Improving the Rigor, Reproducibility and Predictive Validity of Preclinical Research for Alzheimer’s Disease

-Alzheimer’s Preclinical Efficacy Testing Database, AlzPED-

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NIA Webinar:
Increasing Research Rigor, Reproducibility and Translatability
October 26, 2020
What is Preclinical Research?

In therapy development **preclinical research** is the stage of research that begins before clinical trials can begin, and during which important iterative testing, feasibility, **efficacy in disease models**, and drug safety data is collected.

**Preclinical Research**
- Target identification/validation
- Lead identification/optimization
- PK-PD/ADME

*Therapeutic Agent Efficacy in a Disease Model*
- Toxicity in Rodents, Canines, NHP

Translation to the clinic is often dependent on the predictive validity of preclinical studies.

**Clinical Trials**
- Safety and
- Efficacy in Humans
What is Predictive Validity?

• How well an animal model successfully discriminates between successful and unsuccessful treatments for the human disease condition.

• How well does the candidate drug testing performed in animal models translate into the clinic.

• Predictive Validity is also known as Translational Validity.
Preclinical to Clinical Translation Gap

- More than 300 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models.

- This success has not translated to success in the clinic. In fact, none of these agents have been advanced to the FDA for approval to market as an effective disease modifying therapy for AD.

- High rate of attrition of AD drug candidates in Phase II (92%) and Phase III (98%) with more than half failing due to lack of efficacy.

- From 2002 to 2012, 244 drug candidates were tested in 413 clinical trials (Ph I - Ph III) only one (memantine) received FDA approval (approval rate of 0.4%; >99% attrition)

- There have been no new FDA approved drugs for treatment of AD since 2003.

  Cummings et al., Alzheimer's Research & Therapy 2014, Cummings et al., Alzheimer’s & Dementia 2018

Zahs & Ashe, Trends in Neurosciences, 2010
TIME

This Alzheimer’s Breakthrough Could Be a Game Changer

Mouse study hints at possible Alzheimer’s cure

The Telegraph

Has Stanford University found a cure for Alzheimer's disease
Factors Contributing to Poor Translation of Preclinical Efficacy Testing

- The AD animal models do not accurately recapitulate human AD.
- Lack of reliable preclinical biomarkers that translate to the clinic.
- Failure to match outcome measures used in clinical studies.
- Lack of standardization and rigor in study design and analysis of data.
- Publication bias due to under reporting of negative results in the literature.
- Poor reproducibility of published data.

Shineman et. al., Alzheimer’s Research & Therapy, 2011
Scientific Rigor in Study Design is Lacking in Preclinical Efficacy Studies

(Including those published in high impact journals)

- Data from 76 animal studies published between 1980-2000 in 7 leading scientific journals (Science, Nature, Cell, Nature Medicine, Nature Genetics, Nature Immunology and Nature Biotechnology).

- Median citation count of 889 (range of 639-2233 citations).

DG Hackam, JAMA, 296:1731-2, 2006
Overarching Goal: Formulate a blueprint for an integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms of Alzheimer’s disease.

NIH AD Summits:
Recommendations Aimed at Increasing the Predictive Validity of Preclinical Studies in AD Animal Models

• Identify consensus experimental design elements and best practices and incorporate them into study design guidelines for preclinical studies in AD animal models.

• Develop a publicly available database that serves as a knowledge platform for data sharing, mining and analysis relating to the preclinical testing of candidate therapeutic agents in AD animal models.

• The database should help identify critical experimental design elements and methodology missing from studies, making them susceptible to misinterpretation and reducing their rigor, reproducibility and translational value.

• The database of preclinical efficacy studies that houses experimental designs and analyses of positive and negative data to overcome publication bias
Recommendations: Best Practices and Study Guidelines for Preclinical Animal Studies

• Power Analysis/Sample Size
• Statistical Analysis Plan
• Inclusion/Exclusion Criteria
• Randomization
• Blinding (treatment allocation and outcome measures)
• Balance for Gender
• Report Age of Animals
• Report details of Strain, Housing, Diet
• Employ translatable biomarkers as key measures
• Use PK/PD, ADME to Characterize Candidate Therapeutic Agents
• Report Toxicology Measures
• Report Potential Conflicts of Interest

• Develop a Publicly Available Database of Preclinical Efficacy Studies (Similar to Clinical Trials.gov.)

