

## Research Awardees: 2009

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### Research Awards

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Ballas, Nurit, Stonybrook University, 2 years, \$100,000

Title: Analyzing the contribution of MeCP2-deficient oligodendrocyte-lineage cells to Rett syndrome neuropathology

#### Lay Summary:

Rett Syndrome (RTT) is a severe neurological disorder in humans that results from mutations in the gene expressing the transcription factor MeCP2. It was shown recently that mouse models that are deficient for MeCP2 and develop Rett-like Syndrome can be rescued by reactivation of MeCP2, suggesting that the damage occurred to the nervous system is reversible. We showed that the damage occurred to neurons in the nervous system is likely due not only to MeCP2-deficiency in neurons but maybe also due to the lack of MeCP2 in glia, which represent a large number of cells in the brain and support the neurons. Specifically, we showed that astroglia that lack MeCP2, likely secrete factor(s), which affect neurons negatively. We propose to analyze in vivo the contribution of different glia to the RTT neuropathology. The proposed studies have the potential to advance our knowledge for the different cell types in the brain involved in manifestation of RTT and for developing therapeutic strategies for treatment of this devastating neurological disorder that strikes one in 10,000-15,000 girls.

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Eubanks, James, Toronto Western Research Institute, 2 years, \$100,000

Title: Assessing Phenotypic Improvement of MeCP2-Deficient Mice By Preservation or Reactivation of Functional MeCP2 in Catecholaminergic Cells

#### Lay Summary:

Rett syndrome is a devastating genetic condition caused by mutations of the MECP2 gene. There is no cure at present, and treatments for Rett syndrome generally attempt to control specific symptoms of the condition. To aid in developing effective treatments, several research groups have generated mouse models of Rett syndrome. These mice develop Rett-like deficits, and serve as useful tools for testing novel treatment ideas, and unraveling how the loss of MeCP2 function affects the brain and body. Work on these mice has recently found that their Rett-like condition can be improved or even corrected by the reintroduction of MeCP2 function – even if this is done late in the progression of the condition. The most successful rescues were seen when MeCP2 function was restored to its normal levels, and throughout the body. Given this success, we propose to test whether a similar restoration of MeCP2 function to its normal levels will provide benefit if rather than being restored to the whole body, function is restored to a specific class of cells. The cells we will target are those that secrete noradrenaline, epinephrine or dopamine throughout the brain and body. Deficits in these cells have been documented in Rett patients, and there is some evidence that pharmacological targeting of this system can partially improve certain behavioral deficits in the mouse models. If successful, these results would open new avenues to developing treatments for Rett syndrome.

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Gray, Steven, University of North Carolina - Chapel Hill, 2 years, \$100,000

Title: rAAV-Mediated Replacement of the MeCP2 Gene in a Rett Syndrome Mouse Model

#### Lay Summary:

Rett syndrome, a form of autism, is a severe neurological disorder that affects about 1 in 10,000 girls. Rett syndrome is usually caused by a defect in a single gene, called MeCP2, that is required for proper brain function. There is no cure for Rett syndrome. However, a recent article in the journal Science from Adrian Bird's laboratory has demonstrated that if you can activate a MeCP2 gene in mice that were born without it, the symptoms of Rett syndrome can be reversed. This study demonstrated that a therapy for Rett syndrome is possible if a correct MeCP2 gene can be delivered to cells in the

brain. However, this landmark study also indicated that a low amount of MeCP2 activation has only a modest positive effect, and eventually the mice die prematurely. Other research has shown that too much MeCP2 can also kill mice. From these findings, two major obstacles remain before a MeCP2 gene replacement therapy for Rett syndrome can be attempted. 1) One needs to be able to deliver the MeCP2 gene to the greater majority of brain cells for any therapy to be effective. 2) One must be very careful about how active the MeCP2 gene is once it is put into brain cells. Using funding from IRSF, we have made significant progress on the first obstacle. Our lab specializes in modifying a non-disease-causing virus called AAV to deliver therapeutic genes to specific tissues in order to treat genetic disorders. For example, a modified AAV virus that our lab made is currently in Phase I human clinical trials to treat Duchenne's Muscular Dystrophy. Our current IRSF-funded project is to improve general gene delivery to the brain. We propose to use our success delivering the AAV virus to the brain to begin an investigation delivering MeCP2. The short-term goal is to identify how much MeCP2 to deliver, with the long-term goal to develop this into a therapy for Rett syndrome patients.

