

## Research Awardees: 2011

### Basic Research Grant Program:

Regular Research Grants

Postdoctoral Fellowships

### Translational Research Grant Program:

HeART Awards

ANGEL Awards

### Regular Research Grants

Maurizio Giustetto, PhD

Chun Jiang, PhD

Peng Jin, PhD

Michael Müller, PhD

Colleen Niswender, PhD

Paul Patterson, PhD

Gina Turrigiano, PhD

Maurizio Giustetto, PhD, of Torino/National Institute of Neuroscience-Italy

“Identification of Novel Neuronal Substrates of Rett Syndrome: A Morphofunctional Analysis of GABAergic Interneurons in Mouse Models”

### LAY DESCRIPTION:

The majority of cases of Rett syndrome are caused by mutations in the gene encoding MECP2, a protein which binds DNA and regulates the expression of other genes, including that of brain derived neurotrophic factor (BDNF), a major neurotrophin involved in brain development. No effective cure is available for this disease. The applicant has gathered a multidisciplinary group made of people expert in molecular and cell biology, physiology and ultrastructural imaging, to study the progression of the disease in mouse models using the high-definition techniques. This should shed light on new alterations underlying the disease and could give the researcher markers to be used to monitor disease progression objectively and to assess the efficacy of experimental therapies. The goal of this project is a detailed analysis of a deficit in the mechanisms controlling the development and functions of the inhibitory networks that they began to characterize in the brain of animal models of Rett syndrome.

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Chun Jiang, PhD, Georgia State University

“Defects in presynaptic norepinephrine-ergic modulation of cranial motoneurons in Mecp2-null mice”

#### LAY DESCRIPTION:

People with RTT show characteristic motor dysfunction in addition to several other neurological manifestations. The motor abnormalities are seen in early developmental period, including failure to crawl or abnormal crawling, defect in skillful hand manipulation and characteristic hand movements. Clinical examinations reveal hypotonia, abnormal body posture, disturbance in locomotion and stereotypical movement. These symptoms suggest the dysfunction of brainstem norepinephrine system. Norepinephrine is known to facilitate motor function at multiple levels, including cortex, cerebellum, brainstem and spinal cord. Several recent studies have shown abnormalities in brainstem norepinephrine system. However, how the defect in the norepinephrine system links to the motor dysfunction remains unclear. The lack of information of the motoneuronal modulation by norepinephrine hinders the therapeutic design to improve the motor dysfunction in Rett syndrome. Therefore, the applicant has proposed experiments to demonstrate the link of norepinephrine system defect with motor dysfunction. Specifically, they plan to study two groups of brainstem motoneurons, hypoglossal and trigeminal neurons, examine their synaptic communications with other inhibitory neurons, and determine how such a cell communication is affected by the norepinephrine system. These studies will be performed in parallel on wild-type mice and mice with the Mecp2 gene deletion. The latter is a well-accepted mouse model of Rett syndrome. Several innovative plans have been made. The information to be generated will have impact on the understanding of the motor dysfunction in Rett syndrome. The information will also have impact on the therapeutic approaches to Rett syndrome using more specific agents that target at the norepinephrine modulation system.

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Peng Jin, PhD, Emory University

“5-Hydroxymethylcytosine-mediated Epigenetic Modulation in Rett Syndrome”

#### LAY DESCRIPTION:

Rett Syndrome (RTT) is a neurodevelopmental disorder mainly caused by mutations in the X-linked gene methyl-CpG-binding protein (MECP2) and primarily affects females. MeCP2 is thought to selectively bind methyl-CpG dinucleotides in the mammalian genome and block gene expression. Recent studies have demonstrated the presence of 5-hydroxymethylcytosine (5-hmC), the 6th nucleotide in the genome. Unlike 5-methylcytosine (5-mC) that has been implicated in the repression of gene expression, 5-hmC has been proposed to play significant role(s) in gene reactivation, which would be important for the pluripotency of stem cells and proper neuronal functions. Using a novel technology that the applicant has developed, they have found that the loss of Mecp2 could alter 5-hmC distribution in brain. In this proposal, they are going to explore the role of 5-hmC-mediated epigenetic modulation in the molecular pathogenesis of Rett syndrome.

