



## **IRSF Translational Research Meeting**

### **Full Report**



**March 23-24, 2010**

**New York, NY**

## **Special Thanks**

The International Rett Syndrome Foundation would like to extend its appreciation to the dedicated professionals who lent their time and expertise to this effort. Their contributions, involvement, and enthusiasm are invaluable. We would especially like to thank John McCall, PhD, President and Founder of PharmMac, LLC for his efforts in capturing and organizing the many ideas and creativity of this precocious group that formed the basis for identifying the recommendations included in this paper.

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## **Executive Summary**

The International Rett Syndrome Foundation (IRSF) sponsored a two-day meeting assembling a blue-ribbon panel of 25 physicians, scientists, researchers, and executives from the FDA, NIH, academia and private industry. The panel met to discuss the current state of drug discovery for the treatment of Rett syndrome (RTT) and made specific recommendations for accelerating the pace of drug discovery and development.

## **Roadmap to New Medicines**

The path to drug discovery is the same for all researchers whether they are in academics or working in for-profit, non-profit, private or government agencies. Whereas traditional basic research is hypothesis driven, translational research is product driven; moving compounds from early stage discovery to the clinic.

Translational projects cross disciplines. One of the main proposals emerging from this meeting was to focus on repurposing drugs previously approved by the FDA and drugs developed for other indications that are currently in the later stages of development or in clinical trials. Such drugs would be carefully chosen to target biological processes that are thought to cause the symptoms of RTT. These drugs will have been developed by funding from other sources – frequently within small biotechnology and pharmaceutical companies. The goal here is to accelerate their movement to clinical trials and ultimately to gain market approval.

## **Approach**

To foster innovation, the panel recommended that IRSF should facilitate the development of cross-disciplinary research and discovery teams, composed of the most gifted and creative thinkers in the RTT field and promote their interactions with leaders in disparate fields such as drug discovery and development. Working in this way we will harness the knowledge gained on the processes involved in causing Rett syndrome and cultivate innovative drug discovery research. Such dedicated groups must conduct research with clear relevance to the improvement in the treatment of Rett syndrome.<sup>i</sup>

The following figure illustrates how repurposing existing drugs can accelerate and potentially de-risk the discovery process by identifying drugs targeting pathways relevant to RTT that are in the later stages of development.

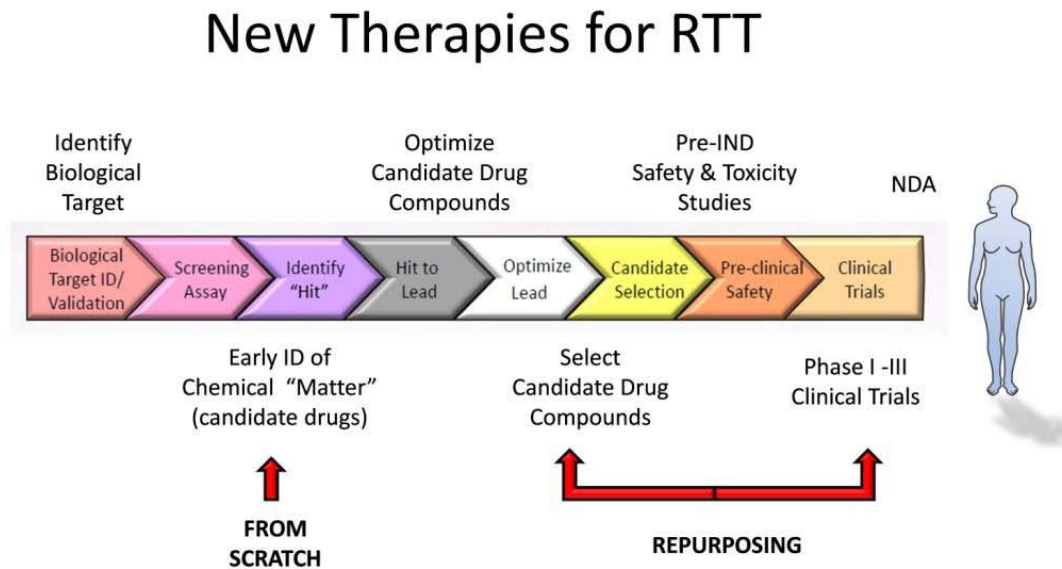


Figure 1: Repurposing of drugs by “parachuting” them into later stages of the drug discovery process

### Topline Recommendations of the Panel

Following the meeting, recommendations were ranked in order of importance based on feedback by the meeting participants. The respondents rated the importance of 14 items on a three-point scale and prioritized the most important projects accordingly.

The top 5 priorities identified by the panel were:

1. Identify and validate novel clinical trial outcome measures
2. Repurpose existing medicines and evaluate in pre-clinical studies
3. Identify and evaluate drugs in development in pre-clinical studies
4. Develop a target-based drug library for testing in RTT animal models
5. Develop cell and animal-based assays for drug evaluation

# Full Report

## Introduction

The constellation of symptoms and behaviors associated with RTT lead clinicians and researchers in the field of drug discovery to look for drugs that unlock the pathogenesis of the disease, but also to look for treatments that address specific issues to alleviate individual manifestations of the disease. The search for drugs to treat – and someday even reverse – RTT has led to the confluence of leading lights in the fields of neurobiology, medicinal chemistry and allied disciplines from academia and private industry, to develop a systematic approach to solutions.

