Potential Treatment Targets in Autism Spectrum Disorder (ASD)

James McCracken, MD
UCLA
Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Research Contract: Psyadon
Honoraria: Alcobra Pharma
Consultant Income: Think Now, Inc
Research Support (Spouse): Merck Foundation
Outline

• Advancing therapeutics for ASD
  – Unmet needs
  – State of the field
• Strategies for finding suitable targets for intervention
• Examples and Pitfalls
• Current research
Therapeutics Development in ASD

- Pace of new treatment testing and development slow
  - Only 2 FDA approved medications in ASD
  - Last approval in 2009
  - Non-pharmacologic intervention development mainly focused on early interventions
  - Less intervention testing on addressing core deficits

- State of the “pipeline”
  - Explosion of basic science findings
  - Genetics results identifying multiple paths to etiology
    - >100 identified risk genes
    - Promise of polygenic risk score application

- Some roadblocks
  - Methods development for intervention studies needed
  - Low Pharma enthusiasm for neurodevelopmental disorders
Targets Probed in ASD and Fragile X

- Glutamatergic dysfunction
  - mGluR5 antagonists
  - D-cycloserine
  - Ampakine agonist
  - memantine
- MMPs/Inflammation—minocycline
- Neuropeptides/Affiliation
  - Oxytocin
  - AVP—V1a receptor antagonist
- IP3 Pathway—lithium
- Abnormal dendritic arborization
  - Insulin Growth Factor-1
- GABAergic deficits
  - Arbaclofen
  - pregnenolone
Failures of mGluR5 Antagonist, D-cycloserine, Ampakine, and Memantine Raise Questions


But 3 other trials also negative

Erickson CA et al Psycharmacology 191:141, 2007

But large RCT stopped due to LOE

But RCT Negative (n=60)

Wrong endpoint, wrong model?

N= 19

CGI-Improvement:
30% vs 11%, NS
(OXT vs PLCB)

Open-Label Treatment Trial of Lithium to Target the Underlying Defect in Fragile X Syndrome

Elizabeth Berry-Kravis, MD, PhD, Allison Sumis, BS, Crystal Hervey, BS, Michael Nelson, PhD, Stephen W. Porges, PhD, Ning Weng, PhD, Ivan Jeanne Weiler, PhD, and William T. Greenough, PhD

Table 4. Baseline Scores and Change in Cognitive Measures after Treatment with Lithium for 2 Months

