Autism Spectrum Disorders: 
Challenges and Opportunities in Medicines Development

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Autism Speaks
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Outline

• Defining the Targets and Unmet Needs Shaping Medicines Development in ASD
• Key Challenges facing Medicines Development in ASD
Clinical Face of Autism
A complex heterogeneity of clinical symptomology and disability.

DSM-IV diagnostic criteria for ASD

Pervasive Developmental Disorders
- 299.00 Autistic Disorder
- 299.80 Pervasive Developmental Disorder - NOS
- 299.80 Asperger’s Disorder
- 299.80 Rett’s Disorder
- 299.10 Childhood Disintegrative Disorder

Clinically relevant co-morbidities:
- Associated psychiatric and neurological conditions.
- Intellectual disability.
- GI disorders, immune dysregulation.

How will DSM-V change things?

299.00 Autistic Disorder (Autism Spectrum Disorder)
- Asperger’s disorder to be subsumed into ASD.
- Childhood disintegrative disorder to be subsumed into ASD.
- PDD-NOS to be subsumed into ASD.

 Syndromes of known etiology excluded:
- e.g. Rett, Fragile X, TSC, or 22q syndromes.
- Clinicians will utilize the specifier, “ASD associated with syndrome X.”

Biology doesn’t care about all this!!
ASD Prevalence

Actively Discussed Drivers Underlying Increase?

- Increased recognition of diagnostic criteria
- Broadening of diagnostic criteria
- Increased awareness
- Improved surveillance
- Increasing parental age
- Unknown environmental factors

Increased demand for **services**.
Increased demand for **research** into cause and prevention.
Increased demand for development of **medical products**.
Understanding the Cost of Autism

Total Annual Cost of Autism Care
$127 B (€95 B)  £34 B (€41 B)

Individual Lifetime Cost of Autism
$1.4 M (€95 M)  £0.9 M (€41 M)

Individual Lifetime Cost of Autism (with Intellectual Disability)
$2.3 M (€1.7 M)  £1.5 M (€1.8 M)
Current Psychotropic Medication Use in ASD

Only two medications have been approved for use in patients with autism.

Intellectual Disability

Core Clinical Features
Associated CNS Symptoms
Somatic Symptoms

Social Deficits
Sleep Deficits
Mood
Anxiety
Attention

Language Impairment
Repetitive Behaviors
Hyperactivity
Tantrums
Self Injury
Aggression

Seizures
GI Disorders
Immune Dysfunction

Approved by FDA: 2006
For use in children ages 5 to 16

Approved by FDA: 2009
For use in children ages 6 to 17
Current Psychotropic Medication Use in ASD

SOC = Off-label pharmacopeia of Rx developed for related (?) indications.

- **Antidepressants**
  - Mechanisms of Action
  - Selective Serotonin Reuptake Inhibition (SSRI):
    - Paroxetine, Sertraline, Fluoxetine, Citalopram

- **Antipsychotics**
  - Mechanisms of Action
  - Dopamine D₂ Receptor Antagonism:
    - Risperidone, Olanzapine, Quetiapine, Ziprasidone
  - Dopamine D₂ Partial Agonism/5-HT₂A Antagonism:
    - Aripiprazole

- **Stimulants/ADHD**
  - Mechanisms of Action
  - Selective Norepinephrine Reuptake Inhibition (NRI):
    - Atomoxetine (Strattera)
  - Non-selective Release of Dopamine:
    - Methylphenidate, Dextroamphetamine, Modafinil

- **Anticonvulsants**
  - Mechanisms of Action
  - Alpha₂Delta1 Calcium Channel Modulation:
    - Gabapentin
  - Sodium Channel Blockade:
    - Lamotrigine, Carbamazepine, Topiramate
  - Unknown:
    - Divalproex sodium (Depakote),