Individual RTT patients present with a series of symptoms of varying severity. These include motor dysfunction (including stereotypical handwringing movements), seizures, anxiety, communication skills, breathing irregularities, autonomic dysfunction, heart rhythm complications, scoliosis, nutritional and gastroenterological problems, osteopenia and sleep disruption. Drugs commonly used today to treat some of these issues individually have made life more comfortable for the girls, and has doubled their longevity to over the age of 50.

But clinicians and researchers are acutely aware of the limitations of this piecemeal approach to treatment. The IRSF Translational Research Meeting in March 2010 extended the work of a group convened originally in December 2008 to tackle RTT by developing an overarching framework and rationale to pursue the path of drug discovery, and a process to propel progress forward in a deliberate and orchestrated way.

The panel listed the issues to be addressed, identified methods for testing disease state and patient functionality and assessed the treatments currently employed. Through this method of analyzing current gaps and collecting resources, the path forward will be driven by matching the identified resources to specific bottlenecks.

The main outstanding questions identified were:

1. How to rationally select candidate molecules
2. How to select and validate biological targets

3. How to select and prioritize ideal drug candidates
4. How to select and validate objective clinical outcome measures

### **Clinical Outcome Measures**

The panel discussed finding the most appropriate measurements in order to conduct clinical trials. For therapies to be evaluated and approved by the FDA, it will be critically important that outcome measures are accurate, reproducible, properly validated and are acceptable to the FDA.

An ideal outcome measure should satisfy some of the criteria listed below:

- Be functionally relevant to RTT
- Detect changes in current severity (be dynamic)
- Have psychometric properties that have distribution and reliability in patients with Rett syndrome
- Track independent variables
- Correlate with a biological marker

As a practical consideration, outcome measures should also accommodate for the communication and motor skill limitations of RTT patients.

A critical task which lies ahead is to the identification of the most appropriate endpoint measures and assessment tools. One approach that was suggested was to utilize clinical endpoints that have been developed for treatment trials in other diseases. These would first be validated using RTT animal models and further validated in RTT patients. This strategy may be particularly appropriate where a therapeutic is being repurposed as a treatment for RTT.

Existing assessment tools measure motor-function, behavior, growth patterns and quality of life issues, several examples are listed below:

- A cognitive/behavioral assessment
- Quantitative physiological measures
- Imaging equipment designed to accommodate RTT patients and that have the ability to identify issues specific to the disease

A number of potential instruments were identified that met the requirements to measure non-verbal, communication, adaptive behavior skills and problem behaviors. Some of these instruments have only partial utility however, or are only useable in assessing certain age groups. To date, none of the existing instruments used for clinical trials in other neurodevelopmental disorders have been assessed specifically for RTT. The panel concurred that adequate tests may exist, but much work must be done to validate assessment tools specifically for the RTT population.

Recommendations on the development of clinical trials outcome measures:

1. Revise/improve existing instruments currently used in RTT trials
2. Discontinue the use of existing RTT 'severity' scales
3. Modify endpoints devised for other diseases that have a good track record in related diseases
4. Develop non-verbal cognitive tests, a communication rating scale, adaptive skills rating scale and a problem behaviors rating scale

A number of outcome measures could be developed using natural history study data. These include such measures as quality of life and behavioral assessments provided that they are repeatable and can be reliably reported by observational studies. Certain functional measures such as the assessment of attention, cognition and motor skills, will require detailed professional observation and/or sophisticated assessment tools. This would necessitate bringing individuals who are experienced in psychometrics, psychology and physiological testing into the RTT field and might require expensive, customized equipment fitted to the task.



## **Existing Therapies and Drugs in Development: Repurposing**

Researchers are looking for drugs that will make improvements at any point in the disease process, as they want to attack RTT on all fronts. Drug candidates may:

- Improve survival
- Provide partial improvement (e.g., address one function such as cognition)
- Achieve normal function

When appropriate endpoints are identified and assessment tools are available to verify outcomes in Rett syndrome, drugs either currently on the market or in development can be tested and approved.

## **Findings and Recommended Activities in the Translational Research Arena**

The group identified 14 activities that would advance research for drug discovery, and those activities were stratified using a follow-up survey. Three tiers of activities were identified by those who participated in the survey.

