Using preclinical data to inform clinical trials: Scientific premise

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Using preclinical data to inform clinical trials: Scientific premise and safety

1. Reproducibility, scientific rigor of design, and transparency in reporting (*Wendy*)

2. Non-clinical prerequisites for clinical studies with an emphasis on FDA requirements (*Dietrich*)
Disclosures

• I am a full time employee of Janssen Research and Development / Johnson and Johnson

• This presentation will not include information on unlabeled use of any commercial products or investigational use that is not yet approved for any purpose
Outline

• Challenges in translating preclinical findings to novel therapies

• Reproducibility in preclinical studies
  – Scientific rigor of study design and conduct
  – Transparency in reporting

• Efforts to address concerns in preclinical (and clinical) studies
Challenges in translating preclinical findings to novel therapies
New Alzheimer’s treatment fully restores memory function

TIME
This Alzheimer’s Breakthrough Could Be a Game Changer

Study hints at possible Alzheimer’s cure

The Telegraph
Has Stanford University found a cure for Alzheimer's disease
Has Stanford University found a cure for Alzheimer's disease? This Alzheimer's Breakthrough Could Be a Game Changer.
### Disease Modifying Therapies: Recent Negative Trials in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Evidence of neuroprotection from preclinical studies</th>
<th>Evidence of neuroprotection from clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasagiline</td>
<td>Antioxidant Monoamine oxidase inhibitor Antiapoptotic</td>
<td>Protects DA neurons in MPTP and 6-OHDA models of PD</td>
<td>Inconclusive: 1 mg rasagiline demonstrated significant effects that were not repeated at 2 mg (Class 1b evidence) Small change in UPDRS scores made results difficult to interpret</td>
</tr>
<tr>
<td>Creatine</td>
<td>Antioxidant Improves mitochondrial bioenergetics</td>
<td>Protects DA neurons in MPTP and 6-OHDA models of PD</td>
<td>Trial involving 1,741 patients terminated early owing to lack of efficacy (Class 1b)</td>
</tr>
<tr>
<td>Ubiquinone (coenzyme Q₁₀)</td>
<td>Antioxidant Electron carrier for mitochondrial complex I and II</td>
<td>Protects DA neurons in MPTP mouse model¹²¹ Delayed progression of PD and nonsignificant improvement in UPDRS scores in an earlier phase II study¹²²</td>
<td>Trial terminated due to lack of efficacy over placebo (Class 1b)¹⁹³</td>
</tr>
<tr>
<td>PYM50028 (Cogane™, Phytopharm, UK)</td>
<td>Promotes release of GDNF and BDNF</td>
<td>Reverses MPP⁺-induced neuronal atrophy in mesencephalic neurons in vitro¹⁸⁴ Protects DA neurons in MPTP models of PD¹³⁴</td>
<td>Trial halted: no benefit over placebo (Class 1b)¹⁹⁵</td>
</tr>
<tr>
<td>Mitoquinone (MitoQ)</td>
<td>Antioxidant Enhances mitochondrial bioenergetics</td>
<td>Protects DA neurons from MPTP-induced and 6-OHDA-induced toxicity¹⁹⁶</td>
<td>No benefit over placebo; study had small sample size and the drug might not have had adequate levels of brain penetration (Class 2b)¹⁹⁷</td>
</tr>
<tr>
<td>TCH346</td>
<td>Anti-apoptotic</td>
<td>Protects DA neurons in vitro and in an MPTP model²⁸</td>
<td>No significant effect (Class 1b)²⁸</td>
</tr>
<tr>
<td>CERE-120 (AAV-neurturin)</td>
<td>Trophic factor GDNF analogue</td>
<td>GDNF protects DA neurons in vitro and in mouse and nonhuman primate models of PD¹³⁸ Intraputaminal injection superior to sham surgery in a previous RCT¹³⁸</td>
<td>Intraputaminal and SNpc injection showed no statistically significant efficacy on the primary end point (change in MDS-UPDRS Part III subscore in the practically defined ‘off’ state; Class 2c) ‘Off’ periods in self-reported motor diaries (secondary end point) did improve significantly (Class 2c)¹⁹⁹</td>
</tr>
</tbody>
</table>

Athauda and Flotynie, Nat Rev Neurol, 2015
Reasons for lack of translation: Mechanisms and models

• Disease mechanisms poorly understood
  – Relevance of mechanism in model to mechanism in human disease? (*e.g.*, *MPTP*)
  – Is the target appropriate for the human disease?

