Roadmap to a Cure

THREE-YEAR STRATEGIC RESEARCH PLAN
The Rett Syndrome Research Trust (RSRT) was created in 2008 to achieve one goal – a cure for Rett Syndrome. To date, we have invested more than $41 million to advance research towards that goal. Every dollar has been contributed by networks of families with an afflicted child and by affected families themselves. During the second half of 2016 we undertook an internal review of our projects coupled with a comprehensive external research landscape analysis.

Armed with scientific data and informed by remarkable progress, we have reached a new phase of Rett research. For the first time, we are in the position to prioritize projects and say: Here is the Roadmap to a Cure for Rett Syndrome.

Starting in 2017, we will implement a three-year, $33 million transformational research plan called the Roadmap to a Cure. The plan consists of the following highly integrated areas:

- **Cure**
- **Treat**
- **Enable**
- **Learn**
Imagine the Symptoms of Cerebral Palsy, Parkinson’s, Epilepsy & Anxiety Disorder all in one little girl.

Rett Syndrome, which afflicts 350,000 worldwide, is caused by random mutations on the MECP2 gene located on the X chromosome. The disease strikes mainly girls and, following a normal infancy, takes effect in toddlerhood. As the cascade of Rett symptoms descends, children regress and lose acquired skills such as walking, talking and control of their hands. Scoliosis, extreme anxiety, tremors, seizures, hyperventilation and digestive problems are common. Tragically, girls and women with Rett understand what is happening around them but are locked in bodies that cannot respond. Most Rett victims live into adulthood, requiring round-the-clock care.
RSRT will not be satisfied with subtle symptom improvement. **We want a cure.**
We aim to make Rett Syndrome the first curable neurological disorder and we have a solid plan to get us there. We invite you to learn about our three-year $33 million strategic research plan. Our goal is to become obsolete by Making Rett History.

**THE Roadmap**

**Cure**
- Gene Therapy
- MECP2 Reactivation
- RNA Editing
- Protein Replacement

**Treat**
- Symptom Improvement

**Enable**
- Patient Cell Lines
- Outcome Measures & Biomarkers Development

**Learn**
- Basic Science
At the core of the plan are four cutting-edge approaches designed to cure Rett by attacking the root cause of the disorder: MECP2. Pursued in parallel, these approaches are applicable to all MECP2 mutations and deletions.

1. **Gene Therapy**

Of the four approaches gene therapy is the most advanced and is our lead program. The concept behind gene therapy is simple: delivery healthy copies of the MECP2 gene to compensate for the mutated ones. Over the past three years the results of our Gene Therapy Consortium have exceeded expectations. The magnitude of improvement in the mouse models of Rett is much greater than that of any drug in development and suggests that significant benefit may be achieved in people. We expect improvements, at least to some degree, regardless of age.
Gene Therapy

Roadmap Goals

Launch a HUMAN CLINICAL TRIAL

Contingent on sufficient funding and requisite FDA approvals, we plan to begin the first clinical trial of gene therapy for people with Rett Syndrome. Ideally, a biotech or pharmaceutical company will license the program and conduct the trial.

2ND GENERATION PROGRAMS

Technological advances in gene therapy are happening quickly with more effective vectors being discovered that can carry larger DNA cargos and target a greater percentage of brain cells. While we anticipate encouraging results with our first clinical trial there will undoubtedly be room to improve. We will therefore support second-generation gene therapy programs to leverage all technological advances.

*To date, RSRT has invested $4.5 Million in gene therapy efforts.*
Like gene therapy, this approach also targets the MECP2 gene. Girls and women with Rett have two copies of the MECP2 gene: one is on the active X chromosome, and one is on the inactive X and is therefore silent. Like all females, girls with Rett have shut down one X chromosome. So in every cell where the mutated gene is active and making defective protein, there is a healthy but silenced copy of the MECP2 gene.

Our goal is to reactivate the silenced MECP2 gene on the inactive X chromosome. We began spearheading this approach eight years ago. What began with a single lab has grown to a consortium of seven labs. Over the next three years they will discover and evaluate drug candidates to enable preclinical testing that could lead to clinical trials.

To date, we’ve invested $6.4 Million in reactivation efforts.
RNA Editing

The possibility of editing RNA has profound therapeutic potential, but has remained largely theoretical. Focused investments by RSRT have already demonstrated the potential for correcting MECP2 mutations at the level of RNA. We are currently increasing our investment to aggressively pursue this therapeutic approach.

Goals during the next three years are to improve specificity and efficiency of editing RNA in the brain and to identify optimal delivery methods.

Protein Replacement

The MECP2 gene makes an MeCP2 protein. One can either deliver the gene (a one-time fix) or one can deliver the protein (will require ongoing supplementation). We are collaborating with a biotech company which has developed a creative way to shuttle proteins into the brain. Other technologies are also being developed to deliver proteins into the brain. We will monitor, evaluate and pursue worthy approaches.
Our four curative approaches intervene at all three stages of the “gene to protein” process. This multi-pronged strategy greatly increases our chances of success.
While we expect that correcting the cause of Rett at its very source will provide profound recovery of function, drugs and therapeutic interventions that are downstream of MECP2 may improve some of the symptoms. These downstream interventions, which include all the current treatments being explored (Ketamine, IGF1, Trofinitide, Sarizotan, copaxone, statins, etc.), should be considered as treatments rather than cures. We will closely monitor all development programs and selectively invest in those most likely to have significant impact on symptoms.
Thanks to RSRT, clinical breakthroughs are now emerging. But we don’t yet know for sure which ones will translate most effectively to children and adults with the disorder. To cover all the most important bases, RSRT will advance the research on several fronts, ranging from therapeutic strategies with emphasis on gene therapy to basic science.

