# Setting Priorities for Therapy Development in Rett Syndrome

**Bethesda Hyatt Hotel**
**Bethesda, MD**
*September 25–27, 2011*

## Agenda

**Sunday, September 25, 2011**

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| 4:30–5:00 p.m. | **Registration**<br>*Lalique Suite* |
| | **Session I. Developing a Therapy Development Program for Rett Syndrome**<br>*Lalique Suite* |
| 5:00–5:15 p.m. | **Welcome and Opening Remarks**<br>*Robert Finkelstein, Ph.D., Director, Division of Extramural Research, NINDS/NIH* |
| 5:15–5:30 p.m. | **Goals of the Workshop**<br>*Laura Mamounas, Ph.D., Program Director, Neurogenetics Cluster, NINDS/NIH* |
| 5:30–6:00 p.m. | **Lessons Learned From a Successful Therapy Development Program**<br>*Ed Kaye, M.D., AVI BioPharma* |
| 6:00–6:30 p.m. | **FDA Perspective and Guidelines for Product Development in Rare Disorders**<br>*Anne Pariser, M.D., Center for Drug Evaluation and Research (CDER), FDA* |
| 6:30–7:00 p.m. | **Complexities of the Clinical Phenotype in Rett Syndrome**<br>*Jeff Neul, M.D., Ph.D., Baylor College of Medicine* |
| 7:00–7:30 p.m. | **Therapy Development Strategies for Rett Syndrome**<br>*John McCall, Ph.D., PharMac LLC* |
| 7:30 p.m. | ***Sponsored Dinner*** *(hosted by the International Rett Syndrome Foundation)* with presentations on **Opportunities To Advance Translational Research in Rett Syndrome** |
| | **NIH Blueprint Neurotherapeutics and NINDS Translational Research Programs**<br>*Jill Heemskerk, Ph.D., NINDS/NIH* |
| | **The SMART Library Initiative**<br>*Janice Ascano, Ph.D., International Rett Syndrome Foundation* |

**Monday, September 26, 2011**

7:30 a.m. **Continental Breakfast**
*Lalique Suite*

**Session II. Defining Preclinical Outcome Measures in Mouse Models of Rett Syndrome**
*Lalique Suite*

8:00–10:00 a.m. **Working Group Reports: Summary of Phenotypic Data in Rett Mouse Models**

**Charge of the Working Groups**
*David Katz, Ph.D., Case Western School of Medicine*

**General Health and Locomotion**
*James Eubanks, Ph.D., Toronto Western Research Institute, University of Toronto*

**Respiratory and Autonomic Function**
*David Katz, Ph.D., Case Western School of Medicine*

**Sensory Function, Social Interaction, Learning, Memory, and Anxiety**
*Joanne Berger-Sweeney, Ph.D., M.P.H., Tufts University*

**Synaptic and Circuit Function, Cellular Pathology, and Seizure**
*Lucas Pozzo-Miller, Ph.D., University of Alabama at Birmingham*

**Molecular Markers**
*Huda Zoghbi, M.D., Baylor College of Medicine*

10:00–10:15 a.m. **BREAK**

10:15–11:15 a.m. **Discussion: Evaluation of Current Models and Phenotyping Data**

Discussion Facilitators:

*Laura Mamounas (moderator), Joanne Berger-Sweeney, James Eubanks, David Katz, Lucas Pozzo-Miller, Huda Zoghbi, Mary Blue, Jacky Guy, Peter Huppke, Jonathan Kipnis, Vinodh Narayanan, Jeff Neul, Nino Ramirez, Rodney Samaco, Juan Young, Joe Zhou*

Discussion Topics:

- Discrepancies/disagreements and key gaps in knowledge about specific models and/or measures
- List of pressing experiments needed to close gaps
- Should the field adopt standardized assays/tests and protocols whenever possible?
- What are the best models (allele, gender, strain/genetic background) for use in animal trials?

**Monday, September 26, 2011, *continued***

11:15 a.m.–1:00 p.m. **Discussion: Clinical Perspectives—Evaluating and Validating the Predictive Value of Current Mouse Models and Phenotyping Data**

Discussion Facilitators:

*Jeff Neul (moderator), Stuart Apfel, Rita Cantor, Jacqueline Crawley, Sasha Djukic, Peter Huppke, Monica Justice, David Katz, Walter Kaufmann, Omar Khwaja, Vinodh Narayanan, Alan Percy, Andrew Pieper, Nino Ramirez, Shlomo Shinnar, Huda Zoghbi, Richard Paylor (teleconference)*

Discussion Topics:

- Perspectives from clinical trials
- What models and assays/tests will be most predictive of clinically relevant outcomes?
- Is there a need to develop better models (e.g., targeted mutations) and/or assays/tests that recapitulate the clinical pathology in Rett syndrome?
- Is correction of a cellular or molecular abnormality (as opposed to behavioral or functional, for example) in a Rett mouse model sufficient to launch a translational program?
- How many phenotypes should be modified to warrant a therapeutic trial in humans? Is reversal of one phenotype sufficient to move forward?

