rett syndrome research trust

PRESS RELEASE

RSRT Awards $8.6 Million in 2019 to Advance the *Roadmap to a Cure*

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TRUMBULL, CT — The Rett Syndrome Research Trust (RSRT) committed $8.6 million in 2019 for breakthrough research focused on curing Rett, bringing the total research dollars invested since RSRT's inception to $66 million.

RSRT's mission is to accelerate the development of a cure for Rett Syndrome and *MECP2* disorders. *Roadmap to a Cure*, launched in 2017 is a strategic research plan comprised of four pillars: Cure, Treat, Enable, and Learn. These pillars guide RSRT funding, with projects aimed at Cure, front and center, in the 2019 awards.

Rett Syndrome is a devastating neurological disorder characterized by loss of language, hand skills, and motor function. As the disorder progresses it brings breathing difficulties, seizures, anxiety, tremors, gastrointestinal and muscular skeletal problems. Rett Syndrome results from a dominant mutation in a gene on the X chromosome, *MECP2*, which is expressed in all tissues, but is especially abundant in the brain.

Highlights of our 2019 funding include:

- **An award of $765,607 to James Wilson, MD, PhD,** who heads the world's largest academic gene therapy program at UPENN. Dr. Wilson led the discovery of the adeno-associated virus vector, AAV9, that is the current gold standard for gene therapy delivery to the brain. This latest award builds on the ongoing RSRT-funded Rett gene therapy program at UPENN with the goal of advancing a Rett gene therapy into a clinical trial in 2022.

- **$3.3 million of continued funding to the MECP2 Consortium** comprised of top international researchers: Gail Mandel, PhD, Oregon Health Sciences University; Adrian Bird, PhD, University of Edinburgh; and Michael Greenberg, PhD, Harvard University. The Consortium has made landmark discoveries creating a platform of knowledge critical in the search for a cure. The Bird lab upended the prior incomplete view of MeCP2 as a gene-specific transcriptional repressor showing that instead the protein binds broadly across the neural genome. The lab also identified a novel binding partner of MeCP2, NCOR/SMRT, opening the door to new therapeutic avenues. The Greenberg lab discovered that MeCP2 plays an important role in regulating long genes that are primarily expressed in the brain and are critical for normal brain function. The Mandel and Bird labs were the first to show that Rett symptoms could be reversed using gene therapy in symptomatic mice. The Mandel lab introduced the RNA editing field to Rett and is making remarkable progress. The MECP2 Consortium, funded by RSRT since 2011 is a highly collaborative team of scientists with a record of delivering high quality, foundational research.

Highlights of our 2019 funding (continued):

- **An award of $359,856 to Thorsten Stafforst, PhD, University of Tübingen, Germany,** a pioneer in the field of RNA editing. Dr. Stafforst has developed a simple, efficient and specific RNA editing platform called RESTORE that doesn't require viral delivery. Potential advantages of non-viral delivery include decreased immunogenicity and improved delivery to the brain. He will assess efficacy of the RESTORE platform to correct the mutations that cause Rett syndrome.

- **An award of $275,000 to Peter Glazer, PhD, and Mark Saltzman, PhD, at Yale University** for a novel non-viral delivery system. The system uses synthetic nanoparticles that are uniquely designed to target, bind and edit specific mutations.

- **The Jackson Laboratory was awarded $417,690** to expand the number of mutant mouse models available for research and provide baseline characterization of these models. This award provides the foundation for what will become the "go to" facility for academia and industry alike to test potential therapeutic agents rigorously in a systematic standardized and objective fashion at a world-renowned institute.

- **$520,000 awarded to Beth McCormick at the University of Massachusetts Medical School (UMass) t**o define gut microbiome alterations in individuals with Rett Syndrome and assess efficacy of dietary interventions to improve gut health and overall wellbeing. The study is expected to begin in the spring and will enroll girls 6 years of age and older with a documented MECP2 mutation.

"Our 2019 awards reflect RSRT's commitment to funding the boldest research that attacks Rett Syndrome at its core," said executive director Monica Coenraads. *"I made a promise to my daughter that I won't rest until this research can profoundly change her life. That promise extends to every child and adult with Rett or a related MECP2 disorder. I am inexpressibly grateful that we have a tremendous team helping us achieve that goal. It's a team that includes our funded researchers, RSRT's internal scientists, staff and trustees, the remarkably strong and tenacious families that fundraise for us, and our loyal and generous donors."*

Awards also included two projects totaling $1 million financed by the MECP2 Duplication Syndrome Fund at RSRT. Anastasia Khvorova, PhD, UMass Medical School RNA Therapeutics Institute, will be developing a therapeutic approach to reduce levels of the MECP2 protein via small interfering RNA. Ronald Cohn, MD, The Hospital for Sick Children, in Toronto will be pursuing a genome editing approach that removes the duplicated gene.

