Developing Targeted Therapeutics in Autism: Challenges for Clinical Trial Readiness

Alexander Kolevzon, MD
Clinical Director, Seaver Autism Center
Director, Child and Adolescent Psychiatry
Mount Sinai Health System

Disclosures of Potential Conflicts

<table>
<thead>
<tr>
<th>Source</th>
<th>Research funding</th>
<th>Advisor/consultant</th>
<th>Employee</th>
<th>Speakers’ Bureau</th>
<th>Books, Intellectual Property</th>
<th>In-Kind Services</th>
<th>Stock of Equity</th>
<th>Honorarium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seaver Foundation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism Science Foundation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simons Foundation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Psychiatric Publishing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>New York Community Trust</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vencerx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ovid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AACAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Mount Sinai and Joseph Buxbaum hold a shared patent for IGF-1 in Phelan-McDermid syndrome
The following presentation contains information concerning a use that has not been approved by the U.S. Food and Drug Administration
Symptom Domains and Associated Features of ASD

Social/Communication Deficits
- Sensory Sensitivity
- ADHD Symptoms
- Expressive/Receptive Language Disorders

Autism Spectrum Disorder
- Impulsivity/Aggression
- Obsessive Compulsive Disorder

Restricted, Repetitive Behaviors
- EEG Abnormalities

Variable Faces of ASD
Developing Novel Therapeutics

Genomic architecture of ASD

De Rubeis et al., Nature, 2014

Dolen & Bear, 2009
## Autism as a Synaptopathy

![Autism as a Synaptopathy](image)

### Advances in autism genetics: on the threshold of a new neurobiology

*Brett S. Abrahams and Daniel H. Geschwind*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>LBE3A (and others)</td>
<td>&gt;40%</td>
<td>1-2%</td>
<td>101-103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTPN2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1-2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60-80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>
A new view on autism spectrum disorder

Before

After

Phelan-McDermid Syndrome

- global developmental delay
- intellectual disability
- absent or severely delayed speech
- hypotonia
- dysmorphic features
Gene Discovery - SHANK3

- SHANK3 is a master scaffolding protein which forms a framework for the connections between nerve cells.
- SHANK3 protein induces the formation of nerve cells and promotes growth.
- SHANK3 and associated proteins represent novel targets for drug intervention.

Model Systems – Synaptic Deficits in PMS

Bozdagi et al, 2010
Effect of IGF-1 on Synaptic Deficits

Bozdagi et al, 2013
Reversal of motor deficits in Shank3-deficient mice (Het) after treatment with IGF-1

Bozdagi et al, 2013

SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients

Jarrive Simon, Salk Institute for Biological Studies
A Double-Blind Placebo-Controlled Crossover Trial of IGF-1 in Children with Phelan-McDermid Syndrome

![Diagram showing the trial design](image)

**Placebo**
- wash-out
- 12 weeks
- IGF-1

**Placebo**
- 12 weeks
- wash-out
- 4 weeks
- IGF-1

**Placebo Placebo**
- 12 weeks
- IGF-1

**IGF-1 IGF-1**
- 4 weeks
- 12 weeks

---

**RESEARCH**

Open Access

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolingeon(1,2,4,7), Lauren Suth(1,2,4,7), A Ting Wong(1,2,4,7), Danielle Haberm(1,2,4,7), Yozshl Frans(4,7,9)

David Grodberg(1,2), Robert Taussig(1,2), Teresa Tanasich(1,2), William Chapman(1,2), Latha Sowa(1,2)

and Joseph J. Busbae(1,2,4,7)

---

**Graphs**

[Mean Change in ABC Social Withdrawal](image)

[Mean Change in MBU Social Withdrawal](image)
Change in scores at week 12 in social withdrawal and restricted behavior

Change in scores at week 12 in hyperactivity
Change in scores at week 12 in sensory reactivity
IGF-1 in ASD

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

A Pilot Treatment Study of Insulin-Like Growth Factor-1 (IGF-1) in Autism Spectrum Disorder

This study is currently recruiting participants. (see Contacts and Locations)
NCT01970345
First received: October 22, 2013
Last updated: May 9, 2014
Last verified: May 2014

Sponsor:
Mount Sinai School of Medicine

Collaborators:
Autism Science Foundation

Information provided by (Responsible Party):
Alexander Kreizman, Mount Sinai School of Medicine

Molecular Psychiatry (2016) 00, 1–16

Altered proliferation and networks in neural cells derived from idiopathic autistic individuals

Biomarkers for Clinical Trials

Electrophysiological Markers

- **Identify subtypes** of neurodevelopmental disorders based on excitatory/inhibitory (E/I) profiles
- Inform **personalized treatment** approaches
- Monitor **treatment response** and determine optimal responders
- Identify associations between neurophysiological responses and **clinical outcomes**