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Group Mean ± SD</th>
<th>Subjects Attempting Test at Baseline (N)</th>
<th>Subjects Attempting Test at 2 Months (N)</th>
<th>Group Mean Change ± SD</th>
<th>Subjects Attempting Test at Both Visits (N)</th>
<th>Number Improved</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Card task-color</td>
<td>3.0 ± 1.6</td>
<td>10</td>
<td>8</td>
<td>0.9 ± 2.2</td>
<td>8</td>
<td>4</td>
<td>0.315</td>
</tr>
<tr>
<td>Card task-number</td>
<td>1.9 ± 1.9</td>
<td>7</td>
<td>7</td>
<td>−0.8 ± 1.3</td>
<td>4</td>
<td>1</td>
<td>—b</td>
</tr>
<tr>
<td>CPT: visual-omissions</td>
<td>0.7 ± 0.8</td>
<td>11</td>
<td>11</td>
<td>0.4 ± 1.2c</td>
<td>10</td>
<td>2</td>
<td>0.709</td>
</tr>
<tr>
<td>CPT: visual-commissions</td>
<td>16.3 ± 23.8</td>
<td>11</td>
<td>11</td>
<td>0.6 ± 13.7c</td>
<td>10</td>
<td>6</td>
<td>0.389</td>
</tr>
<tr>
<td>CPT: auditory-omission</td>
<td>2.2 ± 4.4</td>
<td>9</td>
<td>9</td>
<td>−1.5 ± 3.4c</td>
<td>8</td>
<td>3</td>
<td>0.789</td>
</tr>
<tr>
<td>CPT: auditory-commissions</td>
<td>13.8 ± 21.7</td>
<td>9</td>
<td>9</td>
<td>5.8 ± 11.0c</td>
<td>8</td>
<td>3</td>
<td>0.389</td>
</tr>
<tr>
<td>NVALT learningd</td>
<td>34.0 ± 16.4</td>
<td>12/6e</td>
<td>14/9e</td>
<td>0.2 ± 7.0</td>
<td>12/7d</td>
<td>6</td>
<td>—b</td>
</tr>
<tr>
<td>NVALT reversalf</td>
<td>35.7 ± 14.7</td>
<td>6/3e</td>
<td>9/5e</td>
<td>2.7 ± 14.7</td>
<td>6/4d</td>
<td>2</td>
<td>—b</td>
</tr>
<tr>
<td>NEPSY tower</td>
<td>2.1 ± 1.1</td>
<td>9</td>
<td>9</td>
<td>−0.2 ± 1.1</td>
<td>9</td>
<td>3</td>
<td>0.621</td>
</tr>
<tr>
<td>RBANS: list learning</td>
<td>10.0 ± 7.4</td>
<td>10</td>
<td>11</td>
<td>4.1 ± 5.0</td>
<td>10</td>
<td>8</td>
<td>0.028</td>
</tr>
<tr>
<td>RBANS: story memory</td>
<td>5.6 ± 4.5</td>
<td>9</td>
<td>9</td>
<td>3.6 ± 1.1</td>
<td>9</td>
<td>4</td>
<td>0.512</td>
</tr>
<tr>
<td>PPVT</td>
<td>56.9 ± 16.6</td>
<td>15</td>
<td>15</td>
<td>1.7 ± 13.0</td>
<td>15</td>
<td>9</td>
<td>0.512</td>
</tr>
</tbody>
</table>
A Randomized Double-Blind, Placebo-Controlled Trial of Minocycline in Children and Adolescents with Fragile X Syndrome

Mary Jacena S. Leigh, MD,*† Danh V. Nguyen, PhD,‡ Yi Mu, MS,‡ Tri I. Winarni, MD,§ Andrea Schneider, PhD,*† Tasleem Chechi, BS,*† Jonathan Polussa, BS,*† Paul Doucet, BA,† Flora Tassone, PhD,†‖ Susan M. Rivera, PhD,‖† David Hessl, PhD,†‖ Randi J. Hagerman, MD*†

Table 2. Primary Outcome Measures and Ad-Hoc Visual Analog Scale (VAS) Analysis

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th></th>
<th>Minocycline</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SE</td>
<td>LSmean</td>
<td>SE</td>
<td></td>
<td>LSmean</td>
<td>SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Clinical Global Impression—Improvement Scale*</td>
<td>55</td>
<td>—</td>
<td>—</td>
<td>2.49</td>
<td>0.13</td>
<td></td>
<td>2.97</td>
<td>0.13</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>2a. VAS Categorized by Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Analog: Severity of Target Behavior 1*</td>
<td>55</td>
<td>2.28</td>
<td>0.21</td>
<td>4.60</td>
<td>0.31</td>
<td></td>
<td>4.44</td>
<td>0.30</td>
<td></td>
<td>.67</td>
</tr>
<tr>
<td>Visual Analog: Severity of Target Behavior 2</td>
<td>55</td>
<td>2.62</td>
<td>0.23</td>
<td>4.91</td>
<td>0.31</td>
<td></td>
<td>4.16</td>
<td>0.29</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Visual Analog: Severity of Target Behavior 3</td>
<td>50</td>
<td>2.80</td>
<td>0.27</td>
<td>4.88</td>
<td>0.36</td>
<td></td>
<td>4.13</td>
<td>0.35</td>
<td></td>
<td>.10</td>
</tr>
</tbody>
</table>
GABA\textsubscript{B} Agonist Arbaclofen

Generated post hoc revised ABC-SW subscale--significant

Sure looked good in open label!

