Opportunities and Challenges in Drug Discovery for Autism Spectrum Disorders

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LW Fitzgerald Consulting

Tend Therapeutics

GeneticaLens
Autism – Spectrum of disability with significant unmet medical need

Core symptoms
- Social Communication Deficits
- Fixed interests and repetitive behaviors

Adjunct symptoms
- Aggression/irritability
- Anxiety
- Intellectual disability
- Inattention
- Hyperactivity
- Stimulants
  (off-label)

Comorbid illness
- Epilepsy
- Intellectual disability
- Inattention
- Hyperactivity

Medications
- Risperidone (Abilify, FDA approved)
- SSRIs (off-label)
- Stimulants
  (off-label)
- Sleep disorder
# Autism Prevalence (US/UK)

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>Age (y)</th>
<th>M:F</th>
<th>Period</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brick Township, NJ¹</td>
<td>17,792</td>
<td>3-10</td>
<td>2.7:1</td>
<td>1998</td>
<td>0.67% (1/149)</td>
</tr>
<tr>
<td>Metro Atlanta²</td>
<td>289,456</td>
<td>3-10</td>
<td>3.8:1</td>
<td>1996</td>
<td>0.34% (1/294)</td>
</tr>
<tr>
<td>NHIS, US National³</td>
<td>18,885</td>
<td>4-17</td>
<td>3.7:1</td>
<td>2003-4</td>
<td>0.57% (1/175)</td>
</tr>
<tr>
<td>NSCH, US National⁴</td>
<td>79,590</td>
<td>4-17</td>
<td>3.7:1</td>
<td>2003-4</td>
<td>0.55% (1/182)</td>
</tr>
<tr>
<td>Cambridgeshire UK⁵</td>
<td>NA</td>
<td>5-11</td>
<td>4:1</td>
<td>1999</td>
<td>0.57% (1/175)</td>
</tr>
<tr>
<td>South Thames, UK⁶</td>
<td>56,946</td>
<td>9-10</td>
<td>3.3:1</td>
<td>1999-2001</td>
<td>1.16% (1/86)</td>
</tr>
<tr>
<td>CDC ADDM Network⁷</td>
<td>363,749</td>
<td>8</td>
<td>4.5:1</td>
<td>2010</td>
<td>1.47% (1/68)</td>
</tr>
</tbody>
</table>

Autism prevalence – why the trending?

- Estimates regarding the prevalence of autism (and later ASD) have increased exponentially
  - For decades, the prevalence was thought to be 4 to 5 cases per 10,000 children in the US
  - In a 2014 report, CDC network study (covering 2010) resulted in a revised estimate of approximately 1 child in every 68 in the US will have an ASD
  - Approximately 50% will have significant to borderline intellectual disability where as 50% will have average to above average IQ

- Increased prevalence is likely driven by publicity, reduction in stigma, broadening/defining diagnosis (e.g., ID→ASD), public services
Autism is among the most heritable of all neuropsychiatric disorders...some of genetic changes are spontaneous!

Concordance rates
- 82-92% for monozygotic twins; 1-10% for dizygotic twins

Multiple underlying genes
- complex disorder, phenotypic variability
- chromosomal abnormalities
- CNVs - copy number changes (duplication/deletions; e.g., 15q11, 22q13),
- rare single gene mutations - Monogenic syndromic ASDs (FXS, Rett, Angelmans, TSC) and others (Shank3, Pten)
Life time costs of autism

- Life-long costs of ASD
  - $2.4 Million when autism involves ID
  - $1.4 Million when ID not present

- In childhood, majority costs are special education services and loss of income/productivity of parents

- In adult years, it is mostly comprised of residential and supportive services and loss productivity/employment of individual


Neuroscience has a proven commercial track record

Neurologic, Psychiatric, and Ophthalmologic disorders comprise one of the largest global pharmaceutical markets accounting for **$121 billion in sales in 2009**