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Michael Müller, PhD, University of Göttingen

“Mitochondrial dysfunction and cytosolic redox imbalance in Rett syndrome”

#### LAY DESCRIPTION:

Rett patients and mouse models of Rett syndrome, i.e. mice carrying mutations in the gene coding for the transcriptional regulator MeCP2, suffer from highly irregular breathing with temporary arrest of breathing, which gives rise to repeated episodes of reduced systemic oxygen supply (hypoxia). Yet, instead of desensitization or neuronal adaptation to such intermittent hypoxia, we rather found an increased hypoxia susceptibility of the hippocampus and brainstem of MeCP2-deficient mice. In hippocampal pyramidal neurons we confirmed a dysfunction of K<sup>+</sup> channels and a disturbed regulation of intracellular Ca<sup>2+</sup> levels. Also, the function and metabolism of mitochondria – the cellular “power plants” – is affected. Acting as multi-purpose cell organelles, mitochondria are the most important supplier of cellular energy, contribute to cellular Ca<sup>2+</sup> regulation, constitute a major source of reactive oxygen species (ROS) and may thus critically modulate neuronal activity and excitability in various ways. In patients and mice MeCP2-deficiency is well known to affect mitochondrial structure and function, and there are clear signs of increased ROS-mediated oxidative damage of cellular components. Therefore, we are now aiming to decipher the interplay of mitochondrial dysfunction, the associated ROS-mediated redox imbalance and cellular Ca<sup>2+</sup> regulation and its resulting impact on neuronal function in MeCP2-deficient mouse hippocampus. Using high-resolution microscopy and novel optical probes will allow to rate mitochondrial function and correlate it with cytosolic and mitochondrial ROS levels. Quantitative optical recordings of intracellular Ca<sup>2+</sup> levels combined with detailed electrophysiological analyses will address the efficiency of cellular Ca<sup>2+</sup> regulation under various ROS-levels in correlation with neuronal activity and plasticity. These studies will be complemented by biochemical assays rating the efficiency of mitochondrial metabolism under normal and limited oxygen supply. We consider a detailed molecular understanding of this fascinating neurochemical interplay and its impact on the function of complex neuronal networks as a crucial contribution to the molecular understanding of the neurobiology of Rett syndrome and the development of novel successful pharmacotherapy. Following this concept we will clarify whether modulating Ca<sup>2+</sup> homeostasis and redox balance is capable of restoring neuronal plasticity.

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Colleen Niswender, PhD, Vanderbilt University

“Metabotropic glutamate receptor 7: a potential novel candidate for the treatment of Rett Syndrome”

## LAY DESCRIPTION:

Rett syndrome is a devastating neurological disorder caused the by the loss or mutation of the protein MeCP2. We hypothesize that a receptor in the brain that responds to the neurotransmitter glutamate, called metabotropic glutamate receptor 7 (mGlu7), may be encoded by a gene that is regulated by MeCP2 activity. Our experiments will determine if abnormal functioning of mGlu7 contributes directly to Rett syndrome symptoms and we will also assess the ability of compounds that block mGlu7 activity to regulate the abnormal signaling between brain cells that is observed in mice lacking MeCP2. Positive results from our studies would indicate that mGlu7 could be an ideal target for therapeutics development for the treatment of Rett syndrome.

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Paul Patterson, PhD, California Institute of Technology

“Characterization of IKK $\alpha$ -MeCP2 interactions”

## LAY DESCRIPTION:

MeCP2 protein, which is mutated in Rett syndrome patients, plays a crucial role in the production of many neuronal genes and is important for brain development. The binding of MeCP2 to other cellular proteins may determine which genes are turned on or off. We have identified a protein known as I $\beta$ B kinase  $\pm$  (IKK $\pm$ ) as a modifier of MeCP2 activity in human neurons. IKK $\pm$  is an enzyme that can promote gene expression by various mechanisms. We find that IKK $\pm$  binds to and phosphorylates (adds a tag) MeCP2. Phosphorylation of MeCP2 is a signal that regulates the expression of certain genes such as brain-derived neurotrophic factor (BDNF), a growth factor that is implicated in the pathogenesis of Rett syndrome. IKK $\pm$  enhances the production of BDNF and growth factors that promote neuronal survival and communication. Thus, studying the interaction between MeCP2 and IKK $\pm$  in human neurons may lead to identification targets that can be used to develop therapeutics for Rett syndrome.

