Alzheimer's Preclinical Efficacy Database (AlzPED): A new resource to improve the predictive validity of drug efficacy research in Alzheimer's disease animal models

Poster Presentation

21st International Conference on Alzheimer's Drug Discovery

Background

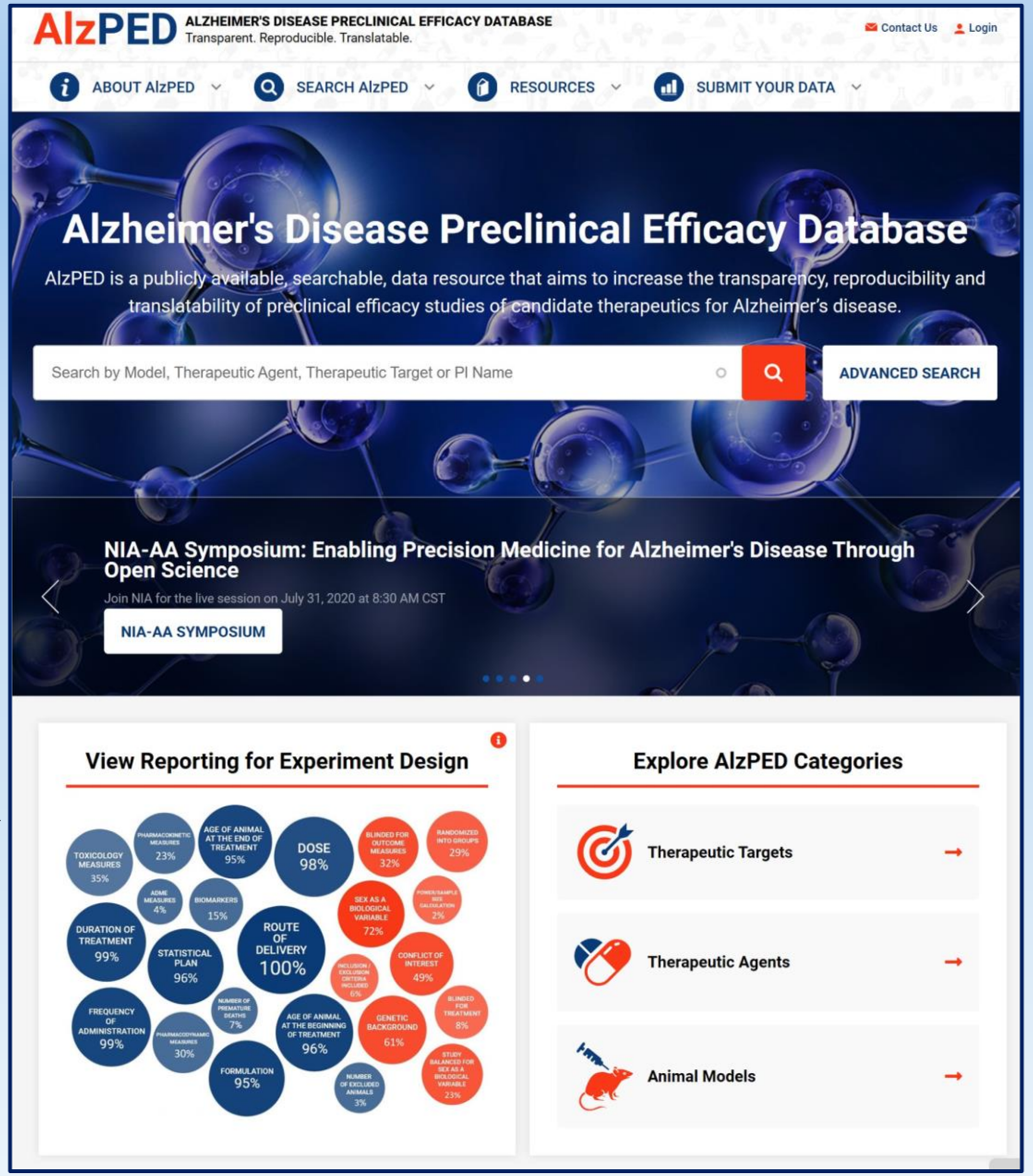
Key Factors Contributing to Poor Translation of Drug Trials in AD Animal Models to the Clinic:

- Poor rigor in study design and methodology
- Poor reproducibility of published data
- Publication bias in favor of reporting positive findings and under reporting negative findings

NIH AD Summits in 2012 & 2015

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.



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 1030 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

Sample of a Curated Record on AlzPED

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

VIEW | EDIT

BIBLIOGRAPHIC | THERAPEUTIC AGENT | ANIMAL MODEL | EXPERIMENTAL DESIGN | OUTCOMES

Bibliographic

Year of Publication: 2009

Contact PI Name: J Steven Jacobsen

Contact PI Affiliation:
Wyeth Research, Departments of Discovery Neuroscience

Co-Authors:
Robert L. Martone, Hua Zhou, Kevin Atchison, Thomas Comery, Jane Z. Xu, Xinyi Huang, Xioahai Gong, Mei Jin, Anthony Kreft, Boyd Harrison, et al

Primary Reference (PubMED ID): 19671883

Funding Source:
Wyeth Research

Study Goal and Principal Findings:
Gamma secretase is widely regarded as a viable target to achieve therapeutically relevant reductions of Aβ 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 begacestat.In summary, the preclinical data for GSI-953 demonstrate a potent Abeta lowering activity, with nano molar potency, and in vitro selectivity against Notch processing. Cellular assays of Notch cleavage reveal that this compound is approximately 16-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 Abeta levels and the reversal of Abeta-dependent cognitive deficits in Tg2576 mice. Finally the drug was found lower of plasma Abeta (a potential biomarker) levels in humans. These data provide evidence supporting GSI-953 treatment as a potential disease modification in the development of AD.