Common Critical Elements of Clinical Trial Study Design
NIA Response to Recommendations

Recommendations Aimed at Increasing Predictive Power of Preclinical Testing in AD Animal Models:

1. House experimental details relating to the preclinical testing of candidate therapeutic agents in AD animal models.

2. Identify critical elements of design and methodology missing from studies.

3. House experimental details of positive and negative data to overcome publication bias.

https://alzped.nia.nih.gov
Scope and Capabilities

- Provide researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the elements of rigorous study design and requirements for transparent reporting – hosts curated summaries from 1,030 preclinical efficacy studies published between 1996 and 2019.

- Influence the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.

- Provide search capability across relevant translational criteria data sets and external databases:
  - Therapy Type (14 Therapy Types)
  - Therapeutic Agent (890 Therapeutic Agents)
  - Therapeutic Target (173 Therapeutic Targets)
  - Animal Model (188 Animal Models)
  - Principal Investigator
  - Funding Source
  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and Drug Bank)
  - Therapeutic Targets (Open Targets and Pharos)
  - Animal Model (Alzforum)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Related Patents (Google Patents and USPTO)

- Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.

- Provide a platform for creating citable reports/preprints of unpublished studies, including studies with negative data.

- Report on the rigor of each study by summarizing the elements of experimental design.
AlzPED Catalogues **890 Therapeutic Agents and 173 Therapeutic Targets**

Graphs show the diverse types of therapeutic agents and therapeutic targets tested. Data presented as percentages from 1030 published preclinical studies curated to AlzPED.
6 animal species, 41 animal model types and 188 AD animal models are utilized in preclinical efficacy studies. Data presented as percentages calculated from 1030 published preclinical studies curated to AlzPED.
AlzPED Catalogues 21 Major Outcome Measures

Each curated study provides an individual snapshot of the measures tested and outcomes achieved in response to the therapeutic agent tested. AlzPED defines 21 different outcome measures. Data presented as percentage reported, calculated from 1030 published preclinical studies curated to AlzPED.
Published data is extracted from the scientific literature and curated in these 5 categories – bibliographic, therapeutic, animal model, experimental design and outcomes.

Unpublished data (positive and negative data) will be obtained directly from researchers. A citable D.O.I. will be generated for an accepted study. A downloadable PDF will be hosted on the AD Knowledge Portal.
Sample of a Curated Record on AlzPED

**Begacstat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer’s disease.**

**Experimental Design**

<table>
<thead>
<tr>
<th>Is the following information reported in the study?</th>
</tr>
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<tr>
<td>✓ Power/Sample Size Calculation</td>
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<td>✓ ADME Measures</td>
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<td>✓ Route of Delivery</td>
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<tr>
<td>✓ Duration of Treatment</td>
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<tr>
<td>✓ Frequency of Administration</td>
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<tr>
<td>✓ Age of Animal at the beginning of Treatment</td>
</tr>
<tr>
<td>✓ Age of Animal at the End of Treatment</td>
</tr>
<tr>
<td>✓ Sex as a Biological Variable</td>
</tr>
<tr>
<td>✓ Number of Perioperative Deaths</td>
</tr>
<tr>
<td>✓ Study Balanced for Sex as a Biological Variable</td>
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<tr>
<td>✓ Number of Excluded Animals</td>
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<tr>
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**Therapeutic Agent**

| Therapy Type: Small Molecule                      |
| Therapeutic Agent: GSI-953 (Begacstat)            |
| Published: PubMed, PubChem, ClinicalTrials, Patents |
| Therapeutic Target: Gamma secretase                |
| Open Targets, Pharos                              |

**Animal Model**

| Model Information:                                  |
| Species: Mouse                                      |
| Model Type: APP                                     |
| Model Name: Tg5276 ALZF01UM                        |
| Strain/Generic Background: Not Reported             |

| Species: Rat                                       |
| Model Type: Non-transgenic                         |
| Strain/Generic Background: Sprague-Dawley          |

| Species: Dog                                       |
| Model Type: Non-transgenic                         |
| Strain/Generic Background: Not Reported             |