*Global Neuropharmaceutical Sales by Indication, 2009*

- **Addiction**: $2.4 billion
- **Retinal Disorders**: $2.4 billion
- **Obesity**: $1.0 billion
- **Antipsychotics**:
  - **Strattera** (atomoxetine HCl)
  - **Olanzapine**
- **Pain**:
  - **OxyContin** (oxycodone HCl controlled-release tablets)
- **Antidepressants**:
  - **Prozac** (fluoxetine hydrochloride)
- **Antiepileptics**:
  - **Keppra** (levetiracetam)
- **Antineuroinsensibility**:
  - **Cymbalta** (duloxetine HCl)
- **Anxiolytics**: $5.6 billion
- **Alzheimer’s Disease**: $6.9 billion
- **Multiple Sclerosis**: $9.0 billion
- **Parkinson’s Disease**: $4.4 billion
- **Sleep Disorders**: $4.1 billion
- **Attention Disorders**: $4.0 billion
- **Migraine**: $2.9 billion
- **SOURCE**: NeuroInsights, IMS Health
Serendipity has enabled CNS (Psychiatric) market success

<table>
<thead>
<tr>
<th>Drug</th>
<th>Original use</th>
<th>Psychiatric use</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Bronchodilator</td>
<td>Attention, Obesity</td>
<td>1937</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Epilepsy</td>
<td>Bipolar Mania</td>
<td>2004</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Chemical dyes</td>
<td>Anxiety</td>
<td>1960</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Surgical relaxation</td>
<td>Psychosis</td>
<td>1954</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tuberculosis</td>
<td>Depression</td>
<td>1958</td>
</tr>
<tr>
<td>Lithium</td>
<td>Gout</td>
<td>Mania/BP</td>
<td>1970, 1974</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Preservative</td>
<td>Anxiety/tranquilizer</td>
<td>1950</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Antihypertensive</td>
<td>Psychosis</td>
<td>1954</td>
</tr>
<tr>
<td>Valproate</td>
<td>Epilepsy</td>
<td>Bipolar disorder</td>
<td>1995</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Anesthesia</td>
<td>Tx-resistant Depression</td>
<td>????</td>
</tr>
</tbody>
</table>

It is notable for ASD, despite its incidence, that it has not benefited from serendipity!
…..followed by the emergence of target and structure-based drug discovery

**Pharmacology-inspired**

1946
Diphenhydramine (Benedryl)

1970
Antidepressant activity

1972
Monoamine Uptake Blockade

1987+
SSRIs: Prozac, Zoloft, Paxil
NRIs: Strattera
SNRI: Cymbalta
NSRI: Effexor

**Medchem structure-inspired**

1966
dibenzazepine (TCA antidepressants)

1971
clozapine (first atypical antipsychotic)

1989
clozapine (reintroduced for Tx-resistant psychosis); Pharmacology studied

1990-2000’s
Zyprexa
Risperdal
Geodon
Seroquel
Abilify

Examples of new psychiatric medicines that emerged prospectively from a modern model of disease are quite lacking!

---- since 2007, no new MOA’s approved by FDA only reuptake blockers and atypical APDs
Transition from pharmacology models to disease mechanisms has been difficult – case example, antidepressants

**Reuptake blockers (1980-2000’s)**

- Benadryl

**Experimental Tests:**
1) Measure 5-HT/NE/DE uptake
2) Specific In vivo rodent tests

**Prediction!!**

**Target ID/validation**

**Prediction/Translation**

**New target mechanism (1990’s to present)**
1) CRF
2) Vasopressin
3) 5-HT2
4) Substance P

**Blockbuster Antidepressants**

- Prozac
- Paxil
- Effexor
- Zoloft

**Experimental Tests:**
1) Shift to animal/human translation
2) Modeling disease mechanisms - neurobiology, behavior, genomics

**POM/POC Phase 1/2**

**1980-2000s**

**2000-present**
Drug discovery ecosystem shows a decline in innovation & growing neglect of key disease areas and markets

Sources of capital

Universities, Gov’t
- Knowledge generating centers

Corporate R&D, NGO
- Gov’t, Venture $$
- Private R&D $100B+
- NIH $31B

Pharma, Biotech
- Product/value generating centers

Why?
1980’s
- Poor research model prediction/translation
- Knowledge gaps in biology/medicine
- Soft clinical endpoints, patient heterogeneity
- Inadequate scientific reliability/reproducibility
- Business reasons
  - Organizational turmoil (M&A/restructuring)
  - Risk aversion
  - Misaligned incentives
  - Neglect markets – CNS, Antibiotics
    ✓ 80% world’s patients w/o insurance