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Hong, Heekyung, Northwestern University, 2 years, \$100,000

Title: Genetic Dissection of of Rett Syndrome: a Screen for Modifiers of MeCP2 in the mouse

Lay Summary:

Since the identification of mutations in the MECP2 gene as the cause of Rett syndrome, significant progress has been made in unraveling the developmental and biological basis of the disease. Despite this breakthrough however, treatment for the disorder is essentially symptomatic and supportive, and will likely remain so without identification of additional aspects of MECP2 that might suggest therapeutic targets. In most, if not all, biological processes, proteins function by interacting with one another, which then initiate numerous cascades of cellular events. For McCP2, we are only just beginning to identify its interacting partners and understand how MeCP2 works at the cellular level. In this project, we propose to use a genetic technique known as mutagenesis screening to identify MeCP2 partners (also called "modifiers") that are not yet known. Specifically, we will use mutagenesis screening techniques to build on the current MeCP2 mouse model, generating novel mouse models that may help us to further understand the disease process while also providing insights into the development of therapeutic approaches for Rett syndrome.

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Kilpatrick, Daniel, University of Massachusetts Medical School, 2 years, \$99,998

Title: Transcriptional Dys-Regulation in Rett Syndrome

#### Lay Summary:

Rett Syndrome causes severe neurological changes in affected females, including seizures, motor dysfunction and autism, and it is a leading cause of mental retardation in girls. Mutations that disrupt the function of the Mecp2 protein in neurons are a major cause of this disease. However, the pathways that are affected by disruption of Mecp2 and that mediate its effects on the nervous system remain poorly understood. Defining these pathways is critical in the development of new therapeutic strategies to ameliorate the neurological disorders associated with Rett. Recent studies by our lab and others have found that the transcription factor Rest is elevated in brain tissue from Mecp2-deficient mice and Rett patients. Rest regulates many genes in neurons, and its dysregulation may be a critical factor underlying Mecp2-deficiency and Rett. We propose to test this by decreasing Rest levels in a mouse model of Rett Syndrome to determine if this treatment reverses Rett-like neurological defects. The strategies employed may provide a valuable new translational approach in the treatment of this devastating disease.

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Neul, Jeffrey, Baylor College of Medicine, 2 years, \$100,000

Title: Characterization of cardiac abnormalities in Rett syndrome

#### Lay Summary:

A significant number of girls and women with Rett syndrome die sudden and unexpectedly. Although the exact cause of these deaths is unknown, it is believed that changes in the way the heart functions might cause these deaths. Some people with Rett syndrome have alterations in the way the electrical system in their hearts work which is discovered by performing an electrocardiogram (ECG). This change is called a long QTc and it can lead to the development of an unstable heart rhythm called ventricular tachycardia (VT). This unstable heart rhythm will lead to a sudden death and it is thought that the sudden deaths seen in people with Rett syndrome may be due to this alteration in the electrical system in their hearts. Mouse models of Rett syndrome have been created that show many of the same problems found in people with Rett syndrome. For example, these mice have changes in their breathing patterns that is similar to people with Rett syndrome. We have found that these mice also have the same changes in their heart electrical system as that found in people with Rett, a long QTc. We also found that we could cause the unstable heart rhythm, VT, in these mice much easier than in normal mice. In the work proposed, we seek to understand the reasons these mice develop this heart problem. We will look at the role these heart problems play in the early death in these mice, the molecular machinery involved in heart electrical activity, and determine which tissues are important in the development of this heart abnormality. Understanding the way this heart problem develops in mice will help us understand how the same problems develop in people with Rett syndrome. With this understanding, we will be able to develop new methods to treat these problems in mice and ultimately in people.

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Patterson, Paul H., California Institute of Technology, 2 years, \$100,000

Title: Regulation of MeCP2-mediated gene expression by I $\kappa$ B kinase alpha

#### Lay Summary:

MeCP2 plays a crucial role in the expression of many neuronal genes and is important for brain development. Communication between MeCP2 and other cellular proteins is a determining factor in which genes are turned on or off. Thus, it is important to identify MeCP2 partners and examine how they influence its function. Based on preliminary evidence, we predict that I $\kappa$ B kinase  $\pm$  (IKK $\pm$ ) is a modifier of MeCP2 activity in neurons. IKK $\pm$  is an enzyme that can promote gene expression by various mechanisms. We find that IKK $\pm$  binds to and phosphorylates MeCP2. Phosphorylation of MeCP2 is a trigger that enhances 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. Thus, studying the interaction between MeCP2 and IKK $\pm$  may lead to identification a molecular circuit that regulates BDNF expression and possibly other neuronal genes, and may help in the development of therapeutics for Rett syndrome patients.