• Animal models do not recapitulate human disease
  – Progressive course
  – Clinical and pathologic features of disease
Reasons for lack of translation: Drug properties

• Does the intervention get to the target?
• Does it engage the target?
• At a sufficient concentration?
• In a biologically active form?
• Is the dosage sufficient?
• What is the toxicity?
• What is the maximum tolerated dosage?
Reasons for lack of translation: Lack of reproducibility

• Preclinical study design
• Lack of transparency in reporting / publication of results
Should clinicians care about preclinical animal research?

Neurologists participate in therapy development efforts by conducting preclinical research, designing and executing clinical research, or referring patients to clinical trials. In these endeavors, clinicians need to trust that the rationale for moving into the clinical translation phase is sound. It is not surprising, therefore, that the community relies on peer review to ensure that published studies were conducted rigorously, and that the conclusions are supported by high-quality data. But here lies the problem. Numerous recent articles have underscored the fact that many preclinical studies do not provide key information on experimental design, conduct, and data analysis. This raises 2 questions: How feasible is it for reviewers, journal editors, or readers to identify methodologic flaws? How can the neurologic community critically evaluate claims made in studies that do not report key methodologic parameters?
Reproducibility in preclinical studies: Design and reporting
The problem

firm Amgen in Thousand Oaks, California, tried to confirm published findings related to that work. Fifty-three papers were deemed ‘landmark’ studies (see ‘Reproducibility of research findings’). It was acknowledged from the outset that some of the data might not hold up, because papers were deliberately selected that described something completely new, such as fresh approaches to targeting cancers or alternative clinical uses for existing therapeutics. Nevertheless, scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result.
Preclinical studies: Factors contributing to lack of reproducibility

- Insufficient training of researchers in experimental design
- Increased emphasis on making provocative statements rather than presenting technical details
  - Over-interpretation of creative “hypothesis-generating” experiments
- Publications lack information on basic elements of experimental design

Collins and Tabak, Nature, 2014
Preclinical studies: Critical considerations

- Lack of publication of negative data
- Limited publications on limitations / scientific flaws of published results
- Difficult to access unpublished data

Collins and Tabak, Nature, 2014
NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.
Design of preclinical studies: Critical elements

- Blinding
- Randomization
- Replication
- Sample size calculation
- Effect of sex differences

Collins and Tabak, Nature, 2014
Preclinical Methodology

Figure 1. Methodological Quality of Animal Trials (n=76)

- Quality Criteria
- Dose-Response
- Clinical Outcomes
- Long-term Outcomes
- Disease Spectrum
- Physiological Monitoring
- Safety Outcomes
- Optimal Time Window
- Blinding
- Adjusted for Multiplicity
- Randomization

- 7 leading scientific journals
- >500 citations
- Published between 1980-2000

DG Hackam, JAMA, 296:1731-2, 2006
Efforts to address lack of reproducibility, lack of transparency, and methodological issues in preclinical studies
A call for transparent reporting to optimize the predictive value of preclinical research

3-Page reporting checklist

Nature, April 2015

Reporting Checklist For Life Sciences Articles

This checklist is used to ensure good reporting standards and to improve the reproducibility of published results. For more information, please read Reporting Life Sciences Research.

▶ Figure legends

☐ Check here to confirm that the following information is available in all relevant figure legends (or Methods section if too long):

• the exact sample size (n) for each experimental group/condition, given as a number, not a range;

• a description of the sample collection allowing the reader to understand whether the samples represent technical or biological replicates (including how many animals, litters, culture, etc.);

• a statement of how many times the experiment shown was replicated in the laboratory;

• definitions of statistical methods and measures: (For small sample sizes (n<5) descriptive statistics are not appropriate, instead plot individual data points)
  ○ very common tests, such as t-test, simple \( \chi^2 \) tests, Wilcoxon and Mann-Whitney tests, can be unambiguously identified by name only, but more complex techniques should be described in the methods section;
  ○ are tests one-sided or two-sided?
  ○ are there adjustments for multiple comparisons?
  ○ statistical test results, e.g., \( P \) values;
  ○ definition of ‘center values’ as median or mean;
  ○ definition of error bars as s.d. or s.e.m. or c.i.
Rigor and Reproducibility

Scientific rigor and transparency in conducting biomedical research is key to the successful application of knowledge toward improving health outcomes. The information provided on this website is designed to assist the extramural community in addressing rigor and transparency in NIH grant applications and progress reports.

