Genetic Reversal
Dr. Huda Zoghbi
Baylor College of Medicine

The study has been undertaken in the lab of an eminent physician-scientist, Dr. Huda Zoghbi, at Baylor College of Medicine in Houston, TX. Through sophisticated genetic engineering, the Zoghbi lab will design an experiment that will carefully analyze disease symptoms in an animal model following deactivation of the second MECP2 gene. Encouraging data suggesting the disease is reversible will set the stage for a drug development initiative.

Pharmaceutic Screen
Dr. Huda Zoghbi
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A drug to lower MeCP2 would be the simplest way to do this for patients, so for this project the goal is to find drugs that can reduce MeCP2 protein levels or identify good drug targets that can be used to design drugs to treat MDS.

Two major approaches to find drugs that lower mecp2 are being pursued.
1. Testing almost all the current FDA-approved drugs to see if any of them can affect MeCP2 levels. Such strategies have worked to find treatments for other diseases, and if one is found, the path to clinical use will be dramatically accelerated since the drug will already be available and its safety profile will be known.

2. Testing every gene in the genome to identify those that regulate MeCP2 levels. Once MeCP2 regulators are identified efforts to find drugs that might inhibit them can then be sought. This approach was pilot tested and indeed several MeCP2 regulators were found.

A drug to inhibit one of regulators was then tested in MDS mice and some of the mice's symptoms were improved. For this project, all the regulators will be followed up as well as any new ones discovered, with additional mouse studies to determine which are the best drug targets and if they can work even better when used in combination.

The Zoghbi lab is trying to find as many drug targets and drugs as possible to maximizechances of finding those that are most effective and safe and can be brought to the clinic to treat MECP2 Duplication Syndrome.

Antisense Oliglionucleotide Therapy
Dr. Huda Zoghbi
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Mecp2 duplication syndrome is a neurological disorder caused by the duplication ofgenetic material on chromosome x, spanning the MeCP2 gene. As a result of the duplication, the MeCP2 protein is excessively produced at two times the normal levels.

In collaboration with Ionis pharmaceuticals inc., we developed an antisense drug (ASO) that can specifically reduce the levels of MeCP2. We have used the ASO molecule to reverse the symptoms of MECP2 Duplication Syndrome in mature adult symptomatic mice and showed that normalizing MeCP2 levels resulted in improvement of all the features of the syndrome. Even when starting the treatment at the advanced age of 6-8 months the animals benefited and stopped having seizures. These results give us hope that there is a potential to reverse the symptoms in people if we can deliver the ASO and safely control the MeCP2 levels.

To prepare for clinical studies we must generate and characterize mice, that, like people with duplication, have two copies of the human gene (and no mouse gene). We have generated such mice and are now characterizing them. We also need to use a new method of ASO's administration that has been shown successful in human infants.

In contrast to our previous work, where the ASO's where gradually infused over a period of 4 weeks using mini-osmotic pumps, in this new research we will use the single -bolus intracerebroventricular injection strategy. Based on the experience of our Ionis collaborators in recent clinical trials, the single-bolus injection strategy results in a much broader distribution of the drug, compared to slow and gradual infusion. Because having the right MeCP2 levels is critical for brain function, we must determine the ideal dose of ASO that bring MeCP2 levels from twice normal to normal.

We need to define the dose carefully so that the levels do not dip below the expected normal to avoid complications from too little mecp2. All these studies to optimize the infusion of the ASO, the dosing, and the titration of the dose will be done in the new mouse model, that, like the humans, expresses two copies of the human gene.

Gene Therapy: Vector-Based RNAi
Dr. Kevin Foust
Ohio State

The Gene Therapy experiment in the lab of Dr. Kevin Foust involves using Vector-Based RNAi. Essentially, what this project endeavors to do is knockdown or knockout the duplicated MECP2 gene through RNAi.

Stem cell-derived 'mini-brains' reveal potential drug treatment
Dr. Alysson Muotri
University of California-San Diego

Using 'mini-brains' built with induced pluripotent stem cells derived from patients with MECP2 Duplication Syndrome, researchers say they have identified a drug candidate that appears to 'rescue' dysfunctional cells by suppressing a critical genetic alteration.

siRNA Therapy
Dr. Anastasia Khvorova
UMass Medical Center

One way to silence genes is through small interfering RNA oligonucleotides (siRNAs). SiRNA interferes with the translation of targeted proteins by binding to and promoting the degradation of their RNA. In Dr. Khvorova's project an MeCP2 siRNA will guide molecular scissors to the MeCP2 RNA for destruction, thereby reducing the level of MeCP2 RNA in the cell.

Dr. Khvorova has developed a new RNA interference scaffold that in animal models shows robust siRNA distribution throughout the brain and spinal cord. Her approach suggests that the siRNA treatment would need to be dosed every 9 to 12 months in humans and may have a better safety profile than other forms of gene silencing.

Dr. Khvorova is a pioneer in the field of oligonucleotides and is part of the RNA therapeutics institute at UMass that brings together a critical mass of scientists with RNA expertise, including Nobel Laureate Craig Mello. The institute has a strong emphasis on developing therapeutics for neurological disease.

CRISPR Therapy
Dr. Ronald Cohn
The Hospital for Sick Children

Dr. Cohn, President and CEO of the hospital for sick children, is a highly respected physician scientist and a wonderful addition to the MeCP2 duplication syndrome (MDS) research community. He and his team have an impressive track record in the development of genome editing strategies.

This project 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 is guided to the duplicated MeCP2 DNA sequences and cuts at the exact same locations in the DNA, marking the duplicated region that needs to be spliced out. The cell corrects the cuts by removing the intervening DNA, leaving only one full copy of MeCP2. A mouse model that would allow testing of this strategy has already been developed and is ready to go.

Dr. Cohn and his colleagues have already shown that this strategy works successfully in MDS patient fibroblasts. They have also shown symptom improvement in a mouse model of Duchenne muscular dystrophy using the same approach.

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

MDS Clinical Studies for Drug Treatment
Dr. Davut Pehlivan
Baylor Colege of Medicine

MDS is still relatively poorly characterized with newly identified features continuing to be identified. The accurate frequency of each symptom also varies significantly between each cohort and needs to be more reliably established. The Texas Children's Hospital (tch) Rett center in Houston currently has detailed genetic information on about 100 patients. Importantly, most of them have been clinically evaluated at TCH. A team of experts who are familiar with mecp2 related disorders and severity scale development has been assembled. These experts will formulate and develop the first set of domains in the severity scale. Additional survey studies that cover core features of the syndrome will be added. These studies will provide crucial information for the scale development and help us to understand the natural progression of MDS better. Once developed the scale will be shared with all interested stakeholders, affected families and care providers, therapists, physicians, researchers, and industry.

Understand how and to what extent genomic structural differences contribute to patients' severity.

Cutting-edge technologies such as high-resolution array comparative genomic hybridization, optical mapping, and whole-genome sequencing will be used to identify the various genomic duplications. Protein levels will also be analyzed and compared to the genetic structure and clinical severity. Develop biomarker(s) to use as a guide for dosing of ASO to ensure safety. Biospecimens including blood, skin, and cerebrospinal fluid have been collected to identify biomarkers from 10 MDS patients and 10 male Rett patients. Plans are to continue the enrollment of additional patients. Various analyses will be done to identify biomarkers that track with disease severity.