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Gina Turrigiano, PhD, Brandeis University

“Disrupted Homeostatic Synaptic Plasticity as a Potential Cause of Cortical Dysfunction in Rett Syndrome”

## LAY DESCRIPTION:

Rett Syndrome (Rett) is one of the leading genetic causes of mental retardation in females. Most Rett cases are due to loss of function of MeCP2, but we still have only a rudimentary understanding of how loss of MeCP2 dysregulates brain circuits. Previously in a mouse model of Rett we found an imbalance of synaptic excitation and

inhibition within cortical brain circuits that just precedes the onset of symptoms. This balance is critical for proper brain function, and is normally maintained by a set of “homeostatic” plasticity mechanisms that keep network activity stable. In preliminary experiments we found that this process is disrupted in Rett, raising the intriguing possibility that one of the underlying causes of Rett is a defect in homeostatic synaptic plasticity. Here we will test the hypothesis that loss of MeCP2 causes cortical networks to lose the ability to homeostatically regulate synaptic strength and number during experience dependent postnatal development, thus leading to a progressive imbalance in excitation and inhibition that ultimately leads to Rett.

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#### Postdoctoral Fellowships

Darren Goffin, PhD

Anna Kalashnikova, PhD

Wei Li, PhD

Ana Abdala Sheikh, PhD

Han Xu, PhD

Darren Goffin, PhD, University of Pennsylvania

“Investigating Neurophysiological Biomarkers for Rett Syndrome”

#### LAY DESCRIPTION:

Rett syndrome is caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2). The manifestation of the symptoms in this disorder is thought to arise from dysfunctions in the network activity of neurons in the brain. It is possible to study the network activity of these neurons by measuring their electrical activity. Additionally, it is possible to examine how these neurons process information by measuring the changes in electrical activity before and after the presentation of an external stimulus such as sound. Using these techniques the applicant has shown that neurons in mice lacking MeCP2 protein or those mice carrying a mutation observed in Rett Syndrome are more excitable than normal mice carrying non-mutated MeCP2. Furthermore, he has demonstrated that these mice show deficits in their processing of auditory stimuli revealing deficits in neuronal network activity. In this proposal, his plan is to understand whether other mouse models of Rett Syndrome exhibit similar deficits in neuronal network activity with and without auditory stimulation and to understand which particular types of neurons are responsible for these deficits. It is the hope of this proposal that if successful, they will understand how MeCP2 mutations lead to Rett syndrome and use similar methodologies for examining whether new pharmaceutical products are effective in the treatment of patients with Rett syndrome.

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Anna Kalashnikova, PhD, Colorado State University

“Crystallization of the MeCP2 C-terminal domain in complex with DNA and full length MeCP2 in complex with nucleosomal arrays”

#### LAY DESCRIPTION:

The lack of a high resolution structure of MeCP2 represents one of the main obstructions to the rational development of pharmaceutical therapies for Rett syndrome. The crystallization studies of MeCP2 are challenging, because the protein does not adopt a well folded conformation when free in solution. However, MeCP2 forms regular structures when bound to chromatin, and its isolated CTD domain possesses some transient order. We will perform crystallization study of MeCP2 in complex with model nucleosomal arrays and its CTD domain in complex with DNA. The applicant has obtained promising crystals in her preliminary studies of both full-length MeCP2 and its CTD domain. These structures will provide essential structural information needed for understanding the role of MeCP2 in the molecular pathophysiology of RTT, and for development of potential rational therapies for treatment of RTT.

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Wei Li, PhD, University of Alabama-Birmingham

“A new approach for treating Rett syndrome: restoration of interneuron function by BDNF”

#### LAY DESCRIPTION:

Epilepsy occurs commonly in individuals with RTT, and exploring the underlying brain mechanisms may lead scientists to prevent or slow this neurodevelopmental disability. Epileptic activity involves dysfunctional inhibitory interneurons that may be caused by reduced expression of a growth factor called brain-derived neurotrophic factor (BDNF). We have found that BDNF released onto surrounding cells in the brain induces membrane currents and Ca<sup>2+</sup> entry, which are indicators of interneuron function that can be observed by state-of-the-art electrophysiological and imaging techniques. In this proposal, we will mainly use this method to determine whether BDNF-induced currents and Ca<sup>2+</sup> signals are decreased in mice lacking Mecp2, a molecule that is highly associated with RTT. In addition, we will administer BDNF mimetics that have greater ability to enter brain than BDNF to Mecp2 mutant mice and evaluate treatment effectiveness. This study will lead to better characterization of this disease and development of novel therapeutic interventions.