By attracting the best scientists and clinicians, RSRT will be in pole position to deliver on the pre-clinical work showing that Rett Syndrome will be a curable disorder.

Adrian Bird, PhD
RSRT TRUSTEE & SCIENTIFIC ADVISOR
Buchanan Professor of Genetics, University of Edinburgh
RSRT will play a vital role in creating conditions that will enable the most impactful pharmaceutical and biotech industry investment in Rett research. Historically, approval of new drugs has been hampered by the absence of several key resources:

1) Lack of accurate, FDA-approved outcome measures for clinical trials, including devices that can accurately measure these outcomes,
2) The ability to identify the right patients for the right trials, and
3) Lack of human cells from patients to test new therapies in the lab.

The following projects will address these issues and drive industry investment in Rett research. They are designed to remove barriers of entry and lower risk, thereby shortening the timeline for drug development and facilitating the approval of novel therapeutics.
Outcome Measures & Biomarkers Development

There are currently no FDA-approved outcome measures for use in Rett clinical trials. We have established a consortium of expert Rett physicians to develop outcome measures that are meaningful to patients and their families and that are acceptable to the FDA and other international regulatory agencies. These measures fall into two groups: regulatory-approvable outcome measures and biomarkers that predict or correlate with efficacy. Part of this effort will also include collecting information on Rett symptoms and the needs of individual patients in order to shorten clinical trial enrollment time.

Testing Therapies in Patient Cells

Because no animal model can completely duplicate the human disease it is important to verify results from animal studies using human cells. Today, technology exists to convert skin or blood cells collected from individuals with Rett into brain cells. These cells can be used to replicate results observed in animal models. Since brain cells can be generated from any individual with Rett, this technology also allows us to assess whether there are significant differences among individuals in response to a new therapy.
Our investment in **basic science** has led us to this promising new stage of research. Significant gains in our knowledge about the mutated gene that causes Rett has played a key role in defining important components of gene therapy and other approaches. But the full scope of how the gene and its related protein function is yet to be fully defined. Continuing to expand our understanding of this gene, its protein product and its function are vital to the success of our research.
Maximizing the Impact of Your Support

Since RSRT’s founding, we’ve been committed to maintaining exceptionally low overhead expenses. This will continue, with expenses for fundraising and administration less than 10% of the research plan budget.
About RSRT

*We fund more research than any other Rett organization in the world.*

The $41 million we have strategically awarded to research to date has resulted in the knowledge, data, and partnerships that inform and guide this *Roadmap to a Cure.*

RSRT sets the research agenda by proactively identifying and monitoring promising therapeutic areas, seeking out scientific and industry partnerships and working closely with them to advance programs through the drug development pipeline. We are constantly engaged with scientists, clinicians, industry, investors, regulators and affected families.

The RSRT team is lean and fiercely focused on what matters most: healing our children as quickly as possible.

Our Guiding Principles

**OBJECTIVITY**

Falling in love with the science we fund is dangerous.

**TRANSPARENCY**

Accountability for every dollar donated and its impact on research.

**TRUTH NOT HYPE**

Showing honest results; no sugarcoating or redundant hype.

**TIME MATTERS**

Urgency is an understatement; we fight every single day.
Translating breakthrough scientific discoveries into novel therapeutics requires a team of individuals with deep expertise in multiple disciplines. RSRT does not stop after recruiting and funding top scientists and clinicians; rather, we are intimately involved every step of the way. We coordinate and manage team meetings, continuously monitor progress, foster open communication and sharing of information, address unforeseen obstacles, bring in expertise and provide infrastructure. **Most importantly, we recruit physicians and scientists who share our vision and passion** to develop cures and treatments for all who struggle with this devastating disorder.

Randall Carpenter, MD

Chief Scientific Officer
Rett Syndrome Research Trust
The Time is Now

The Roadmap to a Cure is a comprehensive and integrated strategic research plan. None of the approaches exist in isolation but rather are continuously informed and strengthened by each other. The plan, while based on the best knowledge we have right now, is not set in stone; it is fluid and will nimbly respond to novel data and directions as the science unfolds.

The day my daughter was diagnosed I made her a promise that I wouldn’t rest until we found a cure. We have an opportunity now, as never before, to drive the science that will change lives.

For too long, those with Rett have suffered and been silenced. We know it’s scientifically possible to dramatically change their lives, and we know how to make it happen. The time is now. We believe Rett Syndrome can be cured, but time matters. The Roadmap to a Cure will get us there as quickly as possible.

Monica Coenraads
EXECUTIVE DIRECTOR
Rett Syndrome Research Trust
What You Can Do

To accomplish the scientific goals outlined here we need to **quickly raise $33 million**. To achieve that we will need the passionate involvement and support of the Rett Syndrome community, in the U.S. and abroad.

Well-known foundations, which have funding priorities of their own, are unlikely to make grants to our research. The National Institute of Health (NIH) budget for Rett is small and the research they fund tends to be conservative in nature. Corporations represent a small fraction of funding to RSRT and to philanthropy in general.

Our funding comes almost entirely from individual people who are connected to an affected family. Among your extended family, friends, and colleagues, all of whom care about your future and your child’s future, there is great potential for enthusiastic support of this research.

Rett Families: If you want a cure for Rett Syndrome, **now is the time to act**. Don’t wait for others to give or raise funds; take action yourself to help make it possible for RSRT to carry out the **Roadmap to a Cure**.

Make Rett History

Contact:

Tim Freeman
CHIEF DEVELOPMENT OFFICER

tim@rsrt.org
609.309.5676