Rigor, Reproducibility, & Defining Adequate Rationale for Trials

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Overall success rates of Phase II clinical trials of NCEs fall from 28% to 18% (Nat Rev Drug Discov 10, 328–29, 2011)

How to improve clinical trial success rates for DM?
Reproducibility is a Problem

• Bayer validated only 35% of published preclinical studies sampled (Nat Rev Drug Discov 10: 712, 2011)

• Amgen published similar data…

• Journal impact factor doesn’t seem to translate into reliability

• After 30 candidates, backed by preclinical efficacy data, failed in trials, ALS TDI failed to replicate any of the prior mouse results for 70 different compounds

• Matter of design of the preclinical studies

• “failure…to demonstrate efficacy…leads us to conclude that the majority of published effects are most likely measurements of noise…” (Amyotroph Lateral Scler 2008; 9(1):4-15)
Rigor Impacts Effect Size

- Meta-analysis of 29 FK506 studies in stroke models
- “concerns that estimates of effect size might be too high because of factors such as study quality and publication bias”

A call for transparent reporting to optimize the predictive value of preclinical research

Grant applications & publications should report on core parameters of randomization, blinding, sample-size estimation, & data handling; better reporting of studies will lead to rigorous study design

NINDS’ emphasis was on Reporting
NINDS Rigor Guidelines

• Experimental Design
  • Rationale for the selected models & endpoints; adequacy of the controls; route & timing of delivery/dosing; powering; stats methodology

• Minimizing Bias
  • Methods of blinding; randomization and/or stratification; reporting of missing data; reporting all results

• Results
  • Independent validation/replication; dose-response; robustness & reproducibility; validation of target engagement/modulation

• Interpretation of Results
  • Alternative interpretations; validation from other literature; size of effect re expected clinical impact; potential COIs
New NIH Rigor Requirements

As of 1/25/2016—all NIH applications must address:

1. the scientific premise forming the basis of the proposed research;

2. rigorous experimental design for robust and unbiased results;

3. consideration of relevant biological variables; and

4. authentication of key biological and/or chemical resources.
A 3-Stage Model for Preclinical Efficacy Studies

1. Pilot Study (discovery focus)
   - Initial testing of cmpd/biologic
   - But, recognize these studies can carry unintentional biases

2. Exploratory Preclinical Study (mechanism/target focus)*
   - Efficacy via multiple outcomes

3. Preclinical Trial (cmpd/biologic focus)*
   - Efficacy via predetermined primary outcome, multiple models/large models when possible
   - Gold standard

*Credit: Howard Fillit
ADDF

*randomized, blinded, clinically relevant design
Challenge: Boost clinical trial success rate

Means to an End: Unbiased examination of all aspects of the rationale / scientific premise behind each clinical trial (basic biology to supporting clinical data)
Therapeutic Pipeline: Stage-Specific Activities

Basic Research
- discover relevant gene/mRNA/protein & what it does

Basic/Mechanistic
- learn how gene/mRNA/protein causes NMD; ID drug targets

Preclinical Development
- assays & models; evaluate targets & candidate therapies for safety & efficacy in cells & animal models

Clinical Studies & Trials
- trial readiness (registries, natural history, endpoints, biomarkers, care standards, etc.); run safety/efficacy trials
Seeking Scientific Premise: Starting with the Basic Science

Target ID?
Is there a basic understanding of the biology of the involved gene, RNA, &/or protein?
Do we truly understand the disease mechanism?
Or is a non-disease-mitigating/ancillary event being addressed?
Seeking Scientific Premise: Non-Clinical Triaging

Optimization?
Efficacy; is preclinical POC established? Rigor?
Appropriateness of endpoints?
Delivery route appropriate?
Bioavailability, exposure, PD/PK?
Non-clinical program—tox liabilities?
Kill early attitude!
Seeking Scientific Premise: Clinical Premise Validation


FDA NDA or BLA

Clinical Studies & Trials
Keeping the DM Pipeline Sludge-Free

- **Basic Research**
  - truly understand basic mechanisms; funding, recruiting/retaining talent, & ‘facilitated’ luck

- **Basic/Mechanistic**
  - no ‘translation before it’s time;’ rigor & rationale; clear go/no-go’s

- **Preclinical Development**
  - partnering

- **Clinical Studies & Trials**
  - premise; trial readiness; equipoise; CDEs: early hard data decisions: stage-appropriate conclusions

• Optimizing the pipeline: academic—advocacy—Federal funder—drug developer partnering…
Path to Informed Trials

*Goal:* collectively obtain **adequate** scientific rationale to launch clinical trials & improve on generally poor success rates of those trials

**Adequate** = conducted using best practices to be sufficiently rigorous and well informed

Improving how we make **unbiased** decisions via robust preclinical & clinical evaluation systems