2010’s
Drug discovery process and risk mitigating/value creating milestones

Relative Risk

$\$ Invested and Value Created

Target ID/validation

Screening strategy

Hit/Lead ID

Lead Optimization/Candidate ID

Preclinical Dev

Phase 1 Dev

Phase 2/3/registration

Mechanistic link to human disease

IP Generation and FTO

Adequate safety margin for human testing

Adequate PK, Safety and Efficacy in Humans

Molecules with Drug-like properties; Target Candidate Profile

Target Product Profile

Right target?

Right drug/molecule?

Right patient? Right test?
Bridging the knowledge gap – is it Autism’s time?
R&D strategic opportunities

• Tx of adjunct/comorbid illness (e.g., irritability, ID, ADHD, sleep, mood)
  – Ideal candidates do not exacerbate core symptoms
  – Consider combining w behavioral interventions to show benefits
  – Upside: “winning with low hanging fruit”, Downside: low commercial appeal/no differentiated benefit

• Anchor to rare molecular variant, sequentially expand to other mechanistically convergent (similar) disease segments
  – Utilize genomics, systems and mechanistic biology, translatable biomarkers, patients stratification strategies. Examples, proliferative pathways, I/E balance, protein synthesis
  – Upside: “Targeted medicine, strong mechanistic link to etiology of disease; Downside:
    Efficacy limited to rare and narrow segment, potentially expensive drugs

• Utilized systems biology/neurochemical/behavioral approach to tx symptoms
  – Modulators of specific neural circuits that underlie symptoms domains (e.g., OT)
  – Utilize genetic models and natural rodent strains with symptoms that pass face validity
  – Upside: “broader appeal”, tx diverse forms of ASD” Downside: there is no magic bullet
Risperdal ASD Program - limited clinical trial requirements for FDA approval

- Two, 8 week, placebo-controlled trials in children 5-16 who met DMS-IV criteria for autistic disorder (n=101, n=55)
- Primary outcome measure in both studies was the change from baseline to endpoint in the irritability subscale of the ABC (ABC-I).
Key mechanistic frameworks in etiology of ASD

The balance of synapse formation / maturation / elimination
How to maintain E/I balance → optimal fitness?

Balance can be disrupted by gene-defects regulating protein synthesis!

Kelleher and Bear, Cell, 2008.
Candidate drug target of the synapse

Keith and El-Husseini, 2008
Top–down: Integrative and translational approach to target validation and drug discovery

- **Genetic level**
  - *Human*
    - *OXTR* (rs53576, rs2254298, rs2268493 etc)
    - *CD38*
  - *Animal (Prairie voles, Mice, Rats, Sheep...etc)*
    - *OXTR* knockout mice
    - *CD38* knockout mice

- **Neural level**
  - Medial prefrontal (Anterior cingulate)
  - Striatum, Amygdala
  - Hypothalamus
  - Brainstem

- **Behavior level**
  - Social perception
  - Trust, Empathy
  - Ethno-centrism
  - Autism
  - Pair-bonding
  - Parental care
  - Mate-guarding
  - Monogamy

Treatment effect of exogenous oxytocin or its agonist
Genomic analysis

Identification of risk gene (e.g., FMR1)

Define variation of sequence of risk gene (loss, gain, altered function?)

Determine biologic influence of gene variant in cells or network of cells (e.g., primary cells, iPSCs)

Determine genetic effect on in vivo phenotype in rodents (Mouse model)

Confirm altered function/expression of gene and associated pathways in humans

**Bottom up:** Path for building molecular models of disease for ASD from gene variant to validated target

Target ID

- maternal
- paternal

Target validation
Macrocephaly in early ASD and recapitulated in mice with conditional KO of *Pten*