List of 2019 Awards by Strategic Roadmap to a Cure Pillar

Cure

James Wilson
University of Pennsylvania
MECP2 gene therapy for Rett Syndrome
$765,607

UPENN Vector Core
$37,999

Joseph Jacobson
MIT
Correction of MECP2 mutations with engineered ScCas9 base editors
$50,000 (pilot study)

Stuart Cobb & Chris Sibley
University of Edinburgh (United Kingdom)
RNA trans-splicing therapy in Rett Syndrome
$235,950

Thorsten Stafforst
University of Tübingen (Germany)
RNA editing for MECP2 mutations via RESTORE
$359,856

Alanna Schepartz
Yale University
Evaluating cell-permeant miniature proteins (CPMPs) as a strategy for delivering functional MECP2 into model cells and neurons
$297,716

Joost Gribnau
Erasmus MC, Rotterdam (The Netherlands)
Human in vitro models for X chromosome reactivation
$401,000

Peter Glazer & Mark Saltzman
Yale University
PNA Nanoparticles for Gene Editing of Rett Syndrome
$275,000

Ophidion, Inc.
Development of an cDNA/mRNA delivery system utilizing Ophidion's CNS Carrier Technology (OCCT) to treat Rett Syndrome
$68,000

Treat

Beth McCormick
University of Massachusetts Medical School
Microbiome study for the advancement of novel nutritional supplements
$520,316

Sasha Djukic
Rett Syndrome Program,
Children's Hospital at Montefiore
$75,000

Enable

Coriell Institute
Rett Syndrome Biorepository
$135,000

Emerald
Passive Monitoring of Rett Patients with Emerald
$164,670

Harvard Stem Cell Institute
$101,912

The Jackson Laboratory
The Generation and Phenotypic Assessment of Mouse Models for Rett Syndrome
$417,690

List of 2019 Awards by Strategic Roadmap to a Cure Pillar (continued)

Learn

Gail Mandel, Oregon Health Sciences University; Adrian Bird, University of Edinburgh; Michael Greenberg, Harvard University
A research consortium to define the function of MeCP2: Steps towards the development of therapeutics for treating Rett Syndrome
$3,359,054

Michael Elowitz, Caltech
A system for dosage-independent control of MECP2 expression in Rett Syndrome gene therapy
$212,374

Miscellaneous Pilot Studies
$87,522

List of 2019 Awards | MECP2 Duplication Syndrome

Ronald Cohn
The Hospital for Sick Children
Interrogation of genome editing strategies as a therapeutic modality for MECP2 Duplication Syndrome
$570,000

Anastasia Khvorova
University of Massachusetts Medical School
Development of siRNA based compounds to potently silence MECP2 towards the treatment of MECP2 Duplication Syndrome
$435,515

About the Rett Syndrome Research Trust

The Rett Syndrome Research Trust (RSRT) is a non-profit organization with a highly personal and urgent mission: a cure for Rett Syndrome and related *MECP2* disorders. RSRT operates at the nexus of global scientific activity enabling advances in knowledge and driving innovative research. Since its founding in 2008, RSRT has awarded $66 million, all of it contributed by affected families and their networks, to leading scientists. With an unyielding commitment to efficiency and integrity, RSRT spends an average of 96% of funding on research. In March of 2017 RSRT launched *Roadmap to a Cure*, a three-year, $33 million strategic research plan that prioritizes five potentially curative approaches—gene therapy, MECP2 reactivation, DNA editing, RNA modification, and protein replacement. Exciting and promising progress is being made with each approach. To learn more, please visit www.reverserett.org

About Rett Syndrome

Rett Syndrome is a genetic childhood neurological disorder caused by random mutations of the *MECP2* gene on the X chromosome that affects predominately girls but can rarely also affect boys. Its symptoms typically become apparent between the ages of 12 to 18 months. Rett Syndrome is devastating as it deprives young children of speech, hand use, and normal movement often including the ability to walk. As the children enter childhood the disorder brings anxiety, seizures, tremors, breathing difficulties, and severe gastrointestinal issues. While their bodies suffer, it is believed that their cognitive abilities remain largely intact. Although most children survive to adulthood, they require total round-the-clock care.