12:00–1:00 p.m. **WORKING LUNCH** *(continuing discussion)*

**Session III. Establishing Criteria for a Successful Preclinical Animal Trial**

1:00–1:40 p.m. **Preclinical Trial Design: Improving the Quality of Preclinical Research Through Rigorous Study Design and Transparent Reporting**
*Shai Silberberg, Ph.D., NINDS/NIH*

1:40–2:40 p.m. **Resources and Testing Capabilities for Preclinical Trials**
*Daniela Brunner, Ph.D., PsychoGenics, Inc.*
*Cat Lutz, Ph.D., The Jackson Laboratory*

2:40–3:10 p.m. **Preclinical FDA Guidelines for First-in-Human Clinical Studies**
*Lois Freed, Ph.D., CDER/FDA*

3:10–3:30 p.m. **BREAK**

3:30–5:30 p.m. **Discussion: Developing Guidelines and Standards for Preclinical Animal Trials in Rett Syndrome**

Discussion Facilitators:

*Huda Zoghbi (moderator), Mary Blue, Daniela Brunner, Jacqueline Crawley, Lois Freed, Maurizio Giustetto, David Katz, Cat Lutz, John McCall, Elizabeth McNeil, Lisa Monteggia, Robert Pacifici, Anne Pariser, Shai Silberberg, Mriganka Sur, Richard Paylor (teleconference)*

**Monday, September 26, 2011, *continued***

Discussion Topics:

- How do we implement best practices for preclinical trial design in Rett syndrome (e.g., randomization, blinding, number of animals, etc.)?
- Is there a need for replication in more than one Rett model?
- What effect size is desired to warrant a therapeutic trial in humans?
- How much detail regarding treatment protocols needs to be established in mouse models before moving to humans (e.g., dosing, duration [acute vs. chronic], and timing of treatment)?
- When should a rigorous, controlled preclinical efficacy trial be launched (e.g., before med-chem optimization)?
- How can independent replication of preclinical trial results be best achieved (e.g., by a CRO, NIH-funded core mouse testing facility, academic laboratory)?
- How and when should FDA nonclinical requirements (safety/toxicity studies) for first-in-human studies be addressed?
- From these measures, define criteria for launching a large-scale preclinical-to-clinical translational program.

6:00 p.m. **Sponsored Dinner** *(hosted by Rett Syndrome Research Trust)*
*Concourse Terrace*

**Tuesday, September 27, 2011**

7:30 a.m. **Continental Breakfast**
*Lalique Suite*

**Session IV. When To Promote a Biological Target and/or Early-Stage Candidate Compound Into a Drug Development Pathway**
*Lalique Suite*

8:00–8:30 a.m. **Criteria Developed and Established for Other Neurological Disorders and/or Translational Programs**
*Chris Austin, M.D., National Human Genome Research Institute (NHGRI), NIH*

8:30–9:00 a.m. **Industry Perspective in Selecting and Prioritizing Targets**
*Robert Pacifici, Ph.D., CHDI Foundation, Inc.*

9:00–9:45 a.m. **Evaluation of Existing Therapeutic Candidates for Rett Syndrome: Characterization and In Vivo Efficacy of Small Molecule TrkB Agonists**
*Frank Longo, M.D., Ph.D., Stanford University*
*David Katz, Ph.D., Case Western School of Medicine*

9:45–10:15 a.m. **Increasing BDNF Levels With FTY720, a Drug Used for the Treatment of Multiple Sclerosis**
*Yves-Alain Barde, University of Basel*

**Tuesday, September 27, 2011, *continued***

10:15–10:30 a.m. **BREAK**

10:30–10:50 a.m. **IGF-1: Mechanisms and Emerging Therapeutics for Rett Syndrome**
*Mriganka Sur, Ph.D., MIT*

10:50–11:15 a.m. **Design and Early Experience From a Clinical Trial of rhIGF-1 in Rett Syndrome**
*Omar Khwaja, M.D., Ph.D., Children's Hospital Boston*

11:15–11:45 a.m. **Readthrough of Nonsense Mutations in Rett Syndrome**
*Peter Huppke, M.D., Georg August University Goettingen*

11:45 a.m.–1:15 p.m. **Discussion: Developing Criteria for Prioritizing Targets/Compounds in Rett Syndrome**

Discussion Facilitators:

*Robert Pacifici (moderator), Stuart Apfel, Chris Austin, Yves-Alain Barde, Kurt Fischbeck, Peter Huppke, Monica Justice, David Katz, Ed Kaye, Omar Khwaja, Francis Lee, Frank Longo, John McCall, Mriganka Sur, Huda Zoghbi*

Discussion Topics:

- Assess the "translatability" of therapeutic candidates (e.g., clinical relevance of the preclinical outcome measures, evidence that compound reaches and engages target as predicted/desired, pharmacokinetic/pharmacodynamic properties, etc.)
- Review data on existing candidates and discuss what additional evidence is needed before launching a full-scale translational program
- Establish criteria for prioritizing targets/compounds in Rett syndrome (which biological targets/pathways are worth pursuing?)

1:15–2:00 p.m. **Working Lunch** with presentations on **NIH Opportunities To Advance Translational and Clinical Research:**

**NIH Programs To Support Translational Research: Therapeutics for Rare and Neglected Diseases (TRND), Molecular Libraries, NIH-RAID, and more…**
*Chris Austin, M.D., NHGRI/NIH*

**NeuroNEXT and other NINDS Programs To Support Clinical Trials Research**
*Elizabeth McNeil, M.D., M.Sc., NINDS/NIH*

2:00–3:00 p.m. **Final Discussion and Next Steps**

Discussion Facilitators:

*Laura Mamounas (moderator), Janice Ascano, Stephen Bajardi, Monica Coenraads, David Katz, John McCall, MaryLou Oster-Granite, Melissa Parisi, Coryse St. Hillaire-Clarke, Huda Zoghbi*

3:00 p.m. **Meeting Adjourns**