**Brain Size Difference in Human ASD by Age**

**Progressive Macrocephaly and Regional Hypertrophy in the *Pten* Mutant Mice**

Courchesne et al., *Neuron*, 2007

STX209 (r-baclofen) corrects synaptic phenotypes in fmr1 ko mice

R-bac reduces spine density

R-bac reverses excess protein synthesis

R-bac reverses excess AMPA receptor internalization

Henderson et al, 2012
A model for neural development and treatment of Rett Syndrome using human induced pluripotent stem cells

Marchetto et al., Cell, 2010, 143:527-539

Walsh and Hochedlinger, Cell, 2010, 143:499-500
From discrete genetic association to more common targets and pathways

Analysis of GeM mice or human iPSC
Common mechanisms underlying behavioral & physiological phenotypes

Q: Can the rare monogenic forms of ASDs inform how to tx larger segments of patients?

Translational strategy

Bridge to ASD patient segments or endophenotypes with biomarkers, clinical features?

Best targets for aggregating segments of patients
Category and utility of biomarkers

*Biomarker is a laboratory measurement or physiological sign in association with a physiological process of therapeutic or diagnostic value*

- **Target biomarker** – measures physical or biological interaction with the molecular target (PET ligand demonstration of receptor occupancy, measurement of enzyme inhibition);
  - benefits: PK/PD (dose selection), demonstrate target engagement
  - PET ligand, e.g., mGlur5 NAM; CSF levels of drug

- **Mechanistic biomarker** – measures a biological effect presumed to be downstream of molecular target
  - benefits: like target + target-mediated activity,
  - may be change in physiological (blood flow), biochemical (substrate turnover), behavioural (reaction time), genetic (gene expression) or proteomic (composition of protein in tissues/biofluids).
  - qEEG, CSF/plasma markers

- **Outcome/surrogate marker** – impact on pathophysiology that links to clinical efficacy. Opportunity for patient segmentation, predict long-term efficacy
  - protein synthesis (\(^{11}\)C-leucine PET), ERP –EEG, fMRI/DTI, eye gazing etc.
Neural systems involved in the development of social expertise in humans

* A combination of associative & instrumental learning

Schultz, Int J Dev Neurosci 2005
Using outcome & mechanistic biomarkers to bridge the gap from target validation to testing efficacy in humans

ERP/face recognition

Eye tracking

fMRI - amygdala and fusiform gyrus
Key clinical questions for clinical protocol design and testing a new therapeutic

1) MOA - Symptomatic or disease modifying agent?
2) Ideal tx period, subject age and length of trial?
3) Patient selection, e.g., severity of symptoms, presence of ID, or other comorbid illness?
4) What is your primary outcome measure?
5) Conditions of doing the subject ratings?
6) Concerns re: placebo effect?
7) Any objective, validated biomarkers for proof of mechanism, or proof of concept?
Validation of ABC-C for Fragile X

Psychometric Study of the Aberrant Behavior Checklist in Fragile X Syndrome and Implications for Targeted Treatment

Stephanie M. Sansone · Keith F. Widaman · Scott S. Hall · Allan L. Reiss · Amy Lightbody · Walter E. Kaufmann · Elizabeth Berry-Kravis · Ave Lachiewicz · Elaine C. Brown · David Hessl

• ABC-C scale originally validated in the MR/ID population
• Multi-site collaboration examined the psychometric properties for ABC in 630 individuals with FXS, ages 3-25 yrs
• Results supported a 6 factor scale structure with one unchanged (inappropriate speech), 4 modified scales (Irritability, Hyperactivity, Lethargy/withdrawal, Stereotypy), and the additional of one new factor, Social Avoidance
• The new reformulated ABC-C scores based on FXS-specific factor structure may provide outcome measure specificity and sensitivity for FXS clinical trials
Epigenetic Modification of the *FMR1* Gene in Fragile X Syndrome Is Associated with Differential Response to the mGluR5 Antagonist AFQ056

Sébastien Jacquemont,1* Aurore Curie,2* Vincent des Portes,2 Maria Giulia Torrioli,3 Elizabeth Berry-Kravis,4 Randi J. Hagerman,5 Feliciano J. Ramos,6 Kim Cornish,7 Yunsheng He,8 Charles Paulding,8 Giovanni Neri,9 Fei Chen,1,10 Nouchine Hadjikhani,10,11 Danielle Martinet,1 Joanne Meyer,8 Jacques S. Beckmann,1 Karine Delange,2 Amandine Brun,2 Gerald Bussy,2 Fabrizio Gasparini,12 Talita Hilse,13 Annette Floesser,13 Janice Branson,12 Graeme Bilbe,12 Donald Johns,14 Baltazar Gomez-Mancilla14†

