Range of Mechanisms Relevant to Repositioning

- For novel compounds pursued by small companies as well as those that are “shelved” by industry prior to reaching man – the NIH Blueprint Neurotherapeutics Network

- Explicit programs such as those of NCATS (National Center for Advancing Translational Science) which fund development of compounds that have at least reached Phase 1 and:
  - Are truly “repositioned” for a different indication than that being concurrently pursued by company
  - Have been shelved for further development and are now selected to be pursued for a different indication than originally targeted
  - Have been shelved and can be revisited for original indication with newer methods

- Specific Institute programs such as NIMH RAPID (ketamine example) and FAST where clinical need and/or availability of better tools for relating MOA to domain of effect generate support
Blueprint Neurotherapeutics Network:
Path for Compounds Shelved Before Phase 1

- Medicinal Chemistry
- PK/Tox
- Bioactivity/Efficacy Studies
- Lead Development Team: Principal Investigator and team of industry-seasoned consultants and NIH staff
- Data Management
- Formulation/Manufacturing
- Phase I Clinical Trials

Activities funded through a custom blend of NIH contracts and/or grant award to PI
Integrated with SBIR Mechanism

• Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44)

• Activity Code

• U44 Small Business Innovation Research (SBIR) Cooperative Agreement – Fast-Track

• See more at: http://grants.nih.gov/grants/guide/pa-files/PAR-14-292.html#sthash.WY8JDi1Z.dpuf
Participating NIH Components

NIH Blueprint for Neuroscience Research ([http://neuroscienceblueprint.nih.gov](http://neuroscienceblueprint.nih.gov))
National Institute of Neurological Disorders and Stroke ([NINDS](#))
National Institute on Aging ([NIA](#))
National Institute on Alcohol Abuse and Alcoholism ([NIAAA](#))
_Eunice Kennedy Shriver_ National Institute of Child Health and Human Development ([NICHD](#))
National Institute of Dental and Craniofacial Research ([NIDCR](#))
National Institute on Drug Abuse ([NIDA](#))
National Institute of Mental Health ([NIMH](#))
National Center for Complementary and Integrative Health ([NCCIH formerly NCCAM](#))
NCATS Mission

To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.
Discovering *New Therapeutic Uses* for Existing Molecules Program (*NTU*):

- **Problem**: 80% of drugs that enter clinic never approved
- **Opportunity**: potential for new treatments via ID of new indications for deprioritized investigational drugs
- **Program**: matches investigational agents from pharma deprioritized for lack of efficacy or business reasons with new indication ideas from academia
  - **NIH provides**: template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, oversight
  - **Pharmaceutical partners provides**: compounds, biologics, in kind support, pertinent data
  - **Academic researchers provides**: deep understanding of disease biology, new concepts to test, access to appropriate patient populations
Assets: Criteria for selection

• Mechanism of action for each Agent must be known and selective
• Pharmacokinetics are suitable to explore the mechanism in a new indication
• Phase 1 clinical trial has been completed
• Safety profile is understood
• Pre-clinical and clinical Agent and placebo will be provided for studies
• Availability of data/information for regulatory documents to enable an investigator to file an Investigational New Drug (IND) application
- NCATS/Company MOU executed
- Template collaboration agreements drafted
- Asset information provided by companies for NCATS website

RFA issued; Info on Agents provided

X02 pre-applications submitted

CDA executed, additional info on compounds provided, UH application submitted, and CRA established

Top tier applicants identified

UH2/UH3 and UH3 Apps submitted

UH applications reviewed

Advisory Council

Awards are made

Projects conducted/managed

First contact between applicant and Pharma partner

Finalize milestones

May 12, 2014

July 15, 2014

October 1, 2014

January 16, 2015

March 2015

May 2015

July 2015

2 – 4 years
<table>
<thead>
<tr>
<th>Disease</th>
<th>Academic Partner</th>
<th>Pharma Partner</th>
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<tr>
<td>Acute Myelogenous Leukemia</td>
<td>VCU</td>
<td>AstraZeneca</td>
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<td>Alzheimer’s Disease</td>
<td>Yale</td>
<td>AstraZeneca</td>
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<tr>
<td>Alcoholism</td>
<td>U Rhode Island/NIAAA</td>
<td>Pfizer</td>
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<td>Calcific Aortic Stenosis</td>
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<td>Kennedy Krieger/UWash</td>
<td>Sanofi</td>
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<td>AstraZeneca</td>
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<td>Lymphangioleiomyomatosis</td>
<td>Baylor</td>
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<td>Peripheral Artery Disease</td>
<td>U Virginia</td>
<td>AstraZeneca</td>
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<td>VCU/Pittsburgh</td>
<td>Janssen</td>
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<td>Schizophrenia</td>
<td>Indiana U</td>
<td>Lilly</td>
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<tr>
<td>Schizophrenia</td>
<td>Yale</td>
<td>Pfizer</td>
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<tr>
<td>Type 2 Diabetes</td>
<td>Allegheny Health Network Research</td>
<td>AstraZeneca</td>
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</tbody>
</table>
AZD Example of Repositioning from CA to AD: fyn - a protein tyrosine kinase target