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Schanen, N. Carolyn, Alfred I. DuPont Hospital for Children/Nemours Children's Clinic at the University of Delaware, 2 years, \$100,000

Title: Suppression of Rett Nonsense Mutations by Pharmacological Agents

#### Lay Summary:

Approximately one third of patients with Rett syndrome carry a mutation in the MECP2 gene that leads to production of an incomplete protein (nonsense mutation). The recent discovery of drugs that can “glide over” nonsense mutations in a defective gene poses an exciting possibility for treatment for patients with Rett syndrome caused by this kind of mutation. These drugs allow production of a full-length protein from the faulty gene, although our preliminary studies show this process is not efficient however our previous testing approach had problems with sensitivity. Importantly, before this type of agent can be considered for treating patients or even animals, several types of studies must be performed including testing the potency, efficacy and the time-course for production of the complete protein using cells growing in culture. We propose to use a highly sensitive assay to examine the ability of four different drugs for their ability to produce a complete protein in cells carrying the five most common MECP2 nonsense mutations found in patients with Rett syndrome to determine these basic properties of the compounds. Studies using the antibiotic gentamicin, which has similar activity in terms of “gliding over” nonsense mutations, have shown that the drug does not generate a completely normal protein in many cases, but that it puts in a different amino acid (missense mutation) at the site of the premature stop signal. We will use protein sequencing to determine whether the complete protein made after treatment with these drugs is a normal protein or whether it introduces an error at the site of the original mutation. We will also test the ability of the full-length protein made after treatment with these drugs to bind normally with DNA and other proteins that MECP2 normally interacts with in the nucleus. Together these studies will provide important “pre-clinical” information that is needed as the foundation for developing these drugs for potential treatments for MECP2 mutations.

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Sun, Yi Eve, University of California - Los Angeles, David Geffen School of Medicine, 2 years, \$100,000

Title: The role of microRNA dysregulation in MeCP2-deficient neurons

Lay Summary:

Rett Syndrome (RTT), a major autism-spectrum neurological disorder affecting females, is caused by mutations in MECP2 (Methyl-CpG Binding Protein 2). MeCP2 is a member of a group of proteins that play a role in epigenetic regulation of number of cellular processes. One of the major epigenetic mechanisms, microRNAs (miRNAs), functions by blocking the translation of their target mRNAs. Although, the miRNAs may participate in the progression of RTT, it is not known whether MeCP2 can directly regulate miRNAs. Using mouse models of RTT, we identified a number of miRNAs dysregulated in the cerebellum at early-symptomatic stage. In this application, we propose to define how dysregulated miRNAs interfere with neuronal function in MeCP2 deficient neurons.

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Vincent, John, The Centre for Addiction & Mental Health, University of Ottawa, 2 years, \$97,802

Title: Comparative Functional Studies Of The Two MeCP2 Isoforms, MeCP2\_e1 and MeCP2\_e2

Lay Summary:

Rett syndrome is typically the consequence of a mutation within or disrupting the gene, MECP2. However, we now know the gene can be processed in several different ways to produce 2 proteins, MeCP2\_e1 and MeCP2\_e2, which differ slightly from each other at the front end of the protein. These 2 protein 'isoforms' are expressed at different amounts in different tissues, and it appears that, because of this, MeCP2\_e1 expression may be more relevant to the symptoms that develop in Rett syndrome. We also now know that there are a few rare gene mutations in Rett girls that affect MeCP2\_e1 but not MeCP2\_e2, but to date there have been no instances of mutations in Rett girls that affect MeCP2\_e2 but not MeCP2\_e1. We would like to show conclusively that disrupting MeCP2\_e1 is sufficient to result in Rett, but that disrupting MeCP2\_e2 doesn't result in any Rett-related symptoms. We have designed a series of experiments that will do this in transgenic mice. In specially bred mice, we will knock out first MeCP2\_e1, leaving MeCP2\_e2 in tact, and observe the neurological, cognitive, behavioural and other effects on the mice. We will then do the same, but eliminating MeCP2\_e2, leaving MeCP2\_e1 in tact. We have also designed many controls into the experiment, to ensure the result is purely due to the elimination of one

isoform leaving the other entirely at normal levels. These tests will allow us to determine the contribution of each of the

two MECP2 isoforms to the phenotype separately, which will be fundamental to the future direction of research on MECP2 and RTT syndrome. Altogether, understanding the differences between the two MECP2 isoforms will have important implications, particularly for understanding the neurobiology of the disease, and since gene therapies for RTT are currently under development, it is essential that these therapies target the correct isoform of MECP2.