Adapted from Oswald & Sonenklar, 2007
% Comorbid Psychiatric Diagnosis

70.8 Any Disorder
62.8 Any Main Disorder
44.4 Any Emotional Disorder
41.9 Any Anxiety Disorder
29.2 Social Anxiety Disorder (SAD)
10.1 Panic Disorder
8.5 Simple Phobia
8.2 Obsessive-Compulsive Disorder (OCD)
7.9 Agoraphobia
0.5 Separation Anxiety Disorder
1.4 Any Depressive Disorder
0.9 Major Depressive Disorder
0.5 Dysthymic Disorder
30.0 Oppositional or Conduct Disorder
28.1 Oppositional Defiant Disorder
3.2 Conduct Disorder
28.2 Attention-deficit / Hyperactivity Disorder
24.7 Other
11.0 Enuerisis (bedwetting)
9.0 Chronic Tic Disorder
6.6 Encopresis (soiling of clothes)
4.8 Tourette syndrome
3.9 Trichotillomania (hair pulling)

1 Includes: Attention-deficit/hyperactivity disorder, oppositional and conduct conduct disorder.
2 Includes: All anxiety disorders, phobias, and mood disorders.

Simonoff et al 2008
### Opportunity Drivers for Medicines Development

**A clear value proposition for developing biomedical treatments for ASD.**

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<tr>
<th>Category</th>
<th>Details</th>
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<td><strong>Unmet Need</strong></td>
<td>- Lack of evidence supporting efficacy and safety current off-label used agents.</td>
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<td>- Absence of treatments that address the core, and most associated, symptoms.</td>
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<td>- Only two approvals to date, and both are limited by familiar side effect profiles.</td>
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<td><strong>Population Size</strong></td>
<td>- Prevalence rates similar to schizophrenia and Alzheimers. NOT an orphan indication</td>
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<td>- Adult population often not considered in opportunity assumptions, but much larger.</td>
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<td>- Increased expectation for services, demand for new/better treatment options.</td>
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<td><strong>Limited Competition</strong></td>
<td>- Dedicated R&amp;D investment among Pharma/Biotech nascent, but growing.</td>
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<td>- Current pipeline of development activity inadequate to address existing unmet needs.</td>
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<td>- Approvals to date fail to address core symptoms.</td>
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<td><strong>State of the Science</strong></td>
<td>- Genetics have provided construct validity to translational research approaches.</td>
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<td>- Druggable target space has begun to emerge (there are targets).</td>
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<td>- Mechanistic fit of agents developed for other indications with ASD (repositioning ops).</td>
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<td><strong>Available Leverage</strong></td>
<td>- Synergies to realize from historic investments in Psychiatry and Neurology.</td>
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<td>- Foundations taking increased role in de-risking critical parts of value chain.</td>
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<td>- Emerging pre-competitive partnerships (e.g. EU-AIMS)</td>
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# Limitations/Issues with Current Rx Use in ASD

