

Research Awardees: 2012

ANGEL Awards

HeART Awards

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Walter Kaufmann, MD, Children's Hospital Boston

Daniel G. Glaze, MD, Baylor College of Medicine

N. Carolyn Schanen, MD PhD, Nemours Research Institute/Alfred I duPont Hospital for Children

Walter Kaufmann, MD, Children's Hospital Boston

"A Phase 2b placebo-controlled cross-over study of rh-IGF1 (mecasermin [DNA] injection) for treatment of Rett syndrome and development of Rett-specific novel biomarkers of cortical and autonomic function"

Lay Description:

RTT is a severe genetic form of autism in girls. Girls with RTT have abnormal growth, movement problems, and abnormal patterns in breathing and heart rate. There is no treatment for RTT. Mice with the equivalent genetic change have symptoms similar to those of human patients. Treating these mice with a drug called IGF-1 relieves a large number of these symptoms. IGF-1 is already available for use in children. We propose to evaluate the safety and effectiveness of IGF-1 when given to girls with RTT through the use of non-invasive tools to measure improvements in brain activity, breathing, and heart rate during treatment with IGF-1. We anticipate that our results will set the groundwork for a larger investigation of the efficacy of using IGF-1 in children with RTT and related developmental disorders.

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Daniel G. Glaze, MD, Baylor College of Medicine

"A randomized, double-blind placebo controlled trial of NNZ-2566 (IGF-1{1-3}, glycyl-L-2-methylprolyl-L-glutamine acid) with open label extension in adults with Rett syndrome"

Lay Description:

Rett syndrome (RTT) is a severe disorder that causes a catastrophic loss of function in early infancy. The disorder affects many parts of the body and can produce seizures, cause curvature of the spine, and alter heart and breathing function.

There is no treatment for Rett Syndrome and affected people are at greater risk of sudden death than the general population. In this project we propose to investigate a new drug called NNZ-2566 to see if it is safe and effective in the treatment of adult Rett syndrome patients. The project will involve two phases. Phase 1 will involve a 5 day open label drug treatment in which patients know they are receiving the drug. In phase 2 subjects will be assigned randomly to different groups and each group will either receive a placebo (sugar pill) or a low or high dose of the drug. In phase 2 patients and investigators will not know who is receiving drug treatment. Measures of drug safety and effectiveness will be the major focus of this study and will be collected during both study phases.

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N. Carolyn Schanen, MD PhD, Nemours Research Institute/Alfred I duPont Hospital for Children

“Nonsense suppression as a therapeutic approach to Rett syndrome”

Lay Description:

Almost all patients with Rett syndrome (RTT) have mutations of the gene that makes a protein called Methyl CpG Binding Protein 2 (MeCP2). Approximately one-third of patients have "nonsense" mutations, which result in an incomplete MeCP2 protein. Recently, a number of new chemicals have been identified that allow cells to make complete proteins by 'reading through' nonsense. These include two chemicals, PTC124 and PTC7207, which were discovered by PTC Therapeutics (New Jersey). PTC124 and PTC7207 can be given by mouth and are less toxic than many other chemicals that have the same activity. PTC Therapeutics currently is testing PTC124 in patients with cystic fibrosis and Duchenne muscular dystrophy.

To study 'read through' of MeCP2 mutations, we helped IRSF develop a mouse strain that has a R255X mutation, which is like a mutation found in ~7% of patients with RTT. Other laboratories created mice that do not make any MeCP2 and they have very similar characteristics. We propose to treat male and female mice with PTC124 and PTC7207 to determine whether the symptoms are less severe and see how this correlates to the amount of MeCP2 protein that is made. We will use cells that come from these mice to optimize the read through process and will develop a test that can be used to screen for new chemicals that can read through the four most common MeCP2 nonsense mutations. Together, these studies will help determine whether this kind of treatment is potentially useful for RTT patients.

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HeART Awards

Daniela Brunner, Ph.D, PsychoGenics Inc.