Fig. 3. (A and B) A comparison of the effect of AFQ056 and placebo treatments on the change from baseline to day 19 or 20 on the ABC-C score in individual patients with (A) full methylation at the *FMR1* promoter and (B) partial methylation at the *FMR1* promoter. A decrease in ABC-C score indicates an improvement in behavioral symptoms.
Phase 2 results of Arbaclofen in FXS: post-hoc analysis on social withdrawal

Subjects with ABC-Social Withdrawal ≥ 8 at screening, baseline1 & baseline2

<table>
<thead>
<tr>
<th></th>
<th>STX209 (mean ± SD)</th>
<th>Placebo (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-Social Withdrawal</td>
<td>-4.3 ± 6.3</td>
<td>-0.4 ± 7.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Vineland – Socialization (raw)</td>
<td>14.2 ± 19.0</td>
<td>4.6 ± 10.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CGI-I</td>
<td>2.7 ± 1.1</td>
<td>3.5 ± 1.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CGI-S</td>
<td>-1.0 ± 1.1</td>
<td>-0.3 ± 0.9</td>
<td>= 0.01</td>
</tr>
<tr>
<td>Treatment preference (clinician)</td>
<td>63%</td>
<td>19%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Treatment preference (parent)</td>
<td>67%</td>
<td>19%</td>
<td>= 0.001</td>
</tr>
<tr>
<td>Responders (CGI-I = 1 or 2, and ABC-SW improvement ≥ 25%)</td>
<td>42%</td>
<td>7%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ABC-Social Avoidance</td>
<td>-2.1 ± 2.9</td>
<td>0.04 ± 2.9</td>
<td>= 0.011</td>
</tr>
</tbody>
</table>

* Provided by Paul Wang MD, Seaside Therapeutics, GRC meeting June 2012
Mitigating Phase 2 efficacy (PoC) risk in FXS (Seaside, Roche and Novartis)

**Preclinical**
- Loss of function of FMR1
- Increase dendritic protein

**Candidate selection**
- Clinically relevant spine morphology? (spine density, immature spines)
- Target-linked pathophysiology? (AMPA receptors/LTD)
- Clinically Relevant behavioral phenotypes? (seizure, arousal, anxiety? Cognition?)

**Proof of Mechanism**
**Proof of Principle**
- Phase 1B
  - Target/mechanistic biomarker for demonstrating target engagement and picking doses
  - Outcome surrogates links target with correction of pathology and offers segmentation

**Proof of Concept**
- Phase 2A
  - Patient entry criteria/ segmentation
  - Trial design and outcome measures
Neuren’s NNZ-2566 successful in demonstrating clinical benefit in Rett syndrome Phase 2 trial

Highlights:

- Achieved primary endpoint - both dose levels of NNZ-2566 were well tolerated after 28 days of treatment and no safety concerns were identified
- Higher dose (70mg/kg twice daily) exceeded the pre-specified criteria for improvement in core efficacy measures compared with placebo
- The clinical benefit in the trial encompassed core symptoms of Rett syndrome and was observed in both clinician and caregiver assessments
- Meeting with FDA expected in Q1 2015 to discuss further development in Rett syndrome
- Results will enable applications for both Orphan Drug and Breakthrough Therapy designation

Melbourne, Australia, 12 November 2014: Neuren Pharmaceuticals (ASX: NEU) today announced top-line results from its Phase 2 clinical trial in Rett syndrome, which successfully demonstrated clinical benefit from treatment with NNZ-2566. Neuren intends to submit applications to the US Food and Drug Administration (FDA) for both Orphan Drug and Breakthrough Therapy designation. Neuren expects to meet with the FDA in the first quarter of 2015 to discuss the trial results and the requirements for the further development of NNZ-2566 in Rett syndrome.