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Ana Abdala Sheikh, PhD, University of Bristol

## “Understanding and rescuing respiratory arrhythmias in a mouse model of Rett Syndrome”

### LAY DESCRIPTION:

Breathing is the most important process controlled by the brain; it is a rhythm that happens non-stop from birth until death. It constantly changes to allow for other behaviors such as speech, singing, exercising, eating, drinking, coughing... Frequent periods of breath holding are a very common feature of Rett syndrome. When severe, the breathing irregularity can be distressing for both patients and parents reducing the quality of life and general health of Rett syndrome girls. This symptom has also been associated with sudden death, and currently there are no successful treatments to alleviate the breathing irregularities from Rett syndrome. In this project, the applicant will confirm that the brain cells from the Kölliker-Fuse area of the brain which control the duration of exhalation are overly excited in a mouse model of Rett syndrome and will verify whether this is the main reason for the breathing abnormalities. She will also identify substances that control the activity of these cells in order to find therapeutic alternatives for treating this symptom. Finally, she will also test a combination of two drugs, Riluzole and Buspirone, to try to treat the breathing irregularities in the mouse model. These two drugs are already used to treat children for other clinical conditions, but could be effective in treating Rett syndrome over a dose range that is neither sedative nor depresses breathing.

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Han Xu, PhD, New York University

## “Contribution of cortical GABAergic interneuron populations to Rett syndrome pathology”

### LAY DESCRIPTION:

Rett syndrome (RTT) is a severe neurological disorder characterized by mental retardation, seizures, repetitive behaviors and abnormal social interactions. Imbalance between excitation and inhibition in the brain caused by mutations in the methyl-CpG-binding protein 2 gene (MeCP2) is thought to underlie Rett pathology. While most studies have focused on investigating excitatory neurotransmitter systems, recent studies indicate that MeCP2 is crucial for normal function of inhibitory neurons. Indeed, a recent study demonstrates that MeCP2 deficiency in inhibitory signaling is sufficient to mediate many Rett symptoms in mice. In mammalian brain, exquisite inhibition is mediated by diverse types of inhibitory neurons using GABA as neurotransmitter. However, the contribution of individual types of GABAergic neurons to RTT pathology is unknown. To understand the pathogenesis of RTT and design proper treatments, it is necessary to determine which GABAergic neuron populations are affected by MeCP2 loss and what are the cellular changes that underlie specific behavioral deficits. In this proposal, mouse models will be used to study how MeCP2 deficiency affects the normal development and function of subtypes of cortical GABAergic neurons, and will further investigate the behavioral and functional abnormalities produced by MeCP2 removal specifically from subtypes of GABAergic neurons. The findings from the proposed studies will help understand the pathogenesis of Rett syndrome at a cellular level, and will advance the development of future therapies.

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## HeART Awards

Yves-Alain Barde, MD

John M. Bissonnette, MD

Joseph Bressler, PhD

Qiang Chang, PhD

Aleksandra Djukic, MD, PhD

Jenny Downs, PhD

James Eubanks, PhD

Steven J. Gray, PhD

Walter Kaufmann, MD

Jeffrey Neul, MD, PhD

Lucas Pozzo-Miller, PhD

Jay R. Shapiro, MD

Yves-Alain Barde, MD, Biozentrum- University of Basel

“Increasing BDNF levels with the sphingosine-1 phosphate receptor agonist fingolimod (FTY720)”

### Lay Description:

The goal of this work is to use an approved drug to elevate the levels of the growth factor BDNF in the brain of patients suffering from Rett Syndrome. Mouse models of the disease have indicated that the levels of BDNF are decreased in the brain and that increasing BDNF improves motor function and performance. The applicant plans to use (“repurpose”) the drug designated fingolimod or FTY720 that is already used for the treatment of multiple sclerosis. It reaches the brain by passing through the blood brain barrier and his work with mouse models of Rett syndrome indicates that it increases BDNF levels, both in wild type and in MeCP2 mutant mice. Most importantly, its administration leads to an improvement of the motor behavior of animals lacking MeCP2. The main goal of this work is to understand the mode of action of FTY720 in the brain by examining the distribution and role of its receptor and to investigate whether the benefits of FTY720 involve BDNF. They also plan to measure BDNF levels in available samples of patients treated with FTY720, both in blood and in CSF and to start a small clinical trial with Rett syndrome patients in collaboration with clinicians in Basel who have been involved in the development of FTY720 for the treatment of multiple sclerosis and have considerable expertise with the use of this drug in humans.