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Williams, John, Oregon Health Sciences University, 2 years, \$99,000

Title: Dopamine cells and movement disorders: identifying a cellular basis for Rett syndrome  
Dopamine cells and movement disorders: identifying a cellular basis for Rett syndrome

Lay Summary:

The early symptoms in Rett syndrome include a variety of movement disorders that can result from defects in the physiology of multiple brain areas. The pathways between dopamine cells in the midbrain and basal ganglia make up a prominent component in the regulation of movement, as it is well known that the disruption of dopamine neurons in Parkinson's disease has devastating motor consequences. Although the movement disorders are only one component of Rett syndrome the role of the dopamine system has not received much attention.

The work outlined in this proposal will use a mouse model of Rett syndrome where the expression of MeCP2 is lost in 50% of cells, both neurons and glia. Recordings from dopamine cells in brain slices will be used to characterize differences in the physiology between wild type and mutant mice. Female mice of widely different ages will be studied, such that dopamine cells will be characterized, prior to, during the development of and finally after behavioral abnormalities have developed fully. A very important part of this study will be directed toward the determination if the neurons in mutant females that express MeCP2 are the same or different from neurons in wild type animals. These experiments will test the hypothesis that the lack of MeCP2 results in cell autonomous effects. The alternative hypothesis is that the lack of MeCP2 in a significant proportion of neurons (or glia) result in the disruption of neuronal function in a multineuronal or system wide manner. Finally with the use of another mouse model, MeCP2 will be re-expressed in mice at various ages, and the consequences on the physiology of dopamine cells will be characterized. The exciting aspect of this model is that the re-expression of MeCP2 often results in a dramatic improvement in motor behaviors. The work planned with the use of these animals will identify cellular components that are involved in the dramatic improvement in behavior.

The identification of specific functional components that are affected by the loss in expression of MeCP2 at the cellular level is vital in the understanding of the development of Rett syndrome. Examination of the altered regulation of dopamine cells specifically is of significance not only because of their role in motor function, but also and perhaps more importantly, because these neurons project widely in the nervous system and are involved in many aspects of learning and memory.

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Zhao, Xinyu, University of New Mexico, School of Medicine, 2 years, \$100,000

## Title: Role of Mecp2-regulated microRNAs in the pathogenesis of Rett Syndrome

### Lay Summary:

Although the mutation of X-linked MeCP2 gene is known to cause Rett syndrome (RTT), function of MeCP2 during development is not clearly understood. With previous support from IRSF, we have determined that young neurons in Mecp2 null mice have reduced maturation. With an ongoing collaboration between the two PIs, we have identified novel mechanism underlying MeCP2 functions in brain development. Particularly, we have found that one small RNA, called miR-137, is likely is key mediator of MeCP2 function. Small RNAs are a newly discovered class of gene regulators that have profound functions in brain development. The goal of this project is to investigate how miR-137 helps MeCP2 to regulate brain development. We will use neural progenitor cells and neurons isolated from mouse models for this study. We also plan to generate genetic mutant mice that either have enhanced miR-137 expression or reduced miR-137 expression. By breeding these mice with MeCP2 mutant mice, we will determine whether miR-137 changes can rescue or potentiate MeCP2 mutation. Our long term goal is to discover methods that can be used therapeutically for alleviating the neurological symptoms of Rett Syndrome. The propose project will set the stage for our committed effort in achieving this goal.