Aleksandra Djukic, MD, PhD, Montefiore Medical Center, Albert Einstein College of Medicine

Lee-Way Jin, MD PhD, Regents of the University Of California - Davis

Daniela Brunner, Ph.D, PsychoGenics Inc.

“PPAR-sparing insulin sensitizers for Rett Syndrome”

Lay Description:

Mitochondrial function deficit and reduced BDNF levels are key precipitators of Rett syndrome. In particular, mitochondrial dysfunction may result from an imbalance in the components of the respiratory complex of the mitochondrial electron transport chain secondary to the loss of MeCP2 function (fundamental component leading to proper energy balance in living cells). Compounds that help restore the balance of mitochondrial function and BDNF function, therefore, might have a positive effect. MSDC-0160 is a PPAR-sparing insulin sensitizer that is currently undergoing clinical development for type 2 diabetes (Phase 2b) and Alzheimer's disease (Phase 2a). This compound is a member of a new class of agents that spares PPAR activation having its primary action on mitochondrial metabolism. In mice, the pharmacology of this compound is correlated with an increased expression of mitochondrial proteins. Recent evidence demonstrated that a 3 month treatment of female 5X FAD mice, an Alzheimer's model, with daily 30mg/kg MSDC-0160 affects several processes that might be predicted to positively impact the symptoms in RTT. We will test whether MSDC-0160 can impact the behavioral and health deterioration course of male Mecp2 RTT mouse model and also assess the compound effects on mitochondrial mass and brain BDNF levels.

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Aleksandra Djukic, MD, PhD, Montefiore Medical Center, Albert Einstein College of Medicine

“Language comprehension and processing in Rett syndrome: A pilot study of eye tracking”

Lay Description:

Girls with Rett Syndrome (RTT) have severe communication impairments; most communicate through vocalizing, facial expressions and eye gaze. Severely limited hand function prevents them from pointing or manipulating objects, making attempts to assess receptive language abilities through conventional tools inconclusive. Anecdotal evidence, however, indicates that girls with RTT have more language knowledge than what standardized testing, inventory and natural observation have revealed but it is not at all clear how to assess language abilities accurately. Because vision and gaze are the most important ways in which girls with RTT relate to the world, assessing their knowledge using eye tracking technology appears to be an ideal methodology. Our study of nonverbal cognitive processes in 50 consecutive girls revealed that the use of eye tracking technology is feasible and can provide quantifiable and reliable outcome measures. We propose to continue our study of cognitive functioning in girls with RTT using eye tracking technology to examine their language comprehension. Two other studies have done so with conflicting results. Our study will be based on eye tracking paradigms developed for studying language abilities of infants and young children and older children and the techniques we have developed that enabled us to successfully assess nonverbal cognitive processes. We will compare these results with assessment tools typically used with girls with RTT and correlate the findings with a descriptive analysis of the characteristics of the girls, their development and clinical features.

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Lee-Way Jin, MD PhD, Regents of the University Of California - Davis

“Preclinical studies of allopregnanolone, a positive GABAA receptor modulator”

Lay Description:

Major debilitating symptoms of Rett syndrome (RTT) include seizures and respiratory disorders. Recently, the loss of the inhibitory signals in the brain conducted by the neurotransmitter GABA has been shown to play a significant pathological role in RTT mouse models. Augmenting GABA neurotransmission has been shown to improve the respiratory function in a line of RTT mice and to prolong survival. A reasonable therapeutic approach, therefore, would be to induce long-term enhancement of GABA neurotransmission, which could suppress seizure activity and improve respiratory function in girls with RTT. However, all currently clinically available drugs are either with significant side effects or inducing tolerance, therefore not suitable for long-term use. In this proposal, we plan to test the therapeutic effects of a naturally occurring brain steroid called allopregnanolone. We have studied allopregnanolone for many years and know how it works in suppressing seizures and how it is distributed and metabolized in the body. Importantly, this drug has little side effects. Recently we have improved the drug properties of allopregnanolone by dissolving it in canola oil that is completely safe for human consumption orally. In addition, we have a batch of FDA-approved GMP (Good manufacturing Practice) material, ready for clinical trials. With the help of the IRSF HeART award, we will examine the effects of this oral formula of allopregnanolone on the RTT model Mecp2-/+ mice. We hope that experiments proposed in this application could enable the rapid development of a new and mechanistically novel drug for the treatment of RTT.