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Week 8</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-Irritability</td>
<td>27.0 ± 7.61</td>
<td>17.7 ± 10.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABC-Lethargy/Social withdrawal</td>
<td>17.3 ± 8.18</td>
<td>12.6 ± 89.30</td>
<td>0.001</td>
</tr>
<tr>
<td>ABC-Hyperactivity</td>
<td>29.7 ± 12.14</td>
<td>21.1 ± 12.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABC-Inappropriate speech</td>
<td>7.0 ± 3.53</td>
<td>6.0 ± 4.04</td>
<td>0.081</td>
</tr>
<tr>
<td>ABC-Stereotypy</td>
<td>9.3 ± 6.77</td>
<td>6.6 ± 6.90</td>
<td>0.002</td>
</tr>
<tr>
<td>Social responsiveness scale (total score)</td>
<td>117.0 ± 33.75</td>
<td>103.0 ± 29.62</td>
<td>0.037</td>
</tr>
<tr>
<td>CY-BOCS-PDD</td>
<td>14.8 ± 4.12</td>
<td>11.6 ± 4.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD-IV rating scale (total score)</td>
<td>34.2 ± 11.38</td>
<td>26.1 ± 12.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CASI-anxiety</td>
<td>20.4 ± 10.56</td>
<td>16.5 ± 13.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CGI-I</td>
<td>–</td>
<td>2.5 ± 0.92</td>
<td>–</td>
</tr>
<tr>
<td>CGI-S</td>
<td>5.1 ± 0.91</td>
<td>4.4 ± 1.16</td>
<td>–</td>
</tr>
</tbody>
</table>


Erickson C et al, JAADD 44:958, 2014
Pregnenolone in ASD Open Label Trial (N = 12)

<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>Baseline</th>
<th></th>
<th>Week 12&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Paired t test</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td><strong>Aberrant behavioral checklist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC-Irritability</td>
<td>17.4</td>
<td>7.4</td>
<td>11.2</td>
<td>7.0</td>
<td>2.5</td>
<td>0.028&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ABC-lethargy/social withdrawal</td>
<td>18.1</td>
<td>8.0</td>
<td>12.8</td>
<td>8.7</td>
<td>2.3</td>
<td>0.046&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ABC-stereotypy</td>
<td>9.8</td>
<td>5.5</td>
<td>8.7</td>
<td>6.5</td>
<td>0.7</td>
<td>0.522</td>
</tr>
<tr>
<td>ABC-hyperactivity</td>
<td>20.5</td>
<td>16.1</td>
<td>16.1</td>
<td>8.9</td>
<td>1.8</td>
<td>0.098</td>
</tr>
<tr>
<td>ABC-inappropriate speech</td>
<td>5.8</td>
<td>4.3</td>
<td>4.8</td>
<td>4.4</td>
<td>1.0</td>
<td>0.356</td>
</tr>
<tr>
<td>Short sensory profile—total score</td>
<td>137.7</td>
<td>21.5</td>
<td>147.6</td>
<td>15.3</td>
<td>−3.2</td>
<td>0.009&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Social responsiveness scale—total score</td>
<td>84.9</td>
<td>8.1</td>
<td>84.5</td>
<td>9.2</td>
<td>0.2</td>
<td>0.848</td>
</tr>
<tr>
<td>Vineland&lt;sup&gt;b&lt;/sup&gt;—adaptive behavior composite score</td>
<td>37.3</td>
<td>13.1</td>
<td>42.9</td>
<td>16.5</td>
<td>−1.3</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Fung LK et al, JADD 44: 2971, 2014
Results of Early Intervention

Most programs incorporating behavioral strategies show 50% improved

- “Rich get richer”
- 30% never develop functional language
- Results of programs for older kids not studied
- New targeted treatments (JASPER) may boost those who lag behind (Kasari et al, 2010)
- Treatment progress slow

5 million
Best Early Intervention Outcomes Modest

Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model

AUTHORS: Geraldine Dawson, PhD, a,b,c Sally Rogers, PhD, a Jeffrey Munson, PhD, a,f Milani Smith, PhD, a Jamie Winter, PhD, a Jessica Greenso, PhD, a Amy Donaldson, PhD, a and Jennifer Varley, MS a

WHAT'S KNOWN ON THIS SUBJECT: Previous studies on the efficacy of early behavioral intervention for improving outcomes for preschool-aged children with autism have yielded promising results. However, no randomized clinical trials of early developmental behavioral intervention designed for toddlers with autism have been conducted to date.