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### Post Doctoral Fellowship Awards

Carromeu, Cassiano

Lilienkampf, Annamaria

Paul, Anirban

Ren, Jun

Shen, Yin

Carromeu, Cassiano, University of California - San Diego, 2 years, \$100,000

### Title:

Modeling Rett Syndrome with human pluripotent stem cells

### Lay Summary:

Rett Syndrome (RTT) is an X-linked neurodevelopmental disorder caused by sporadic mutations in the methyl-CpG-binding protein 2 (MeCP2) gene, which leads to a malfunction of the MeCP2 protein. Recent publications showed partial reversal of the RTT symptoms in a mouse model after restoring the normal MeCP2 protein levels. However, a relevant



human model is still missing. Recently, scientists reported a method to reprogram skin cells to an embryonic-like stage cells. These reprogrammed cells are competent to become any kind of cell type in the body, including neurons. The goal of this proposal is to develop a cellular model to study RTT, using such induced pluripotent stem cells (iPSC). Our preliminary data show that is possible to reprogram RTT skin cells and that neurons carrying MeCP2 mutations display altered neuronal features when compared to normal controls. In this application we will determine the correlation between the gene expression profile and the neuronal abnormalities from human neurons derived from RTT reprogrammed cells carrying different MeCP2 mutations. The outcome of this study will increase our understanding of the mechanism behind RTT, allowing better diagnoses and new therapeutic interventions.

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Lilienkampf, Annamaria, University of Illinois - Chicago, 2 years, \$100,000

Title: The Role of Histone Lysine Methylation Marks in Rett Syndrome - Identification of Novel Histone Lysine Methyltransferase Modulating Agents

Lay Summary:

Rett syndrome, a devastating developmental disorder, is caused by mutation in a protein called MeCP2. MeCP2 is responsible for activating and repressing certain target genes, and its proper function is crucial for normal brain development. MeCP2 acts in synergy with certain enzymes, like histone deacetylases (HDACs) and histone lysine methyltransferases (HKMTs). We aim to investigate if, by chemically controlling the activity of HKMT enzymes, we could affect the levels of MeCP2 in neuronal cells or alter the activity of genes normally regulated by MeCP2 function.

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Paul, Anirban, Cold Spring Harbor Laboratory, 2 years, \$100,000

Title: Novel Function of MeCP2 in mRNA Regulation and Implication in Rett Syndrome

Lay Summary:

Proteins are the building blocks of any cell, notably catalyzing reactions as enzymes, forming structural components and acting as signalling molecules. The information for individual proteins is present as an encoded "hardcopy" (known as genes) inside the nucleus of a cell in the form of DNA. A transient and labile form of the information is made off the

genes by a process called "transcription" and the message (known as mRNA, that is specific for a protein) is exported out of the nucleus into the cytoplasm in multiple copies. These mRNAs are then "read" by another complex machinery through a separate process called "translation" to make a specific protein. To generate and maintain tissue individuality and functional classification not all genes are made into mRNAs hence proteins in every cell but are selected by a finely tuned regulatory mechanism that can act at the level of transcription or translation. Many human disorders arise due to malfunction of transcription or translation process or the its regulation thereof, causing either too little or too much protein to be made at the wrong time and place. MeCP2 is one such protein that was identified to regulate transcription by binding to methylated-DNA and repress unwanted mRNAs from expressing and mutations in MeCP2 was found to be major cause of Rett syndrome. Recent results show that MeCP2 can not only repress but also activate different mRNA production. MeCP2 can also help in preferential production of different variants of the same mRNA (mRNA splicing) resulting in different forms of same protein with altered functions. However, so far little is known about MeCP2 binding to mRNA and influencing downstream processes like mRNA export to the cytoplasm and translation. Fragile-X mental retardation syndrome is one such disorder where Fragile-X protein binds to mRNA. Its absence leads to misregulation in translation process resulting in abnormal protein synthesis causing debilitating conditions with high rates of autism. Here I present compelling preliminary data that MeCP2 can also bind to mRNA and have identified the bound mRNAs. Strikingly the target mRNAs of MeCP2 is highly significant in normal brain functions and lack of MeCP2 causes decreased production of these proteins. Since mRNA levels don't differ for these proteins they have previously escaped detection. Here I propose to expand upon my finding and establish a novel function of MeCP2. Further I will examine in-detail the mechanism of mRNA binding and role of this interaction in Rett pathophysiology. I believe knowing which proteins are being misexpressed and where and how it is happening is central to understanding the disease process. In future this information would be crucial to design better a disease intervention and management procedure.