- Oldest citation of Fyn association with AD


Low levels of immunoreactivity were apparent in neurons from both normal and AD brain. However a subset of neurons in AD brain exhibited intense fyn immunoreactivity.
Strittmatter 2012


- Alzheimer amyloid-β oligomer bound to postsynaptic prion protein activates Fyn to impair neurons.

- **Um JW¹, Nygaard HB, Heiss JK, Kostylev MA, Stagi M, Vortmeyer A, Wisniewski T, Gunther EC, Strittmatter SM.**
Proposed Model Based on 2012 Findings

Fyn kinase – Novel target for Alzheimer’s Disease
AZD0530

- Enzyme inhibitor (Fyn kinase)
  - Src tyrosine kinase family member
- Originally developed for cancer
  - There are on-going, non-AstraZeneca sponsored Phase 2b trials in renal, prostate and breast cancer
Yale/ADCS/AstraZeneca

- Repurposing AZD0530 for mild cognitive impairment/early stage Alzheimer’s disease
- Pre-clinical and Phase 1 trial at Yale
  - Pre-clinical mouse efficacy
  - Phase 1 dosing trial
- Phase 2a trial using Alzheimer’s Disease Cooperative Study sites
  - Subjects will be on drug or placebo for 1 year
Animal data published

- Fyn inhibition rescues established memory and synapse loss in Alzheimer mice.
- Kaufman AC¹, Salazar SV, Haas LT, Yang J, Kostylev MA, Jeng AT, Robinson SA, Gunther EC, van Dyck CH, Nygaard HB, Strittmatter SM.
Yale/Pfizer GlyT1 Example

• PF-03463275 Shelved by Pfizer for Schizophrenia but open question on dosimetry related to possible U shaped curve response in Roche’s experience with compound with putative same mechanism

• Study to explore receptor occupancy (RO) vs pharmacodynamic (PD) response showing, to date, that RO much higher than achieved by Roche may be important to pursue

• Data supports new POC study to potentially “rescue” mechanism for field by exploring wider RO range
GlyT1 Uptake Inhibitor Receptor Occupancy vs Dose

**Healthy control**

○ with baseline scan

**Schizophrenia**

× without baseline scan

\[ ID_{50} = 0.28 \pm 0.04 \text{ mg/kg} \]

\[ ID_{50} = 24.4 \pm 3.1 \text{ mg} \]
Overall Summary Supports 40 mg BID

- **PET:** Yielded 66% occupancy
- **Supported by fMRI study** in healthy subjects
  - Plasma level-related reduction of ketamine effects
  - Positive effects in LPFC and on functional connectivity
  - Reduction in positive symptoms
- **Supported by LTP Study** in schizophrenia patients
  - Restores LTP in patient with deficient LTP
How can we increase the impact of NIMH-funded trials?

- Insel and Scolnick, 2006
We learn little from the standard approach to clinical trials

Typical trial design:
- Convenient drug
- Convenient dose
- Small sample size
- Primary outcome is efficacy

Negative results are meaningless
- Dose too low?
- Too few patients?
- Wrong patients?

Positive results often fail confirmation

$2-4M and 5 years lost
Design Trials to test Hypothesis about Drug Target

1. **Show that the drug reaches the target** (e.g., Receptor occupancy)
2. **Show that the drug affects the target** (Target engagement)
   - Does drug change brain function?
   - Is change dose dependent?
   - Is an adequate dose achievable?
3. **Correlate target engagement with domain/clinical signal** (POC)
   - If Yes: target relevance confirmed, continue development
   - If No: target ruled out, focus on a new target
   - Either Way, Results are Informative
FAST Target Selection Criteria: Ideal

- Specific and testable hypothesis✓
- PET ligand to evaluate receptor occupancy✓
- Brain functional target engagement measures (e.g., fMRI, EEG)✓
- Target-selective, CNS penetrant, IND-ready compound✓
- Consider RDoC principles where appropriate✓
FAST-MAS(Mood/Anixety Spectrum): Targets Discussed

- Kappa Opioid Receptor (KOR) - *KOR Antagonists*
- Histamine H3 Receptor - *H3 Antagonists*
- Fatty Acid Amine Hydrolase Enzyme - *FAAH Inhibitors*
- Nociceptin Orphanin FQ Peptide (NOP) Receptor
- Histone Deacetylase - *HDAC Inhibitors*
- Neuroinflammation
- Glycine Transporter Type 1 - *GlyT1 Inhibitors*
**Kappa Opioid Receptor (KOR)**