WHAT THIS STUDY ADDS: This study assessed the efficacy of the Early Start Denver Model, a comprehensive developmental behavioral intervention, for improving outcomes of toddlers with ASD. The intervention, which was initiated when children were less than 2½ years, resulted in significant improvements in IQ, language, adaptive behavior, and autism diagnosis.

Early Start Denver Model (2 years) -- +15 vs 7 point IQ increase, but all still retained ASD diagnosis

Dawson G, Pediatrics 125:e7-e23, 2010
Unmet Needs from ASD Outcome Studies

- Follow up studies not showing improved outcomes
- Adaptive functioning
  - Generally low
  - Majority of results report some improvements, especially in daily living and communication skills—but not socialization
  - Concern over plateau or loss of skills
- Social integration and independence
  - Most rated poor or very poor
  - 50% or more dependent on parents or caregivers
  - 40-50% reported as having no contact with peers
  - One Utah study had best outcomes (Farley et al, 2009)
  - Best outcome study—27% full-time/27% part-time employed
Trajectory of Daily Living Skills in ASD

Unmet Needs in ASD

• Diagnostic stability
  – Vast majority retained diagnosis
  – Even those no longer meeting criteria very impaired (Piven et al, 1996)

• Cognitive ability
  – Wide variability across studies
  – Of 11 studies, only two reported *increases*
  – Two reported mean *decreases*
  – Variability—one study of 41 subjects found 6 subjects to have 1 SD increase while 5 subjects showed 1SD decrease
Behavioral Comorbidity in ASD is High

- Children and Adolescents
  - Comorbidity is high (70%) even in non-referred samples
  - Challenging behaviors often reported as major source of parenting stress, even greater than child’s disability
  - Comorbidity reflected by patterns of psychotropic use
Lifetime Prevalence in ASD (10-14)

Simonoff E, et al JAACAP, 2008
Strategies for Target Choice in ASD Drug Development

• Clinical
  – Behavioral dimension
  – Augmentation approach of existing intervention

• Intermediate Phenotype
  – Makes use of available biological or system-level knowledge

• Molecular
  – Most proximal to etiology

• For encouragement, see Jeste & Geschwind, 2016
Clinical Target: Repetitive Behaviors

- Intensity of repetitive behaviors (RBs) is often so severe as to interfere with educational and therapeutic success
- Despite behavioral interventions, these can remain impairing
- Earlier conceptualization of RBs as “OCD-equivalent” largely discarded
  - Identification of subgroup of persons with anxiety-driven RRBs may be responsive to drug treatment
No Citalopram Effects on Repetitive Behaviors (N = 149)

Repetitive Behaviors (CYBOCS-PDD Score)

Week

P=NS

King BH, et al, Arch Gen Psychiat, 2009
Risperidone Reduces Repetitive Behaviors


25% vs 6%; \( p = 0.005 \) \( d = .55 \)
Aripiprazole Reduces Repetitive Behaviors in ASD in Two Controlled Trials

ASD Potential Target: Repetitive Behaviors

• Repetitive behaviors may respond to drug therapy when severe and impairing
• Response to SGAs is modest
• Understanding the heterogeneity of RRBs is important
  – Two or more types
• Need approach to selection of subgroup most likely to respond
Development of language continues years after JASPER therapy, but progress slow

Strategy: Intermediate Phenotypes as Target

- Multiple processes important to core ASD deficits have been identified
- These represent potential discrete targets for intervention
- Examples
  - Social communication
  - Face Processing
Stimulants Have Social Effects: RUPP PDD Methylphenidate Study

A 6-minute, scripted, two-part interaction assessment was created based on the ESCS.