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Contracts

Walter Kaufmann, Children's Hospital Boston

Helen Leonard, Telethon Institute for Child Health Research

Jeffery Neul, MD, PhD, Jan and Dan Duncan Neurological Institute at Texas Children's Hospital

Alan Percy, MD, University of Alabama at Birmingham

N. Carolyn Schanen, MD PhD, Nemours Research Institute/Alfred I duPont Hospital for Children

Walter Kaufmann, Children's Hospital Boston

“RettSEARCH”

LAY DESCRIPTION:

RettSearch is an international, multi-center collaborative network of clinically-oriented researchers. Its mission is to promote the development of new therapeutic approaches for Rett syndrome by collecting information and pursuing research in areas of relevance to clinical trials in RTT.

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Helen Leonard, Telethon Institute for Child Health Research

"InterRett – IRSF Phenotype Database"

LAY DESCRIPTION:

InterRett collects data on a worldwide basis about Rett syndrome. This international online database examines the clinical features and genetic characteristics of Rett syndrome. InterRett is playing an invaluable role in:

- Development of partnerships between families and clinicians and in advancing knowledge about Rett syndrome
- Increasing the clinical understanding of Rett syndrome
- Providing a new way to help families affected by the disorder, health professionals and the general public learn about Rett syndrome
- Encouraging collaboration with researchers from around the world

For rare disorders such as Rett syndrome, the Internet provides access to a worldwide population, providing higher statistical power than individual centers or even country based research studies. The Internet also provides an ideal medium to disseminate high quality information about a specific disorder to the medical and general community.

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Jeffery Neul, MD, PhD, Jan and Dan Duncan Neurological Institute at Texas Children's Hospital

"Creation of a DNA repository for Rett Syndrome"

LAY DESCRIPTION:

The goal of this contract is the development of a repository of DNA collected from all participants in the Rett Syndrome Natural History project. This repository will allow the identification of genetic causes of RTT other than mutations in MECP2 and the determination of the role various genetic factors play in modifying the clinical severity in RTT.

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Alan Percy, MD, University of Alabama at Birmingham

“Placebo-controlled trial of Lexapro® (escitalopram) for anxiety in Rett Syndrome”

LAY DESCRIPTION:

Mood disorders, as well as panic and fright, are frequently observed in girls diagnosed with Rett Syndrome (RTT). In addition, difficulties with motor performance, breathing and sleep disturbances may also be attributed to this high anxiety state. Thus for these reasons the specific aim of this clinical research study is to examine the efficacy of the Selective Serotonin Reuptake Inhibitor (SSRI), Lexapro® (Escitalopram), in modulating maladaptive behaviors in RTT. In this pilot study, we seek to gather sufficient data that would support expansion to a full clinical trial.

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N. Carolyn Schanen, MD PhD, Nemours Research Institute/Alfred I duPont Hospital for Children

“Development of a Humanized Mouse Line By Knock-In”

LAY DESCRIPTION:

Rett syndrome (RTT) is a progressive neurologic developmental disorder and one of the most common causes of mental retardation in females. While Mecp2 point mutations in the region coding for the highly conserved MBD and disrupting the TRD domain have been shown to be associated with RTT development, the R168X and the R255X mutations are observed at frequencies of 11.8% and 4.9%, respectively. In order to generate a mouse model of this human disease, the R168X mutation will be introduced into the equivalent position with the orthologous murine gene.

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