*Insufficient evidence supporting most psychotropic Rx commonly used in ASD.*

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<tr>
<th>Class</th>
<th>Agent</th>
<th>Primary target symptom(s)</th>
<th>Level of evidence</th>
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<td><strong>Alpha 2 Agonist</strong></td>
<td>Clonidine</td>
<td>Hyperactivity</td>
<td>Insufficient evidence</td>
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<td>Guanfacine</td>
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<td>Insufficient evidence</td>
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<td><strong>Antipsychotics</strong></td>
<td>Aripiprazole</td>
<td>Irritability, hyperactivity, stereotypy</td>
<td>Established evidence</td>
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<td>Haloperidol</td>
<td>Behavioral symptoms</td>
<td>Established evidence</td>
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<td>Risperidone</td>
<td>Irritability, hyperactivity</td>
<td>Established evidence</td>
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<td>Risperidone</td>
<td>Repetitive behavior, stereotypy</td>
<td>Preliminary evidence</td>
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<td>Olanzapine</td>
<td>Global functioning</td>
<td>Insufficient evidence</td>
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<td><strong>Mood Stabilizers</strong></td>
<td>Divalproex sodium/valproate</td>
<td>Irritability</td>
<td>Insufficient evidence</td>
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<td></td>
<td>Divalproex sodium/valproate</td>
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<td>Insufficient evidence</td>
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<td>Lamotrigine</td>
<td>Irritability, social behavior</td>
<td>Insufficient evidence</td>
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<td>Levitiracetam</td>
<td>Irritability</td>
<td>Insufficient evidence</td>
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<tr>
<td><strong>Norepinephrine reuptake Inhib</strong></td>
<td>Atomoxetine HCl</td>
<td>Hyperactivity</td>
<td>Preliminary evidence</td>
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<td><strong>SSRI</strong></td>
<td>Citalopram</td>
<td>Repetitive behavior</td>
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<td></td>
<td>Fluoxetine</td>
<td>Repetitive behavior</td>
<td>Insufficient evidence</td>
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<tr>
<td></td>
<td>Clomipramine</td>
<td>Repet behav, stereotypy, irritability, hyperactiv.</td>
<td>Insufficient evidence</td>
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<tr>
<td><strong>Stimulants</strong></td>
<td>Methylphenidate</td>
<td>Hyperactivity</td>
<td>Promising evidence</td>
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<tr>
<td><strong>Miscellaneous</strong></td>
<td>Amantadine</td>
<td>Hyperactivity, irritability</td>
<td>Insufficient evidence</td>
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<td></td>
<td>Naltrexone</td>
<td>Social behavior, communication, learning, SIB</td>
<td>Insufficient evidence</td>
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<tr>
<td></td>
<td>Naltrexone</td>
<td>Hyperactivity</td>
<td>Preliminary evidence</td>
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<tr>
<td></td>
<td>Pentoxifylline</td>
<td>Irritability, social withdrawal</td>
<td>Preliminary evidence</td>
</tr>
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Adapted from Siegel and Beaulieu, 2011

- ≥4 Adequate RCTs, ≥2 separate sites, ≥2 separate research teams OR ≥2 Strong RCTs
- ≥2 Adequate RCTs
- ≥1 Adequate RCTs
- No conclusion: lack of quality research and/or mixed outcomes across several studies
Limitations/Issues with Current Rx Use in ASD

Defining unmet medical need that will shape translation research priorities.

- Evidence of efficacy
- Core symptom domains
- Side effects
- Adjunctive uses with ABA

"Take them until further testing shows they really aren't effective."
### Snapshot of Current ASD Pipeline

*Not good enough.

#### Current Snapshot of Autism Medicines Pipeline

<table>
<thead>
<tr>
<th>Phase 1 (Development)</th>
<th>Phase 2 (Development)</th>
<th>Phase 3 (Development)</th>
<th>Practice (Market)</th>
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</thead>
<tbody>
<tr>
<td>Carbetocin (OxtR)</td>
<td>STX-209 (GABA___)</td>
<td>AFQ056 (mGluR5)</td>
<td>Risperidone *</td>
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<tr>
<td>RG7314 (V1aR)</td>
<td>RG7090 (mGluR5)</td>
<td>STX-209* (GABA__)</td>
<td>Aripiprazole</td>
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<tr>
<td>RG5028442 (???)</td>
<td>Memantine (NMDA?)</td>
<td>CM-AT (Protease Stim)</td>
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<tr>
<td>Lurasidone (D_2, SHT_2a)</td>
<td>NNZ-2566# (IGF1R?)</td>
<td>Fluoxetine (SSRI)</td>
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</tbody>
</table>

#### Snapshots of other product concepts not included:
- Therapeutic Devices
- Diagnostics
- Other ‘wrap around’ products/services.
Challenges facing Medicines Development

Clarifying Clinical Targets (Labels):
Agreement across the field on which targets have the greatest value to patients and caregivers (Alignment).

Outcome Measures:
Lack of validated instruments that measure clinically meaningful effects, are sensitive to change, and are acceptable to regulatory bodies (e.g., FDA, EMA).