The interaction was repeated each of 4 weeks of the placebo-controlled, MPH cross-over trial in a younger subset of 33 subjects.

Videos were scored for social and self-regulatory behaviors.

Results showed dose-dependent, increased joint attention and self-regulation behaviors.

Effect sizes were moderate: .49 for best dose vs placebo for Joint Attention Initiations and .61 for Regulated Affective State scores.

Clinically significant?

Strategy: Deficit in Face Processing in ASD

- Deficits in face processing in ASD have been documented using multiple measures
- Reduced performance is associated with fMRI differences
- The biological underpinnings of this system are well researched
- Strategies are possible to enhance function
Why Important? Trail of Tears in ASD Drug Development

• Multiple failures in clinical development of hypothesized “targeted treatments”
  – Weaknesses of study designs?
  – Poor choice of endpoints?
  – Samples too heterogeneous?
  – Mostly adults?

• For continued hope, see Jeste & Geschwind, 2016
What are our hoped-for targets?

ASD

Social Interaction

Communication

Repetitive Behavior
Precision Medicine Molecular Targets in ASD Treatment—GABA_A as a New ASD Target

• GABA—Multiple converging findings for GABA deficits
  – Animal models—reduced PV+ neurons in CNTNAP2 model
  – GABA_A receptor expression reduced—post-mortem
  – GAD expression reduced in frontal cortex—post-mortem
  – GABA_A occupancy reduced—*in vivo*
  – GABA reduced *in vivo* by MR spectroscopy
  – Possible clinical links?
    • Anxiety, cognitive, seizures, social, motor
Postmortem—BZR Binding Reductions in ASD

BZD binding decreased 29% in superficial layers and 16% in deep cortical layers

Blatt GJ & Fatemi, 2011
In Vivo GABA$_A$ Binding ($\alpha_1$, $\alpha_2$, $\alpha_3$, $\alpha_5$) in ASD–$^{123}$I-iomazenil in ASD

In Vivo GABA Reduced in ASD by MRS

Preclinical Evidence – GABA<sub>A</sub> Agonist Benefits Social Behavior

**Han S, et al, Neuron, 2014**
Preclinical EEG Effects of AZD7325, a GABA\(_A\) \(\alpha2, \alpha3\) Selective Positive Modulator

Nine compounds produced selective, dose-dependent increases in EEG \(\beta/\gamma\) power in the rat—a translatable biomarker of GABA\(_A\) \(\alpha2, \alpha3\) positive modulation

*Christian E et al, J Neurophysiol 2015*
Study Design

Phase 1 – Biomarker Identification and Screening

Phase 2 – 6-week, randomized, placebo-controlled, flexibly dosed trial of AZD7325
Figure 3. Topographical Locations and Pre- versus Post-Dose Effects of AZD7325 versus Placebo on Resting EEG Spectral Power by Frequency Band in ASD Subjects

a) Delta power at Pz cluster

b) Theta power at POz cluster

c) Alpha power in Fz cluster
d) Beta power in Cz cluster
Initial Results of AZD7325 Trial

- AZD7325 demonstrated predicted target engagement
- EEG effects showed shared and unique effects versus non-selective benzodiazepines
- AZD7325 may have activating effects under conditions of task demand or sensory processing
- Well tolerated
- GABAA target merits further study for optimal dosing and clinical effects
- EEG shows utility as an endpoint
Summary

• Slow progress and failures in ASD intervention development highlight need for improvements
• Multiple strategies to identify targets are valid
• Endpoints can be improved across behavior, cognitive function, and biology to facilitate interpretation
• Strategies to reduce heterogeneity are needed
• Animal models need refinement of social behavior in order to guide drug development
• Results from each well-interrogated target will have important implications for ASD biology and trials
• Optimism for advancements in ASD therapeutics still warranted