**Criteria for target selection:**

- ✓ Specific and testable hypothesis
  - Kappa Opioid receptor antagonists activate circuits related to Anhedonia
- ✓ PET ligand to evaluate receptor occupancy
  - Kappa opioid receptor ligand ([¹¹C]-LY2795050)
- ✓ Brain functional target engagement measures
  - fMRI
- ✓ Target-selective, CNS penetrant, IND-ready compound
  - Lilly KOR antagonist compound (LY2456302)
- ✓ Consider RDoC principles where appropriate
### Domains as Therapeutic Targets

#### Draft Research Domain Criteria Matrix

<table>
<thead>
<tr>
<th>Domains/Constructs</th>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Reports</th>
<th>Paradigms</th>
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<td><strong>Negative Valence Systems</strong></td>
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<td>Sustained threat</td>
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<td><strong>Arousal/Modulatory Systems</strong></td>
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FAST-MAS: Role of the Kappa Opioid Receptor in Anhedonia

Compound: Lilly KOR antagonist (LY2456302)

1. 2 weeks, 10 subjects: PET
   - Anhedonia self-report scale
   - Reward learning task performance
   - fMRI measure of reward circuit activation

2. 8 weeks, 90 subjects:
   - Reward learning task performance
   - Anhedonia self-report scale
FAST-Mood /Anxiety Spectrum: First RDoC Clinical Trial

RDoC Study Design Features

- **Inclusion**: enroll patients based on anhedonia measure
  - DSM diagnoses across the mood and anxiety spectrum

- **Outcomes**: capture multiple aspects of anhedonia

- **Regulatory path**: include traditional clinical depression and anxiety measures to explore correlations
• Metabotropic Glutamate Receptors – *mGluR2/3 Agonists*
• Muscarinic Acetylcholine Receptors - *M1/M4 Agonists*
• Neuroinflammation
• Phosphodiesterase-10 enzyme - *PDE10 Inhibitors*
• N-methyl-D-aspartate (NMDA) Receptor Subunit NR2B
• Glycine Transporter 1 – *GlyT1 uptake Inhibitors*
• Nicotinic Receptors
• Synaptic Vesicle Protein 2A - *SV2A Ligand*
Demonstration of Lilly scientists and collaborators that dose of poma used in Phase 3 trials only minimally affected ketamine induced increase of CNS BOLD signal whereas higher acute doses than those used clinically had clear effect (O.M. Doyle PhD, S. De Simoni MSc, A.J. Schwarz PhD, et al, JPET, 2013 for methods and A. J. Schwarz presentation to NIMH, Nov, 2015)

FAST mechanism used to establish multisite US academic center study of consistency of fMRI signal following ketamine – completed and data being prepared for presentation

FAST mechanism to do new chronic study of mGlur2/3 agonist at higher doses to see if robust reversal can be achieved and maintained. *It is unknown whether acute effects of poma on fMRI are maintained upon repeated administration.*

FAST or other funding mechanisms could support new clinical study in schizophrenia at higher doses depending on results
Goal: Test go/no-go hypothesis about the mechanisms of mental health disorders.

1. Fail Fast: test feasibility before a large investment
2. Fail Smart: learn from results, regardless of outcome

Needed:

1. A molecular target implicated in the disorder
2. A target-selective, CNS penetrant compound
3. A target-specific measure of brain function to monitor target engagement

Clinical trials goals:

1. Determine a dose that adequately engages the target
2. Look for correlations between target engagement and clinical outcomes.
Current Status of FAST Studies

• FAST-AS (J. McCracken)
  - AstraZeneca GABA-A α2/α3 selective positive modulator for adult ASD
  - Established distinctive EEG effects from standard BDZs in a population selected with an “abnormal” EEG pattern

• FAST-MAS (A. Krystal)
  - Lilly Kappa Opioid antagonist for Anhedonia
    - Phase 1 PET RO Study
    - Phase 2a POC Study

• FAST-PS (J. Lieberman)
  - Biomarker development of fMRI ketamine challenge completed activity
  - Revisiting mGluR2/3 agonist (pomaglutamated) to establish optimal doses for POC trials
Mechanisms Relevant to Repositioning: Summary

- NIH Blueprint Neurotherapeutics Network
- SBIR – Small Business Innovation Research
- NCATS (National Center for Advancing Translational Science)
  - Are truly “repositioned” for a different indication while still studied
  - Shelved and now selected for different indication than originally targeted
  - Shelved and revisited for original indication with newer methods
- Specific Institute Programs such as FAST where clinical need and/or availability of better tools for relating MOA to domain of effect generate support whether repositioned for new indication or “rescued” for an existing one