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John M. Bissonnette, MD, Oregon Health Sciences University

"Serotonin and small molecule treatment of respiratory disorders in a mouse model of Rett syndrome"

#### Lay Description:

Chemical compounds, which act like the neurotransmitter Serotonin, have been studied in mice that have exhibited respiratory dysfunctions associated with Rett syndrome. Preliminary findings have shown that serotonin-like compounds can reverse these respiratory symptoms. The chemical compound (F15599) that will be used in this study is more effective in targeting defective brain cells as this has the ability to move out of the blood stream and into the brain. In collaboration with Dr. Jerod Denton, Dr. Bissonnette proposes to study another chemical compound (VU230) that may have fewer side effects because it can specifically target a protein that does not function normally in RTT patients.

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Joseph Bressler, PhD, Hugo W. Moser Research Institute at Kennedy Krieger, Inc.

"The Use of NF kappa B inhibitors In Treating Rett Syndrome"

#### Lay Description:

Much effort is being devoted to drugs that directly restore MeCP2 function or cell implants that replace dysfunctional neurons. These efforts have the potential of correcting the mechanism underlying RTT but they are many years away from implementation. This grant application takes a different approach that has the potential of restoring many functions affected by Mecp2 mutations by using drugs currently under development and in clinical trial that inhibit NF kappa B signaling. Their preliminary studies have found a relation between over active NF Kappa B signaling and MeCP2 dysfunction. NF kappa B is a transcription factor that is over active in cancer and inflammation. Not surprisingly, pharmaceutical companies have focused on NF kappa B signaling because of the promise of a lucrative market. These same drugs have the potential to alleviate many of the symptoms of RTT. To find the best drug, it will be necessary to determine the step in the NF kappa pathway affected by MeCP2. NF kappa signaling is a complicated process with several steps and each step can be targeted by different drugs. They will use three different models to determine the step and these include a monocytes cell line genetically altered to express dysfunctional MeCP2, macrophages from Mecp2 null mice, and blood monocytes from children with RTT. The macrophage type cells are being examined because it allows us to test the drugs directly on biological samples from RTT. The effects of the NF kappa B inhibitors will also be examined on the release of glutamate, which is regulated by both MeCP2 and NF kappa B. In the brain, over production of glutamate by microglia (derived from the macrophage lineage) possibly underlies several of the symptoms displayed by children with RTT. In summary, these studies will provide information needed to choose currently available drugs that have potential beneficial value in treating RTT.

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Qiang Chang, PhD, University of Wisconsin-Madison

## "Establishing Neurons Differentiated from an Isogenic Pair of Rett Syndrome iPSC lines as Cell-Based Assay for Future Drug Screens"

### Lay Description:

Rett syndrome is a devastating brain disease with no effective treatment or cure. Through extensive basic research, a great deal of disease progression has been learned and that disease symptoms can be reversed in a RTT mouse model. However, to accelerate the speed of drug discovery and therapy development, it is critical to establish a robust cell culture based system that 1) can truthfully recapitulate hallmark RTT pathologies, and 2) is suitable for high-throughput screening of drug candidates. Using modern technology, skin cells isolated from RTT patients can become special stem cells (induced pluripotent stem cells (iPSCs)). With proper instructions, these stem cells can become neurons (the main type of cells affected in the brains of RTT patients). The proposed study is designed to define the characteristic RTT defects in these human RTT neurons and test drug efficacy in RTT nerve cells. Dr. Chiang's proposed work will help validate RTT iPSCs as a model system to study disease progression, thus providing a platform for future drug screens.

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Aleksandra Djukic, MD, PhD, Rett Syndrome Center at Montefiore of Albert Einstein College

### "Face perception in Rett Syndrome: Recognition of Emotional Expression"

### Lay Description:

Attempts to assess cognitive functioning in patients with Rett Syndrome (RTT) have been extremely difficult. At the Rett Center at Montefiore, Aleksandra Djukic and her team is developing techniques, using eye tracking technology, to examine cognitive ability in girls with RTT. They propose to continue their study of cognitive functioning in girls with RTT using eye tracking technology now examining their ability to distinguish different emotional expressions. This is an important component of social skills, which is thought to be compromised in girls with RTT. They anticipate that girls with RTT will recognize some face emotions (such as happy face) similar to controls but they will have difficulties recognizing more complex emotional expressions (sad and fearful faces). They are planning to recruit 40 patients with RTT and a control group of typically developing children, matched by age and gender to participate in a pilot study using an eye tracker.

