Rigor, Reproducibility, & Defining Adequate Rationale for Trials

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Care and a Cure

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Translational Success?

Overall success rates of Phase II clinical trials of NCEs fall from 28% to 18%

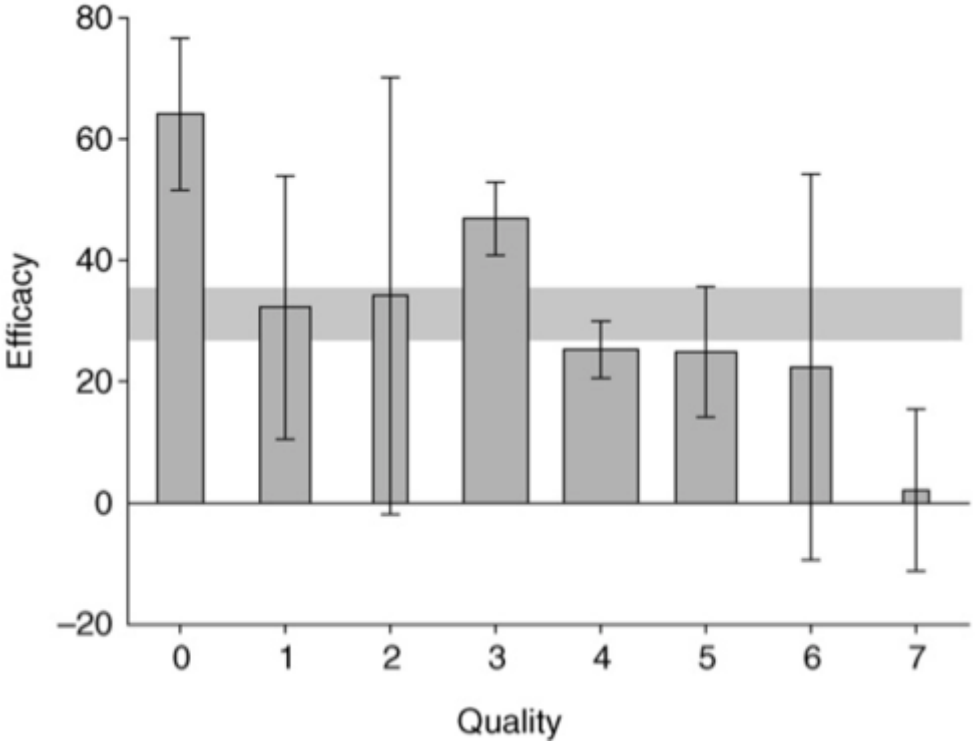
(*Nat Rev Drug Discov* 10, 328–29, 2011)

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



Macleod et al., *J Cereb Blood Flow Metab* 25: 713-21, 2005

- 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"

