The Translational Gap from Basic Neuroscience to Novel Treatments ± Role of Target Validation

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ISCTM, Oct 1, 2013

How Can We be More Successful in Translating from Lab to Clinic?

- Increasing the number and quality of drugs available to treat (CNS) disorders will require advances across the drug discovery and development continuum:
  - Better understanding of disease pathogenesis/pathophysiology
  - **Better validation of drug targets**
  - **Improvements in translational tools and methodologies**
  - Approaches in the clinic to maximize the likelihood that any individual molecule can become a drug:
    µ U H S X U S R V L Q J ´

% of Pharmacologic Targets Validated or Rejected

Adis R & D Database Classification of Classes of Compounds that have at least Entered Phase I

‡>75 Potential Antidepressant Targets

±3 Validated and 3 Rejected

‡ 50 Psychosis/Cognition in SCZ Targets

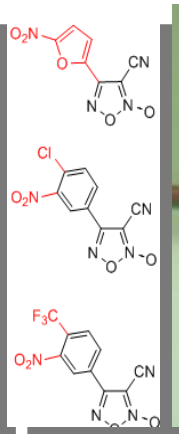
± 1 Validated and 3 Rejected (by Merck)

‡ ! 150 **7 D U J H W V I R U D $ O]**

± 1 Validated and ? Any Rejected

Limited Results Argue for NIH/NIMH Efforts






Disease | Target ID | Assay Dev. | HTS | Probe to Lead | Pre-Clinical | FDA IND | Ph. I | Ph. II | Ph. III | FDA Re-view | CER

Target Validation Space

NIH Supported Basic Research

NIH Molecular Libraries Initiative

TRND

RAID

NIH Clinical Center, CTSAs

HMORN

PCORI

New NIH-FDA Partnerships

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What is a Target?

- In the Brain:
  - Any molecular or structural site of an intervention whether drug, electrical current or whatever
- In the Clinical Realm:
  - Symptom domain associated or not with a specific diagnosis

Research Domain Criteria (RDoC)

- Negative Valence Systems – acute threat (“fear”), potential threat (“anxiety”), sustained threat, loss
- Positive Valence Systems – Approach motivation, responsiveness to reward, reward learning, habit
- Cognitive Systems – attention, perception, working and declarative memory, language behavior
- Systems for Social Processes – facial expresssion ID, affiliation/separation, self & other, social dominance
- Arousal/Modulatory Systems – Arousal & regulation, default readiness, biological rhythms

Domains as Therapeutic Targets

v. 3.3, 01/15/2012	DRAFT RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Facial expression identification								
Affiliation/Separation								
Self & Other								
Social dominance								
Arousal/Modulatory Systems								
Arousal & regulation (multiple)								
Default readiness								
Biological rhythms								

FAST Experimental Medicine Contracts

FAST-AS: Autism Spectrum

- Contractor: UCLA
- Contract-PI: James McCracken, MD

FAST-MAS: Mood and Anxiety Spectrum

- Contractor: Duke University
- Contract-PI: Andrew Krystal, MD

FAST-PS: Psychotic Spectrum

- Contractor: RFMH
- Contract-PI: Jeffrey Lieberman, MD

Components to be Ideally Aligned

- Therapeutic goal/ Target selection
  - Stringent target selection criteria
  - Emphasis on clinical target validation
- Biomarker with Molecule Progression
  - Qualified biomarker associated with target mechanism
  - Sharing biomarker for molecule and therapeutic decision making
  - Clear strategy for use of biomarker: development support or commercial opportunity (companion diagnostic)
- In Vivo Model
  - Mechanism (Pathophysiology?)
  - Animal model that can at least model target mechanism
  - Replicating data across labs
- Proof of Concept (PoC) trial possibilities
  - A well aligned, translatable, pathway to clinical PoC in patients

Goals:

‡ Trials should test a go/no go hypothesis

‡ Fail Fast

‡ Results should be informative regardless of outcome

Strategy:

‡ Focus on early phase trials

‡ Demonstrate target engagement before Phase II

‡ Link target engagement to measures of brain activity

‡ Where possible, align with RDoC principles

Criteria:

‡ Specific and testable hypothesis

‡ Brain functional measures for POC

‡ Target-selective, IND-ready compound available

‡ PET ligand or other measures to inform dose selection

FAST Studies

FAST-AS: Autism Spectrum

‡ EEG validation and proof-of-mechanism study of a GABA-A subtype selective partial agonist in adults with ASD.

FAST-MAS: Mood and Anxiety Spectrum

‡ Two-week KOR antagonist PET receptor occupancy study.

‡ Eight-week KOR antagonist Phase IIa study to asses key neural circuitry related to hedonic response.

FAST-PS: Psychotic Spectrum

‡ Study to evaluate potential imaging biomarkers, using a ketamine challenge procedure, to assess mGluR2/3 target engagement in the brain.

Wider Collaborative Pre-Competitive Effort?

- No single organization or laboratory can prioritize, align and execute studies needed to integrate levels of enquiry
- Biological expertise not enough: physics, **P D W K H P D W L F V , L Q I R U P D W**
- Bring together all interested stakeholders to focus on a question to advance treatment -- ADNI Model

Critical Components…Status & Sources

- Therapeutic concept/ Target selection
  - Lots of Untested and Emerging Possibilities in Public Domain
- Biomarker with Molecule Progression
  - Precompetitive, NIH and Foundation Sponsored Efforts
  - PET ligands variable access and sharing, some proprietary
  - Functional Brain Imaging approaches often involve IP (including academic) and other barriers to implementation
- In Vivo Model Mechanism (Pathophysiology?)
  - Both Academic and Industry Studies not Sufficiently Transparent and Thorough to Allow for Reproducibility and Replication
- Proof of Concept (PoC) trial possibilities
  - Missing Alignment Across Field on What is Validation or Refutation