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Jenny Downs, PhD, Curtin University

### "Daily physical activity in girls and women with Rett syndrome: An important outcome for clinical trials"

### Lay Description:

An important goal of any therapy in Rett syndrome is to improve function in daily life. Girls and women with Rett

syndrome may have difficulties with gross motor skills such as standing, transfers, walking, and participating in physical activity over the course of daily life. There is currently no objective measure of physical activity that has been validated in Rett syndrome. Dr. Down's study will define the optimal method of measuring physical activity in Rett syndrome. Accelerometers are small devices worn on the body that pick up body movements and some are showing promise as measures of physical activity in persons with atypical walking patterns. The proposal aims to expand a previous study, which had tested the accuracy of a single type of accelerometer on RTT girls and women. In this study, three separate accelerometers with different levels of sophistication will be examined in a larger population. These results will lead to an optimal protocol for measuring physical activity that may be used in future clinical trials.

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James Eubanks, PhD, Toronto Western Research Institute

"Evaluating Whether Huperzine-A Improves MeCP2-Deficient Mouse Behavior"

#### Lay Description:

Considerable evidence now suggests that Rett syndrome is a treatable condition. In addition to genetic studies showing Rett syndrome in mice can be reversed, recent drug studies have also shown at least some beneficial effects in MeCP2-deficient mice. While clinical trials for at least two drugs are currently underway, there remains a large need to identify better drugs, or combinations of drugs, that also improve the phenotype of MeCP2-deficient mice in preclinical studies to "fast-track" them to the clinic. There are two predominant strategies: to develop new drugs, and to repurpose existing drugs. While there is clearly a need to develop new drugs, it tends to be long and expensive, and work in this area will lead to the drugs of the future. However, the repurposing of a drug that already has a history of safe and well-tolerated clinical use bypasses many of the hurdles associated with novel drug discovery, and repurposed drugs can more quickly find their way into clinical use. The applicant hypothesizes that the cholinesterase inhibitor Huperzine-A represents a very intriguing candidate whose evaluation in Rett syndrome models is highly warranted. Huperzine-A has been tested in clinical trials, is safe, and its actions will stimulate the brain in a way that should counter many of the neurophysiological deficits caused by the absence of MeCP2. To test this possibility, they will administer Huperzine-A to MeCP2-deficient mice, and determine whether it improves their Rett-like phenotype.

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Steven J. Gray, PhD, University of North Carolina at Chapel Hill

"Development of Optimized AAV Vectors for Intra-CSF Administration in Rett mice"

#### Lay Description:

Gene-replacement therapy of MeCP2 is a potential future treatment option for RTT patients. Although many challenges exist for replacement of MeCP2 in humans, this strategy could represent a comprehensive treatment for RTT, rather than a treatment of the downstream effects of gene loss. A critical component of any Rett gene therapy approach is the availability of a reagent and route of administration to get the most efficient and widespread delivery of MeCP2 across the entire brain. The method of using a non-disease-causing virus called AAV to deliver therapeutic genes to specific tissues in order to treat genetic disorders has been established. The proposed work will use AAV to carry MeCP2 into

the brain cells of RTT mice. Dr. Gray's proposal is a critical component necessary to test the efficacy of a Rett gene therapy in animal models that may eventually translate to a therapy in humans.

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Walter Kaufmann, MD

"Development of a Behavioral Outcome Measure for Rett Syndrome"

#### Lay Description:

Challenging behaviors ranging from autistic symptoms to anxiety and mood liability are major clinical issues in Rett syndrome and affect one's quality of life, independence, and performance. In order to determine whether therapies targeting these challenging behaviors are effective, there is a need for reliable, valid, and sensitive outcome measures. RettSearch, the international consortium of RTT clinical researchers, has identified the development of a behavioral outcome measure as a high priority. The goal of Dr. Kaufmann's study is to create a broad-based behavioral outcome measure for use between the ages of 3-18 that will allow for: 1) a consistent, normalized way to measure behavioral outcomes in treatment trials, and 2) tracking developmental progress and behavioral changes over time.

