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IRSF Awards over \$700,000 for Translational Rett Syndrome Research

The International Rett Syndrome Foundation (IRSF) announced today that it is awarding over \$700,000 to support nine cutting-edge projects that aim to accelerate translational research to develop treatments for Rett syndrome. IRSF is the world's largest private source of funding for biomedical and clinical Rett syndrome research. Since 1998, IRSF has cumulatively funded over \$24M in high quality, peer-reviewed basic and translational research grants that have significantly advanced Rett syndrome research towards finding a cure.

IRSF's Translational Research grant program includes two types of awards, which are the Help Accelerate Rett Therapeutics (HeART) and the Advanced Neurotherapeutic Grant of Excellence (ANGEL) awards. The funding from these grant awards will provide for early and late stage translational research to treat and reverse Rett syndrome (RTT).

The awarded projects from the first round of applications to the Translational Research grant program are geared towards drug discovery and development efforts as well as preparing for later stages of translational research. These funded projects fall into four main categories: (1) the development and testing of potential therapeutic compounds in animal models of Rett syndrome, (2) the development of outcome measures in humans that will be used in future clinical studies, (3) the development of a method for treatment, and (4) the development of a stem cell-based experimental system to be used in high-throughput drug screens. Together, they are in alignment with the objectives of IRSF's Translational Research grant program.

Stephen Bajardi, the executive director of IRSF, commented, "IRSF is pleased with the quality of these research projects and the significant steps they represent in moving Rett syndrome translational research forward."

The awardees and a description of their projects are listed below.

HeART Awards:

John M. Bissonnette, MD, Oregon Health Sciences University

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

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.

Qiang Chang, PhD, of University of Wisconsin-Madison

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

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.

Jenny Downs, PhD, Curtin University

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

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.

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

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

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.

Walter Kaufmann, MD, Hugo W. Moser Research Institute at Kennedy Krieger, Inc.

Development of a Behavioral Outcome Measure for Rett Syndrome

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.

Paul H. Patterson, PhD, California Institute of Technology

Testing Immune Involvement in Rett

Rett syndrome is a devastating brain disorder for which there currently is no effective treatment. Recent studies indicate that malfunction of immune-brain communication is associated with the development of neuropsychiatric disorders such as autism and schizophrenia. *MECP2*, which is mutated and inactivated in the brains of Rett patients, is also found in the immune system. The lack of MeCP2 in the immune system of Rett patients may impair critical immune-brain interactions and contribute to disease progression. A working form of MeCP2 will be introduced into the immune system of Rett mice and examine if this corrects some of their motor and cognitive symptoms. If successful, Dr. Patterson's studies could introduce novel strategies for Rett syndrome therapeutics.

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

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.

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

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.

ANGEL Awards:

Huda Y. Zoghbi, MD, Baylor College of Medicine

Therapeutic intervention to modulate the GABAergic and cholinergic systems in animal models of Rett syndrome

Rett syndrome is quite a complex disorder characterized by a multitude of abnormalities and neuropsychiatric features. Two key neuron cell populations have been identified that mediate key features of Rett syndrome upon loss of *MECP2*, the gene that is mutated in RTT. These are the inhibitory neurons that make the neurotransmitter GABA and the neurons that make the neurotransmitter acetylcholine (ACh). Loss of MeCP2 from GABA neurons causes a modest reduction in GABA levels in these neurons and reproduces almost all the features of Rett, whereas loss of MeCP2 in ACh neurons causes some short-term memory problems and the premature cell death often seen in this syndrome. Dr. Zoghbi's proposed work will study whether readily available drugs that increase the levels or activity of these neurotransmitters, in their respective neuron cell type, 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.