*ABC-C showed no statistically meaningful effect…only their Rett-specific clinical scale
Our past and present: challenges of science business

- **Biotech/ Pharma model is evolving**
  - Drug discovery is hampered by persistent risk and uncertainty
  - Emergence of virtual biotech/pharma unit with flexible/low cost structure
  - Emergence of flexible risk sharing models of public/private partnership (pharma/bio + gov’t/academia, consortia)
  - Shifting drug discovery risk to VC funded enterprise, partnering at value inflection point (phase 2 and later).
Nonprofit pharma like Mend Therapeutics, a new business model for innovation

MEND is a nonprofit pharmaceutical company that seeks to combat diabetes and its complications globally by promoting prevention and early detection, expanding access to quality medical care, and developing life-changing therapies.
Well Child Lens Autism

**Educate and facilitate communication between all healthcare stakeholders**

- www.wellchildlens.com: more than 600 videos on the symptoms, diagnosis, and treatment of ASD, for parents and pediatric HCPs.

- The Well Line App: interactive mobile app, tracks a child’s development birth to age 3, key developmental milestones, connects parents to the pediatric HCP, reminders about screenings.

**Drive efficient, proper and timely diagnosis**

- The Interactive Modified Checklist for Autism in Toddlers (iM-CHAT): (for children 16 – 30 months) digital, video-enhanced version of the M-CHAT, with instant follow-up, scoring and results.

- Well Visit Video Guide: strategies to prompt critical behaviors in toddlers during a well visit.

- CME Courses: 3 accredited courses

**Enhance office workflow optimization to save time and increase revenues**

- EMR Compatible Clinical Version:
  - Dashboards for each doctor
  - Automatic screening reminders
  - Results in the patient record
  - Streamlines the 3-step process for screening and surveillance
  - Saves staff time and resources
  - Automatic codes, search by specific insurance plans, ensure reimbursements and increase revenues

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**What Does Unusual Pointing Look Like**

- [Watch Video](#)
Summary

**Target ID/validation**
- Develop pathophysiological based models and measure multiple efficacy endpoints that are relevant to symptoms and potential translatable in the clinical setting
  - Build quality, detailed, integrated data sets at cellular, circuit, and animal level
  - Iterate on past findings to understand which observation are robust and reproducible
  - Focus on endpoints that have construct not face validity

- Determine points of convergence for genetic models of ASD to cluster disparate forms of ASD and provide common points of intervention for novel therapeutics
  - Possibilities include convergence inferred at the level of circuit, cell function/signaling, genome/transcriptome
  - Points of convergence will likely be symptoms specific... magic bullets are rare
  - How do we reduce this to practice, re: patient segmentation strategies in the clinic

**Translational Science Planning**
- Develop mechanistic and target biomarker for demonstrating target engagement, understanding PK/PD relationship and projecting human dose
- Develop sensitive efficacy/outcome biomarkers starting with animal modeling
  - Confirm impact on disease mechanism prior to registration trials
  - Provide an opportunity to stratify or enrich patients groups that will respond robustly
  - Be conscious of cost and relative ease to validate in clinical setting
Summary – con’t

Clinical trials
• Need to develop optimal clinical design elements for detecting efficacy of therapeutics on core symptoms of ASD
  o How to segment patients, manage patient heterogeneity (etiology/age/ID, severity of symptoms etc), manage clinical trial error/variance, (e.g., rater bias and error), establish ideal primary outcome measures and QOL instruments?
  o We need to deal with our past, problem of robust placebo effects in psychotherapeutics; consider managing expectancy, use trial design like placebo run-in, ID biomarkers
  o Let’s identify more objective, measurable outcome biomarker/surrogates for efficacy

Discovery/development partnerships
• Form strong multidisciplinary teams between private and public preclinical and clinical scientists to guide preclinical and clinical translational research
  o Utilize cross-institutional, public/private funding mechanisms (NCAT, U grants, NIH Blueprint)
  o Encourage greater investment by NGOs in private discovery/development programs

Other Innovations
  o New business models, e.g., sustainable, product focused nonprofit pharma
  o Consider and study behavioral therapy/drug combinations or synergy
  o Health IT solutions that improve symptom/QoL, or drive earlier diagnosis
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