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Jeffrey Neul, MD, PhD Jan and Dan Duncan Neurological Institute at Texas Children's Hospital and Baylor College of Medicine

"Pharmacological treatment of cardiac rhythm abnormalities in Rett Syndrome"

#### Lay Description:

Although many people with Rett syndrome live long lives, up to a quarter of all deaths in Rett syndrome are sudden and unexpected. Although it is not known why these people die, the applicant thinks that problems with the way the heart functions may be the cause. About 1 in 5 people with Rett syndrome have changes in the way their hearts conduct electricity, and this type of problem can make the heart suddenly start beating very fast. This rapid heart beat does not pump blood well and when people develop this, they usually die. They have found that Rett mice also have this same electrical problem in their hearts, and can develop this fast heart beat and die. By giving these animals a single dose of a drug that is used to stop seizures, we were able to change the electrical activity and prevent the animals from having the fast heart rate. Therefore, this may be a better way to treat the problem and prevent sudden death in people. To see if this is true, they will treat the animals for a month and see if this prevents the animals from getting the electrical problem and protect them from the rapid heart rate and death. If this treatment works, we will consider trying this drug or other drugs that work in the same way in people to see if it will fix the electrical problem in their hearts.

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Lucas Pozzo-Miller, PhD, University of Alabama-Birmingham

"IGF-1 and TrkB Agonists as BDNF Mimetics for the Reversal of Dendritic Spine Pathologies and Network Hyperexcitability in the Hippocampus of MeCP2 Mutant Mice"

Lay Description:

Rett syndrome is caused by mutations in the gene coding for MECP2, which controls several genes including BDNF, a member of the neurotrophins. Loss of BDNF in brain cells is inevitably among the crucial factors responsible for a variety of sensory and motor abnormalities associated with Rett syndrome. Consistent with this view, RTT-like symptoms in mouse models can be reversed if BDNF is reintroduced into brain cells. Therefore, BDNF therapy would be an effective pharmacological intervention for the treatment of RTT. However, there are limitations in using BDNF itself, in regards to efficacy. Dr. Pozzo-Miller's proposal is designed to study the therapeutic potential of BDNF substitutes (Insulin-like Growth Factor-1 and TrkB ligands), which have a better ability in reaching the target brain cells in mice that exhibit RTT-like symptoms.

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Jay R. Shapiro, MD., Hugo W. Moser Research Institute at Kennedy Krieger, Inc.

"Treatment of Osteoporosis in Murine Rett Syndrome Models: A Comparison of Zoledronic Acid vs. Teriparatide on Osteoblast Function, Gene Expression and Bone Mass"

Lay Description:

Bone density measurements indicate that approximately 50% of children and adults with RTT have diminished bone mass, and 11% of children have had fractures. Several studies suggest that bone-forming cells (osteoblasts) may be defective in the presence of MECP2 mutations. It is not known whether treatment with an antiresorptive agent, zoledronic acid, or a bone-forming agent, teriparatide, is effective in the RTT population. Both zoledronic acid and teriparatide have been administered to children and/or adults for the treatment of brittle bone diseases. The proposed study aims to evaluate these agents in RTT mouse models to determine their effectiveness in enhancing osteoblast function or in increasing bone mass, prior to considering treatment trials in RTT patients. The results of Dr. Shapiro's studies will form the basis for treatment of osteoporosis in children and adults with Rett syndrome.

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ANGEL Awards

Huda Y. Zoghbi, MD

Huda Y. Zoghbi, MD, Baylor College of Medicine

"Therapeutic Interventions to Modulate the GABAergic System in Animal Models of Rett Syndrome"

Lay Description:

Rett syndrome is quite a complex disorder characterized by a multitude of abnormalities and neuropsychiatric features. Inhibitory neurons that make the neurotransmitter GABA have been identified as a cell population that mediates key features of Rett syndrome upon loss of MECP2, the gene that is mutated in RTT. Loss of MeCP2 in these GABA neurons causes a modest reduction in GABA levels and reproduces almost all the features of Rett. Dr. Zoghbi's proposed work will study whether readily available drugs that increase the levels or activity of the GABA neurotransmitter will reduce Rett symptoms in mouse models. If these drugs prove effective, several of them can then be tested in clinical trials given that they are FDA-approved.

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