### **Tier 1 Projects:**

Develop valid clinical outcome measures - Investigate how to prove the concept clinically

Identify valid biological targets for RTT - This list can be used as a tool for unearthing compounds for repurposing

Repurposing - Identify compounds that are in development that we can use in RTT

Develop Critical Resources – Developing new assays that may be required for drug discovery and development. Includes biochemical, cellular, and animal tests that support the “testing funnel” approach (the course of developing a new drug)

Orphan Drug Designation - Work with FDA to define the path to registration

## **Tier 2 Projects:**

Patient Populations - Define how well and in which patients the common drugs in use for treating RTT symptoms work

Consortia - Create and fund one or more interdisciplinary consortia

Research tools - Develop a high content assay / screen for drug validation

Identification - Biomarker development

“Low hanging fruit” - Popularize NIH blueprint and other funding initiatives, orphan drug designation, and the use of female null mice, model organisms and cell-based assay development

## **Tier 3 Projects:**

Strategic Resource Funding - Provide resources to promote repurposing of compounds

Leverage Information Technology – Acquire/use/develop an informatics platform to capture and disseminate RTT information

## **Existing Clinical Resources**

As IRSF moves closer to the clinic with emerging therapies currently in development there are already resources available to the clinical investigator to draw on.

Resources that facilitate clinical trials in RTT:

- Well-characterized clinical populations
- International patient databases EuroRett, InterRett and the Natural History Study database
- Rational therapeutic targets
- Expanding governmental interest
- International research group comprised in existing consortia, RettSearch

## Repurposing Drugs with the “Testing Funnel” Approach

The process of drug discovery usually begins with the identification of as many as hundreds of thousands of compounds suspected to be active in treating an identified disease-specific target. After eliminating the initial round of candidates that are determined to be ineffective on the target, the group of remaining drug candidates is honed down to a few thousand. Another round of testing and more focused experimentation will reduce this number to hundreds, and eventually to only a few viable “lead” drug candidates that are suspected to effectively act on a target. Finally, after many years of laborious testing, only one most promising candidate is determined to be clinically effective – which means that it works in a live subject, first an animal and later a human being.

The honing of drug candidates is done in what has been referred to as a “testing funnel” due to the process of elimination required. Rigorous scientific testing using validated experimental testing methods which are commonly referred to as screening “assays.”

In testing or measuring the activity of a drug or biochemical, the scientist uses an “assay” which is a procedure to measure the process related to the substance under study. The “assay” must be proven to be accurate in determining the activity or process. Therefore, identification, development and validation of the correct assay is crucial for evaluating potential therapeutics.

The panel pointed out that there is a clear need for novel biochemical, cellular and animal-based screening assays that are a key requirement for the drug discovery and development process.

The main areas of need to address as a priority are as follows:

*In Vitro* Assay Development: To be generated primarily by academic investigators. Various contract research organizations (CROs) have developed proprietary *in vitro* screening assay technologies and could be approached for a large scale screening program or consortium-based approach.

Rationale: Assemble a range of investigators and projects to reach across the industry for opportunities and input.

Timeline: Long-term approach will take 1 to 2 years to develop and validate cell-based screening assays.

In Vivo Assay Development/Assessment of Candidates: Individual academic investigators may be approached in the initial stages of the candidate drug selection process to assess lead compounds for their suitability to be moved further along the development track. At later stages, given the generally prohibitive costs, CRO's are likely to be considered only for validating drugs at the end-stages of a development program on a contractual basis.

Rationale: Reach out to a range of investigators and vendors to expand input and opportunities.

Timeline: Long-term, this will take 1 to 3 years to assess the selected compounds.

### **Selection of Drugs for Repurposing**

The panel suggested that a group of expert biologists with knowledge of the underlying biology of RTT should develop a library of carefully selected drugs in late stage development and evaluate and validate these in cellular and animal-based drug screening tests. Repurposed drugs that have been approved by the FDA and marketed for different indications are a first priority since these have already been approved for use in humans. Drugs that are currently in development for other indications that are not yet approved or that have been shelved by pharmaceutical companies would comprise the second tier. Finally screening of novel compounds that show promise should be selected based upon knowledge of specific, tractable biological targets thought to be involved in RTT.

It is expected to take up to 2 to 3 years to evaluate candidates using *in vitro* and *in vivo* assays.

## **Toward the Future**

The biggest bottleneck is the development of new assays to identify and / or validate promising drug candidates. Specifically, cell-based assays are needed at the early stages of the drug discovery and development process, although they are critically important through the *entire* period of drug development.

Evaluation and proper validation of a particular drug target in Rett syndrome should not only involve genetic knockout models of the target but also at least three structurally diverse compounds whose commonality is that they inhibit or activate the target. Historically, we take single compounds rather than groups of compounds. Single compounds however, do not allow one to distinguish between the on-target effect of the compound and an off-target effect. Thus, future projects that aim to validate a particular biological target should involve the testing of several structurally diverse compounds.

An additional issue is that no compound should be moved forward unless two independent labs have replicated the result. Ideally, this should happen prior to publication of the results so all parties share credit for a particular discovery.

The translational research workgroup harnessed and directed enthusiasm for new therapy discovery and evaluation, and created momentum by endorsing translational strategies. It was agreed that the most efficient path toward drug discovery is repurposing of existing therapies and compounds already in the discovery funnel.

IRSF aims to align its funding and grant approval process to assure that recipients are working on projects consistent with these strategies identified by the panel as the clearest path toward success.

## Attendees

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