Pseudospecificity:
How do we demonstrate the specificity of clinical targets to ASD?

Heterogeneity:
Stratification approaches that reduce clinical heterogeneity, de-risk research investments and improve effectiveness.

Disease Modification:
Is this possible, what would this actually look like, and how would we measure it?

Pediatric vs. Adult development:
Understanding the differences in disability, underlying pathobiology, drug safety and other unique development considerations.

Pediatric vs. Adult development:
Understanding the differences in disability, underlying pathobiology, drug safety and other unique development considerations.
Genetic Etiology(ies) as an Opportunity Driver

Genetics

• **4:1** Bias towards boys
  (Fombonne, 2005; Santangelo & Tsatsanis, 2005)

• **2–8%**: Prevalence among siblings
  (Fombonne, 2005; Muhle, 2004)

• **36–60%**: Concordance among monozygotic twins
  (Bailey, 1995; Folstein & Rutter, 1977)

• **~90%**: Estimated overall heritability of ASD
  (Sousa, 2011)

• **Monogenic disorders** (Fragile X, Rett Syndrome, Tuberous sclerosis)

Miscellaneous

• Advanced paternal age
  (Durkin, 2008; Croen, 2007; Daniels, 2008; Hultman, 2011)

• Low birth weight
  (Pinto-Martin, 2011)
# Genetics Providing Unique Leverage In ASD

## Mouse Models of Human Risk Genes

### Mendelian Syndromes

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<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Syndrome</th>
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<tbody>
<tr>
<td>6q23.3</td>
<td>AHI1</td>
<td>Joubert syndrome</td>
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<tr>
<td>7q35-q36.1</td>
<td>CNTNAP2</td>
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<tr>
<td>9q34.13</td>
<td>TSC1</td>
<td>Tuberous Sclerosis type I.</td>
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<tr>
<td>10q23.31</td>
<td>PTEN</td>
<td>Cowden disease</td>
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<tr>
<td>11q13.4</td>
<td>DHCR7</td>
<td>Smith-Lemli-Opitz syndrome</td>
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<tr>
<td>12p13.33</td>
<td>CACNA1C</td>
<td>Timothy syndrome</td>
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<tr>
<td>15q11.2</td>
<td>UBE3A</td>
<td>Angelman syndrome</td>
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<tr>
<td>16p13.3</td>
<td>TSC2</td>
<td>Tuberous Sclerosis type II</td>
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<tr>
<td>17q11.2</td>
<td>NF1</td>
<td>Neurofibromatosis</td>
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<tr>
<td>Xp21.2</td>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>Xp21.3</td>
<td>ARX</td>
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<tr>
<td>Xq27.3</td>
<td>FMR1</td>
<td>Fragile X syndrome</td>
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<tr>
<td>Xq28</td>
<td>MECP2</td>
<td>Rett Syndrome</td>
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### Rare Variants

<table>
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<tr>
<th>Locus</th>
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<tr>
<td>2p16.3</td>
<td>NRXN1</td>
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<td>3p13</td>
<td>FOXP1</td>
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<td>6q16.3</td>
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<td>16p11.2</td>
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<td>17q11.2</td>
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<td>NLGN4X</td>
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<td>Xq13.1</td>
<td>NLGN3</td>
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### Common Variants

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<td>1q42.2</td>
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<td>7q22.1</td>
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<td>12q14.2</td>
<td>AVPR1A</td>
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<td>17q21.32</td>
<td>ITGB3</td>
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Adapted from Adinger et al Neuron 72, October 20, 2011
Understanding of genetic risk architecture now implicating novel **target space** for drug discovery and opportunities for **clinical diagnostics**.
Biomarkers are the Game-Changer

Mapping the impact on clinical research, development & practice.

