Neurophysiological Correlates and Biomarkers: Rett Syndrome, *MECP2* Duplications, and Rett-Related Disorders Consortium (aka 5212)

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Disclosures

1. RO1 NS076577 (Benke) NIH/NINDS
   Molecular mechanisms linking early life seizures, autism and intellectual disability
   Role: PI.

2. Questcor Pharmaceuticals (Benke) Whole-exome sequencing and ACTH responsiveness in Infantile Spasms
   Role: PI.

3. 1U10NS077277(Vollmer) NIH/NINDS
   Rocky Mountain Network for Neuroscience Clinical Studies (NeuroNext Clinical Site)
   Role: Co-I.

4. U54 HD061222 (Percy) NICHD
   Rett syndrome, MECP2 Duplication Disorder, and Rett-related Disorders Natural History.
   Role: Site Director, Co-I.

5. Rett Clinic at Children’s Hospital Colorado (Benke) Rocky Mountain Rett Association
   Role: PI/Medical Director

6. CDKL5 Center of Excellence (Benke) International Foundation for CDKL5 Research
   Role: PI

7. Neuren: Study of trofinetide, also known as NNZ-2566, for females with Rett Syndrome
   Role: site PI
Topics today

• Background of 5212
• Purpose of 5212
• Outline of 5212
Participating Institutions and Investigators: 5212

Consortium Study Chair: Alan K. Percy, MD, UAB
Principal Investigator and Study Lead Investigator:
   Eric Marsh, MD, PhD, Children’s Hospital of Philadelphia
Principal Investigator and Study Co-Lead Investigator:
   Tim Benke, MD, Ph, University of Colorado
Principal Investigator: Mustafa Sahin, MD, PhD, Boston Children’s Hospital
Principal Investigator: Sarika Peters, PhD, Vanderbilt University
Principal Investigator: Alexander Paciorkowski, MD, University of Rochester
Principal Investigator: Steven Kaminsky, PhD, Rettsyndrome.org
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      Project Scientist: Danuta Krotoski, PhD
   NINDS:
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Neurophysiology Consultants:
   Charles A. Nelson, PhD, Boston Children’s Hospital
   Michela Fagiolini, PhD, Boston Children’s Hospital
   Timothy P. Roberts, PhD, Children’s Hospital of Philadelphia
Background

Multiple lines of evidence for synaptic pathophysiology resulting in network dysfunction in animal and humans with Rett and Rett-related disorders.
Background

Grand average time-frequency representations and topographies from the preliminary data auditory EEG paradigm. Induced gamma power differed for familiar and unfamiliar voices in the RTT group (left) and the MECP2 Dup group (right), showing opposite trends. Peters SU, Gordon RL, Key AP (2015) Induced gamma oscillations differentiate familiar and novel voices in children with MECP2 duplication and Rett syndromes. J Child Neurol 30: 145-152.
Right-sided frontal alpha band EEG asymmetry is common in RTT and shows a trend toward reversal with IGF-1 treatment. Six subjects evaluated before IGF-1 treatment (Pre-OLE) demonstrated $R > L$ asymmetry. Although the degree of asymmetry was variable after treatment (Post-OLE), five of the six showed a decrease in the asymmetry index and in three there was a reversal. A paired-samples $t$ test revealed significant group differences Pre- and Post-OLE. Khwaja OS, et al (2014) Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human-IGF1) for the treatment of Rett syndrome. Proc Natl Acad Sci U S A 111: 4596-4601.
The relationship(s) between neurophysiological findings:
- Visual evoked potentials
- Auditory evoked potentials
- EEG

and

- disease evolution,
- severity and
- specific clinical features

in Rett and Rett-related disorders is unknown.
Purpose of 5212

• Advance understanding of the neurophysiological features of:
  • Rett syndrome (RTT)
  • MECP2 Duplication (MECP2 Dup)
  • CDKL5
  • FOXG1

• Gain insight into disease pathogenesis

• Identify biomarkers of disease evolution and severity

• Intertwined to the core study Natural History of Rett Syndrome and Related Disorders (RTT5211)

• Serve as basis of future translational investigations
  • Refinement of biomarkers & development of outcome measures
Primary Outcome measures

1. Auditory Evoked Potential (AEP) latency (ms)
2. Auditory Evoked Potential amplitude of P1, P2 and N1 peaks (uV)
3. Visual Evoked Potential P1-N2 time (ms)
4. Visual Evoked Potential (VEP) amplitude of N1-P1 (uV)
Secondary Outcome Measures

1. AEP: Change in power of gamma band activity (delta dB at 30-70Hz band between pre-stimulus and post-stimulus).
2. Frontal alpha band activity asymmetry index
3. Other AEP and VEP parameters.
Enrollment: Inclusion criteria

Females and males of all ages must have:

Testing for MECP2, CDKL5, and/or FOXG1 genetic changes.