PERSPECTIVE

Landis et al., *Nature* 490: 187-91, 2012

doi:10.1038/nature11556

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

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

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

* randomized, blinded, clinically relevant design

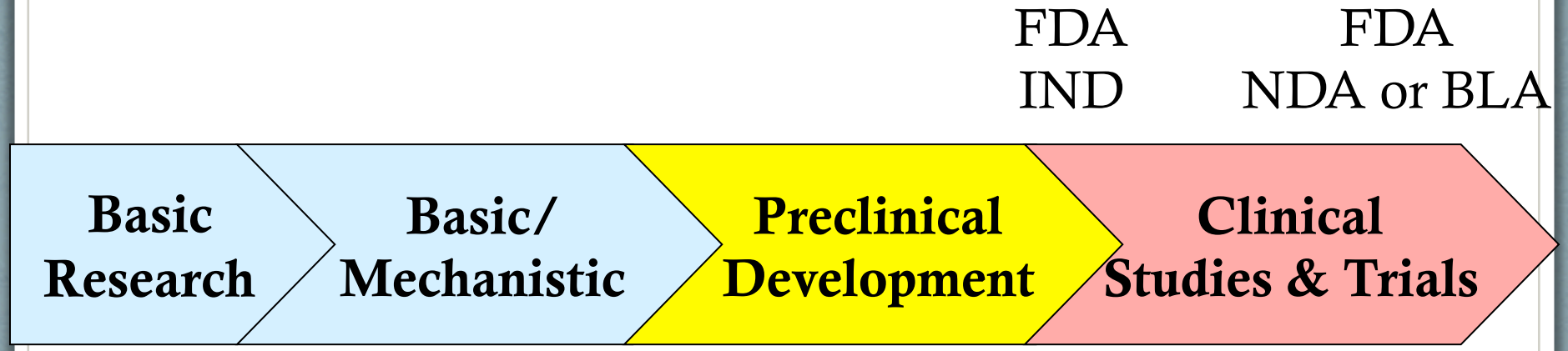
*Credit: Howard Fillit ADDF

Desperately Seeking Scientific Premise

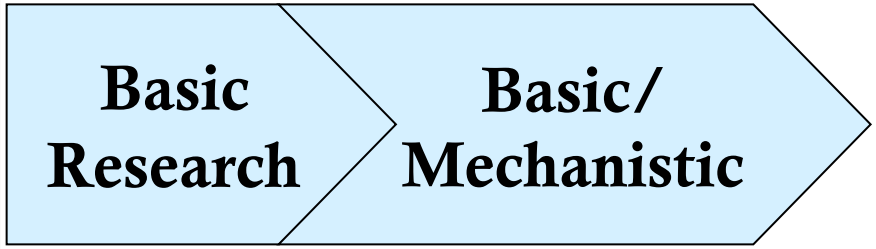
Challenge: Boost clinical trial success rate

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



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!

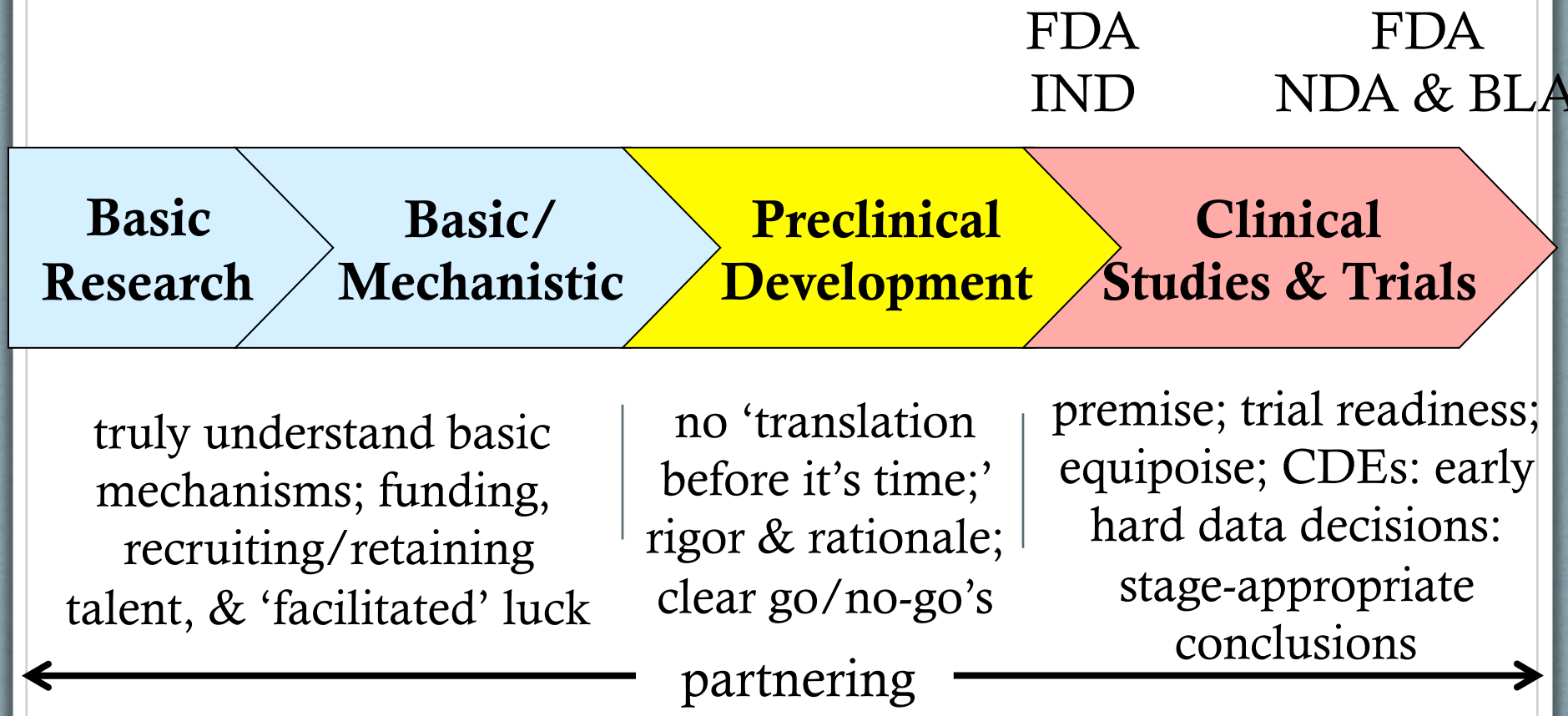
Seeking Scientific Premise: Clinical Premise Validation

FDA
NDA or BLA

Clinical Studies & Trials

Natural history sufficient—modifiable endpoints in place & variability understood? Risk/benefit assessments? Biomarkers?
Early PK/PD assessments?
POC at early stage?
Prior experience with drug / pathway in pts?
Kill early attitude!

Keeping the DM Pipeline Sludge-Free



- 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