- **Preclinical** (Discovery)
- **Phase 1** (Safety/POM)
- **Phase 2** (Proof of Concept)
- **Phase 3** (Pivotal Trials)
- **Market** (Practice)

- Treatment Selection
- Prognostic Classification
- Predictive Classification
- Diagnostic Classification
- Patient Stratification/Enrichment
- Target Engagement
- Dose Selection
- Dose Optimization
- Safety Prediction
- Safety Determination/Monitoring
- eSOE
- Efficacy-Response (Surrogate Endpoint)

- Target ID
- Innovating Discovery
- Reducing the Impact on (De-risking) Clinical Development
- Personalizing Medicine
The Autism Biomarkers Consortium

Eye-Movement

Actigraphy

Neural Imaging

Exploring Utility in Medicines Development

• Patient Stratification
  Which patients are more/less likely to respond?

• Treatment Response
  Did treatment produce a relevant response?

• Diagnosis
  Is there a biological basis for diagnosis?

• Target Engagement
  Did the test drug reach its intended target?
Behavioral Interventions Move Biomarkers Too

Normalization of brain activity (EEG) with behavioral intervention.

Differences in patterns of brain activation in children with typical development, Early Start Denver Model (ESDM) intervention, and community intervention.

Dawson et al, 2012
Leveraging Public-Private Partnerships

European Autism Interventions and Medicines (EU-AIMS)

<table>
<thead>
<tr>
<th>Basic Research</th>
<th>Exploratory</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
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Phases impacted

EU-AIMS: Autism Research in Europe

AGP: Autism Genome Project

A PROGRAM FUNDED BY AUTISM SPEAKS

Leveraging Public-Private Partnerships
Measurement:
Significant need to adapt and develop new measures of outcome and benefit.

Challenges and Concerns:

• Validation:
  Does the instrument measure disease or symptom dimensions it is purported to measure?

• Inter-Rater Reliability:
  Would two independent raters arrive at a similar score for the same patient?

• Intra-Rater Reliability:
  Would the same rater arrive at a similar score for the same patient a different time points?

• Sensitivity to Change:
  Do scores on the instrument change in concordance with scores on other, well established measures?

• FDA Acceptance:
  Would the scale be accepted as a valid and reliable measure by the wider community of physicians who treat the patient population of interest?
Measurement:

Developing a battery of physiological and behavioral assays to derisk new MOAs.

Challenges and Concerns:

• Age-specific validation of in vivo assays and endpoints?
• Sensitivity to change with treatment?
• Can these be used to define Ceff?
• Standardization of training, methods, and equipment across the field.
• Validity Catch 22... No POC, no predictive validity.
• Showing efficacy in altering the developmental emergence of a disease-relevant phenotype.
• Consensus critical path (battery) for a given clinical target?
Measurement:
Efforts to build consensus on endpoints to support medicines development for ASD.

Deliverables:

• Consensus recommendations on validity of current endpoints to support medicines development for 3 labeling concepts in ASD.

• Face-to-face meetings with FDA division of medical products to present consensus statements and obtain feedback.

• 3 Manuscripts describing process and recommendations targeting publication under review.

• Future: Attention, Sleep, GI
Innovative Models for Funding

Working beyond the science to deliver the science.

- Bench: Basic Research, Discovery, Pre-Dev
- Development: Phase 1, Phase 2, Phase 3
- Bedside: Commercialization

Stakeholders:
- Academia/NIH
- Start-Ups / Biotech
- Pharmaceutical Companies

Objectives/Goals:
- Intellectual Property
- Experimental Agents/Prototypes
- Approved Products

Sources of Funding:
- Research Grants
- Venture Capital
- Investment Banks

Translational “Valley of Death”

FDA Approval
Innovative Models for Funding

Working beyond the science to deliver the science.

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**Bench**
- Basic Research
- Discovery
- Pre-Dev

**Development**
- Phase 1
- Phase 2
- Phase 3

**Bedside**
- Commercialization

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**Sources of Funding**
- Research Grants
- Venture Capital
- Investment Banks

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**Translational “Valley of Death”**

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**Venture Philanthropy**

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**FDA Approval**
Thank You . . . . Questions?