Paige Siper, PhD    Jennifer Foss-Feig, PhD
Transient VEPs in PMS

Siper, PM

VEP Quiz

Siper, PM
Effects of IGF-1 on neural responses

Siper, PM

<table>
<thead>
<tr>
<th>Band #</th>
<th>Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-10</td>
</tr>
<tr>
<td>2</td>
<td>12-28</td>
</tr>
<tr>
<td>3</td>
<td>30-36</td>
</tr>
<tr>
<td>4</td>
<td>38-48</td>
</tr>
</tbody>
</table>

n=6
Improvement in VEPs after treatment with IGF-1 in PMS

n=6; p=.048

Improvement in VEPs after treatment with OXT in ASD

n=7
VEP in PMS and ASD

A subset of ~30% of iASD patients fall within 1 SD of the PMS P<sub>60</sub>-N<sub>75</sub> mean and are defined as “PMS-like”

Siper, PM
Foss-Feig, J

Sensory Assessment for Neurodevelopmental Disorders (SAND)

Clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with neurodevelopmental disorders

Siper, PM et al., 2017
Sensory Reactivity in PMS – SAND

Siper, PM

Effects of IGF-1 on Sensory Reactivity

n=6, p = .037

Siper, PM
Auditory Event Related Potentials

Eye Tracking in PMS

Visual Paired Comparison
Rose et al, 2013

Gap-Overlap Task
Elison et al, 2013

Flicker Detection
Farzin et al, 2011
• 18 subjects with PMS underwent comprehensive evaluations.
• Over 542 hours of audio recording from the home environment was collected using LENA.
• 3 hours of audio was randomly selected for each participant and analyzed by human transcribers

Findings
How accurately does LENA distinguish the Key Child from all others?

<table>
<thead>
<tr>
<th>LENA System</th>
<th>Key Child</th>
<th>All Other Sound Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Transcriber</td>
<td>Key Child</td>
<td>12,229 (40%)</td>
</tr>
<tr>
<td></td>
<td>All Other Sound Sources</td>
<td>18,127 (60%)</td>
</tr>
<tr>
<td>Key Child</td>
<td>2,662 (3%)</td>
<td>86,942 (97%)</td>
</tr>
</tbody>
</table>

$k = 0.449 \ (p < .001), \ 95\% \ CI \ (0.443, \ 0.455)$.

Rankine et al., 2017
**Findings**

*How accurately does LENA distinguish Key Child speech-related vocalizations from non-speech sounds?*

<table>
<thead>
<tr>
<th>Human Transcriber</th>
<th>Child Vocalizations</th>
<th>Child Non-Speech Sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Vocalizations</td>
<td>6,800 (84%)</td>
<td>1,313 (16%)</td>
</tr>
<tr>
<td>Child Non-Speech Sounds</td>
<td>1,609 (39%)</td>
<td>2,507 (61%)</td>
</tr>
</tbody>
</table>

$k = 0.455 \text{ (} p < .001\), 95\% \text{ CI (0.437, 0.473).}$

Rankine et al., 2017

**Findings**

*What factors impact LENA performance?*

<table>
<thead>
<tr>
<th></th>
<th>Key Child Inter-rater Agreement</th>
<th>Child Vocalization Inter-rater Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.618 *</td>
<td>-.577 *</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.006</td>
<td>.012</td>
</tr>
<tr>
<td><strong>ADOS-2 Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>.125</td>
<td>-.134</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.620</td>
<td>.596</td>
</tr>
<tr>
<td><strong>ABC Inappropriate Speech Subscale Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.247</td>
<td>-.567 *</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.323</td>
<td>.014</td>
</tr>
<tr>
<td><strong>RBS Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.140</td>
<td>-.242</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.581</td>
<td>.333</td>
</tr>
</tbody>
</table>

Rankine et al., 2017
Gait Analysis

Performed in real time and captured at 240 Hz using 16 electro-magnetic sensors.
All output kinematic features of movement trajectories are analyzed from the head and upper/lower extremities.
Gait is measured during two exercises: 1) walking spontaneously along a six foot marked path; 2) walking along the identical path circumventing a waist-high obstacle.

Characterization of the Statistical Signatures of Micro-Movements Underlying Natural Gait Patterns in Children with Phelan McDermid Syndrome: Towards Precision-Phenotyping of Behavior in ASD

Elizabeth G. Toms*, Jillian Nguyen*, Saiji Mishry†, Carolisa Whipp*, Violen Kalampanidou* and Alexander Koluzho* 

n = 16 PMS; 11 controls
Summary

- Need validated measures specific to syndrome/phenotype
- Develop/validate biomarkers
- Carefully phenotype and select for target symptom/s of interest
- Focus on functional improvements (e.g., motor skills; language; cognition)
- Include younger subjects
- Increase duration of treatment

Acknowledgments

- Seaver Foundation
- Joseph Buxbaum
- Paige Sigler
- Danielle Halpern
- Michelle Gorenstein
- Yitzchak Frank
- Jennifer Foss-Feig
- Pilar Trelles
- Silvia De Rubeis
- Hala Harony-Nicolas
- Michael Breen
- Lynn Hendrickson
- Emily Isenstein
- Jordana Norry
- Kristin Meyering
- Allison Durkin
- Elyana Feldman