**Outcomes**

<table>
<thead>
<tr>
<th>Outcome Measured</th>
<th>Outcome Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Contextual floor conditioning, open-field exploration, spontaneous alternation, object recognition, elevated plus maze, elevated zero maze, novelty suppressed feeding, Y-maze</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Aβ plaque density, Aβ deposition, APP cleavage, tau phosphorylation, neurodegeneration, neuroinflammation, synapse density, microglial activation</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Oral bioavailability, plasma half-life, clearance, metabolism, excretion, distribution, tissue distribution time, area under the curve</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Target engagement, drug biopharmaceutical profile, PK/PD relationship</td>
</tr>
<tr>
<td>Toxicology</td>
<td>Toxicity, genotoxicity, immunotoxicity, reproductive toxicity, carcinogenicity, teratogenicity</td>
</tr>
</tbody>
</table>

**Bibliographic**

- **Year of Publication:** 2000
- **Contact PI Name:** J Steven Jacobsen
- **Contact PI Affiliation:** Wyeth Research, Departments of Discovery Neuroscience
- **Co-Authors:** Robert L. Matzke, Hua Zhou, Kevin Archon, Thomas Comery, Jane Z. Xu, Kenyi Huang, Xiaohai Dong, Mei Jin, Anthony Knef, Boyd Harrison, et al
- **Primary Reference (PubMed ID):** 199719053
- **Funding Source:** Wyeth Research

**Study Goal and Principal Findings:**

Gamma secretase is widely regarded as a viable target to achieve therapeutically relevant reductions of $A_b$ in AD and multiple classes of GSIs have been reported including peptidomimetics and sulfonamides. The goal of this study was to report on the pharmacological properties of the novel thiophene sulfonamide gamma-secretase inhibitor (GSI), GSI-953. Also known as begacstat in summary, the preclinical data for GSI-953 demonstrated a potent Aβeta lowering activity with no motor potency and in vivo selectivity against Nch processing. Cellular assays of Nch cleavage revealed that this compound is approximately 6-fold selective for the inhibition of APP cleavage. In addition, the drug exhibited robust in vivo efficacy for the lowering of brain, CSF, and plasma Aβeta levels and the reversal of Aβeta-dependent cognitive deficits in Tg2576 mice. Finally, the drug was found lower of plasma Aβeta (a potential biomarker) levels in humans. These data provide evidence supporting GSI-953 treatment as a potential disease modification in the development of AD.
AlzPED is designed to monitor the scientific rigor of curated studies with a “Rigor Report Card” consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups.

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Reporting of Standardized Set of Elements of Experimental Design

Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements. Data presented as percentage reported, calculated from 1030 published preclinical studies curated to AlzPED.

Detailed Analytics Summary is available on the AlzPED Analytics page.
Critical Elements of Experimental Design are Under-Reported

Few studies report more than 5 core design elements, most studies are reporting only 2-4 core design elements.

AlzPED further defines 9 core experimental design elements that are critical for ensuring scientific rigor and reproducibility of a preclinical efficacy study, derived from Shineman et al., 2011, Landis et al., 2012, Snyder et al., 2016 and ARRIVE guidelines. Graphs show percentage of studies that reported the 9 core experimental design elements, calculated from 1030 published preclinical studies curated to AlzPED.
Critical Elements of Experimental Design are Under-Reported in High Impact Factor Journals and in Highly Cited Studies

Reporting trends for the 9 core experimental design elements based on journal impact factor and relative citations/year. Data are presented as Mean ± SEM and analyzed using two-tailed t-tests, *p<0.05, **p<0.01 and ***p<0.001.
Why Should Clinicians Care About Preclinical Research?

2002: Preclinical efficacy studies in ALS mice
• All 3 studies showed efficacy in delaying progression of ALS-like disease
• None of the studies used recommended best practices for rigor, i.e., power calculation

2007: Ph III study
• Deterioration was faster in the minocycline group than in the placebo group
• Minocycline has a harmful effect on patients with ALS
Conclusions

• Analysis of more than 1000 curated studies demonstrates serious deficiencies in reporting critical elements of study design and methodology which diminish the scientific rigor, reproducibility and predictive value of preclinical therapeutic studies done in AD animal models.

• Adoption of a standardized set of best practices is very likely to improve the predictive validity of preclinical studies done in AD animal models. This measure is likely to promote the effective translation of preclinical candidate drug testing to the clinic.

• Journals should require investigators to follow these best practices and study design guidelines to ensure that the studies they publish are sufficiently rigorous, transparent and reproducible.

• Funding agencies should require grantees to use accepted best practices and study design guidelines to ensure that the research they fund is rigorous, transparent and reproducible.
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