaluation and pharmacokinetic

5. Manufacturing development
   - Manufacturing process development and quality control

6. Clinical Studies
   - Clinical evaluation and new drug application

7. New Drug Application

Launch
Thank You

Anyone interested in donating or fundraising please contact Monica. To brainstorm different ways to fundraise, you may also contact Tim Freeman.

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