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Ren, Jun, University of Alberta, 2 years, \$100,000

Title: Investigation of Respiratory Dysfunction in a Mouse Model of Rett Syndrome

Lay Summary:

Rett syndrome is a severe neurological disorder that is frequently associated with a specific genetic mutation. Rett patients suffer from a number of behavioral disorders including severe breathing irregularities. Scientists have developed mouse models with defects in the same gene as in children with Rett Syndrome. These mice have many of the same symptoms. In this research proposal, I will use a Rett mouse model toward understanding the specific aspects of brain function that are abnormal to cause the breathing problems. I have preliminary data indicating that signals from regions of the brain activated during stress are interfering with the normal function of the respiratory control centers located in the brainstem.

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Shen, Yin, University of California, San Diego, 2 years, \$100,000

Title: Genomic analysis of MECP2 Function

Lay Summary:

In humans, Rett syndrome (RTT) is a progressive neurodevelopment disorder caused by sporadic mutations in the X-linked gene, methyl-CpG binding protein (MECP2). Many efforts have been spent to study the mechanism of MECP2 in RTT using mouse models. Although studies from mice models helped us gain sights into the mechanism of RTT, however, it also opens a lot of interesting questions. MECP2 was original thought as gene suppressor that binding to methylated DNA sequences. However, searches for MECP2 target genes were not successfully using gene expression data, due to the heterogeneity of tissue samples. In addition, several recent studies suggest the MECP2 binds to active genes that are not heavily methylated, and a lot of MECP2 binding sites are not located near a gene. These findings raise the possibility that MECP2 might play multiple roles in the genome besides being a gene suppressor. The goals of this proposal are to address three questions: 1) Where are the MECP2 binding sites in the human genome, and its correlation with nearby gene expression levels; 2) Is DNA methylated required for MECP2 binding; and 3) How MECP2 function through its target genes during the neuronal differentiation process. I will address these questions by using hESCs as a model system and combining with cutting edge genomic tools. hESCs are pluripotent, and we have developed a protocol to direct hESCs differentiation into neural stem cells, and neurons, which mimic the neuronal development in the human brain. Meanwhile, I will use cutting edge genomic technologies to investigate the function of MECP2 in the human genome. This includes: genome wide ChIP-Chip or ChIP-seq method to find novel MEC2 targeting in the hESCs and hESCs derived neural stem cells, and neurons. RNA sequencing to find the mode of regulatory function of MECP2 to its targeted loci, targeted high throughput bisulfite sequencing to examine the correlation between MECP2 binding and DNA methylation levels, and RNAi technology to investigate the function of MECP2 novel targets during the neuronal differentiation of hESCs. The proposed study will clarify the conflicting models of MECP2 function, and advance our understanding of MECP2's role in RTT.

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## Ad hoc Awards

Khwaja, Omar

Kozikowski, Alan

Khwaja, Omar, Children's Hospital Boston/Harvard Medical School, Clinical Research Grant, 2 years \$200,000

Title: Pharmacological treatment of Rett syndrome by stimulation of synaptic maturation: measurement of the effect of recombinant human IGF-1 treatment on autonomic dysregulation

Abstract: Rett syndrome is a severe genetic form of autism in girls. Girls with RTT have abnormal growth, movement problems and abnormal breathing and heart rate patterns. There is no treatment for RTT. Mice with the equivalent genetic change have similar symptoms to human patients. Giving these mice a drug called IGF1 relieves a large number of these symptoms. IGF1 is already available for use in children. We wish to evaluate the safety and effectiveness of IGF1 when given to girls with RTT. We will use an non-invasive instrument to measure improvements in breathing and heart rate during treatment with IGF1.

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Kozikowski, Alan, University of Chicago - Illinois, Contract, 6 months \$29,866

Title: Scale-up and Evaluation of Histone Deacetylase Inhibitors for Rett Syndrome

### Lay Summary:

Histone deacetylase inhibitors have been investigated as potential treatments for a variety of CNS diseases and disorders in recent years. Rett syndrome is an X-linked dominant neurodevelopmental disorder of relatively high incidence caused by mutations in MECP2, which encodes the methyl-CpG-binding protein 2 (MeCP2). A complex relationship between MeCP2 activity and gene imprinting exists such that a selective defect in postnatal neuronal maturation is observed in Rett syndrome. Thus, the isoform specific HDAC inhibitors may offer promise for therapy in Rett syndrome. The major focus of this grant is to scale up the synthesis of our best HDAC inhibitors and submit them for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling and in vivo studies in the Rett Syndrome animal model.

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