AND must meet these requirements:

Gene positive for a sequence change, duplication or deletion in one of these 3 genes.

AND

Those with Rett syndrome phenotype should meet consensus criteria for typical or atypical Rett syndrome.

AND

Enrolled in RTT5211.
Enrollment: Rett syndrome

60 female subjects evaluated up to 3 times (annual evaluations)
  20 in stage 2 (active regression) or <12 months since last skill loss (~2-5 y.o.)
  20 children in stage 3 (post-regression, >12 months since last skill loss; ~5-12 y.o.)
  20 adolescents/adults (all in stage 3, post-regression; >12 y.o.)

The stage/age groups above will attempt to distribute genetic changes type/severity and clinical severity as follows:

30 with milder MECP2 changes (R133C, R294X, R306C, C-terminal deletions)
30 with more severe MECP2 changes (R106W, T158M, R168X, R255X, R270X, large exons 3+4 deletions)
30 with more severe clinical profile (>22 CSS*)
30 with less severe clinical profile (<22 CSS*)
*Median CSS score from the Natural History Study (Protocol RTT5201)
Enrollment: MeCP2 duplication

18 male subjects evaluated three times (annual evaluation)
  9 in early childhood, prior to onset of epilepsy (~2-10 y.o.)
  9 adolescents/adults, post onset of epilepsy (>10 y.o.)
Enrollment: CDKL5 syndrome

CDKL5 Disorder:
18 female subjects evaluated three times (annual evaluation)
  6 in infancy, during the period associated with infantile spasms (~2mo-2 y.o.)
  6 in childhood, after the cessation of infantile spasms (~2-12 y.o.)
  6 adolescents/adults (>12 y.o.)
Enrollment: FOXG1 syndrome

FOXG1:
14 male/female subjects evaluated three times (annual evaluation)

- 6 in infancy, during the period associated with infantile spasms (~2mo-2 y.o.)
- 5 in childhood, after the cessation of infantile spasms (~2-12 y.o.)
- 3 adolescents/adults (>12 y.o.)
Enrollment: Controls

30 females evaluated up to 3 times (annual evaluation)
   10 females in early childhood (~2-5 y.o.)
   10 females in late childhood (~5-12 y.o.)
   10 female adolescents/adults (>12 y.o.)

30 males evaluated up to 3 times (annual evaluation)
   10 males in early childhood (~2-5 y.o.)
   10 males in late childhood (~5-12 y.o.)
   10 male adolescents/adults (>12 y.o.)
Timeline

NIH approval of 5212 protocol: 5/13/2016
Local IRB approvals: submitted/in-process. Due 9/1/2016
Validation of local data/technology
  Human “phantoms” (Marsh and Roberts)
  Visits to establish cross-site data parity: 9/2016
Initial visits: September 2016 (year 1)
  2\textsuperscript{nd} visit/Year 2: September 2017
  3\textsuperscript{rd} visit/Year 3: September 2018
Challenges and Limitations

Technical:
- Establishing uniformity across sites
- Translating protocol into clinical practice

EEG:
- Not a surrogate for epilepsy assessment
  - limited sample (no sleep or other behaviors)
- EEG “e-bank” needed

Frequency analysis:
- Alternative behavioral correlates (other than AEP/VEP)

Patient numbers/statistical power
- Phenotypic & genotypic variability
- RTT versus Rett-related
Special Thanks!!!

Our patients and families

NHS-Natural History Study:
Eric Marsh, Alan Percy, Jeff Neul,
Alex Paciorkowski, Laura
Mamounas, Tim Roberts, Chuck
Nelson, Sar Peters, Michela
Fagiolini, Walter Kaufmann, etc

IFCR COE: Heather Olson, Elia
Pestana-Knight, Sumit Parikh

Rocky Mountain Rett Association
Ponzio Family Chair in Neuroscience
Research
questions