On This Page:

- Goals
- Guidance: Rigor and Reproducibility in Grant Applications
- Resources
- News
- References

Goals

The NIH strives to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science. Updates to grant applications instructions and reviewer training are intended to:

http://grants.nih.gov/reproducibility/index.htm
NOT-OD-15-103

Enhancing reproducibility through rigor and transparency

• Issued June 9, 2015

• Revised application instructions / review criteria to enhance reproducibility of research findings through increased scientific rigor and transparency

• To take effect for applications with receipt dates beginning January 25, 2016
Four areas for enhancing rigor and transparency

• Scientific premise
  – Consideration of the strengths and weaknesses of published research or preliminary data supporting the application

• Rigorous experimental design and methods
  – How will they achieve robust and unbiased results

• Consideration of relevant biological variables (e.g., sex)
  – Factor into both design and analysis

• Methods to ensure identity and validity of key biological and/or chemical resources used in the proposed studies
  – Cell lines, specialty chemicals, antibodies
Improving the quality of NINDS-supported preclinical and clinical research through rigorous study design and transparent reporting

- **Experimental design**
  - Rationale for models and endpoints; sample size justification; adequacy of controls; statistical methods

- **Minimizing bias**
  - Blinding, randomization, missing data, reporting +/- results

- **Results**
  - Independent replication; target engagement

- **Interpretation of results**
  - Alternative interpretations
NINDS clinical trial funding announcements

• Ensure that the data supporting the proposed clinical trial are referenced and meet the NINDS scientific rigor guidelines

• Preclinical data used to support the rationale for the study will be evaluated for
  – Scientific rigor of the experimental design
  – Strategies used to minimize bias
  – Robustness and reproducibility of the results
  – Consideration of alternative interpretations
Rigor and reproducibility in NIH applications: Resource chart

<table>
<thead>
<tr>
<th>4 AREAS OF FOCUS</th>
<th>WHAT DOES IT MEAN?</th>
<th>WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Premise</td>
<td>The scientific premise for an application is the research that is used to form the basis of the proposed research question(s). Describe the general strengths and weaknesses of the prior research being cited as crucial to support the application. Consider discussing the rigor of previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources. *See related FAQs, blog post</td>
<td>Research Strategy ➔ Significance</td>
</tr>
<tr>
<td>Scientific Rigor (Design)</td>
<td>Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog post, examples from obits</td>
<td>Research Strategy ➔ Approach</td>
</tr>
<tr>
<td>Biological Variables</td>
<td>Biological variables, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response. Explain how relevant biological variables, such as the ones noted above, are factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data or other relevant considerations must be provided for applications proposing to study only one sex. *See related FAQs, blog post, article</td>
<td>Research Strategy ➔ Approach</td>
</tr>
<tr>
<td>Authentication</td>
<td>Key biological and/or chemical resources include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not be generated with NIH funds and: • may differ from laboratory to laboratory or over time; • may have qualities and/or qualifications that could influence the research data; • are integral to the proposed research. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post</td>
<td>Other Research Plan Section ➔ Include as an attachment, Do not include in the Research Strategy.</td>
</tr>
</tbody>
</table>
NINDS clinical trial funding and

- Ensure that the data supporting the proposed clinical trial are referenced and meet the NINDS scientific rigor guidelines.

- Preclinical data used to support the rationale for the study will be evaluated for:
  - Scientific rigor of the experimental design
  - Strategies used to minimize bias
  - Robustness and reproducibility of the results
  - Consideration of alternative interpretations

Should clinicians care about preclinical animal research? YES!
Summary

Using preclinical data to inform clinical trials

- Improve scientific rigor in preclinical studies
- Increase transparency in reporting
- Improve reproducibility
- Permit critical assessment of scientific findings
  - Is the study designed appropriately (rigor)?
  - Has bias been minimized?
  - Have the results been replicated?
  - Have alternative interpretations been considered?
Thank you