Therapeutic Agent

Therapeutic Information:

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

Animal Model

Model Information:

Species: Mouse
Model Type: APP
Model Name: Tg2576 ALZFORUM
Strain/Genetic Background: Not Reported

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

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

Experimental Design

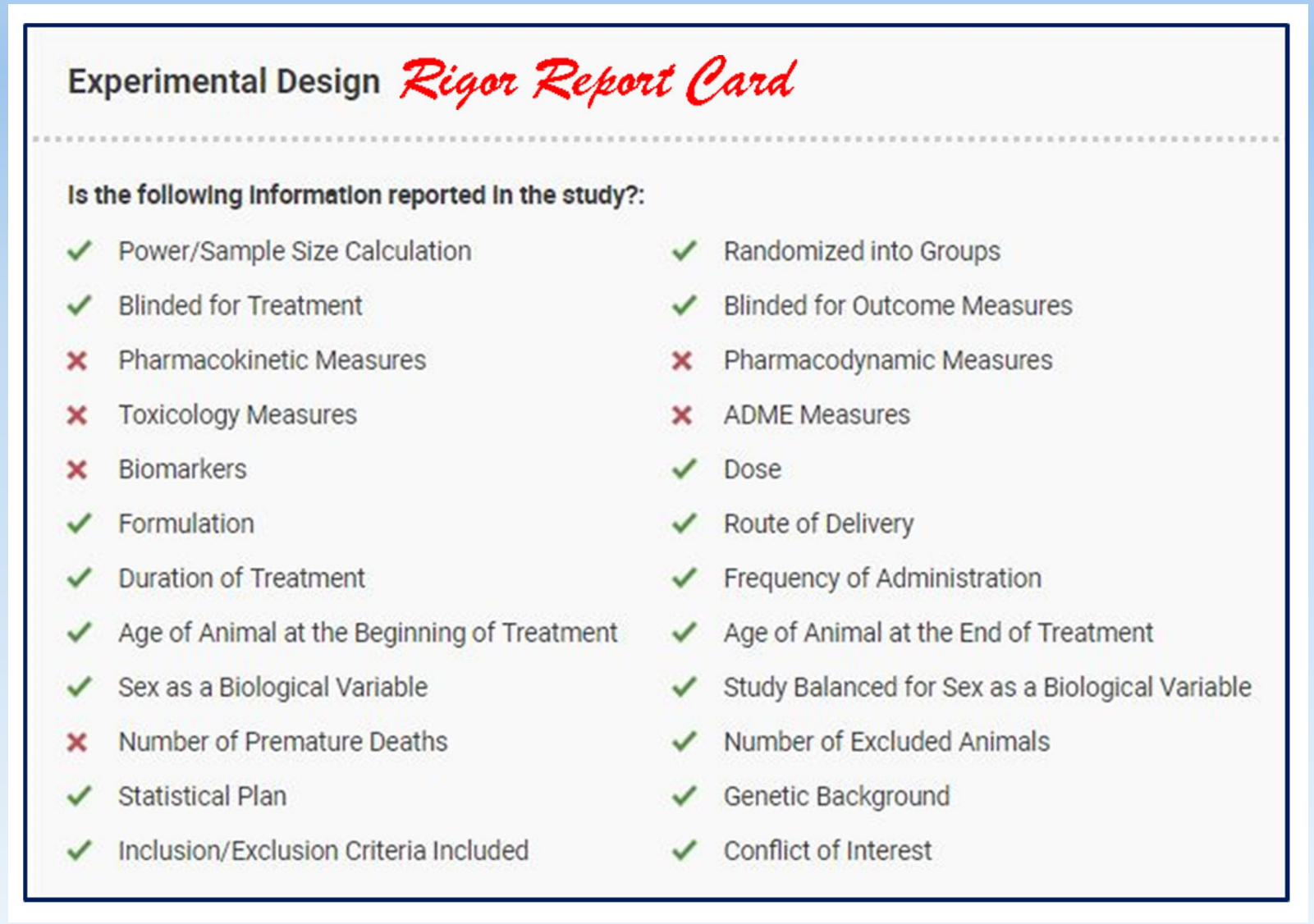
Is the following information reported in the study?:

✗ Power/Sample Size Calculation	✗ Randomized into Groups
✗ Blinded for Treatment	✗ Blinded for Outcome Measures
✓ Pharmacokinetic Measures	✓ Pharmacodynamic Measures
✓ Toxicology Measures	✗ ADME Measures
✓ Biomarkers	✓ Dose
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Administration
✓ Age of Animal at the Beginning of Treatment	✓ Age of Animal at the End of Treatment
✗ Sex as a Biological Variable	✗ Study Balanced for Sex as a Biological Variable
✗ Number of Premature Deaths	✗ Number of Excluded Animals
✓ Statistical Plan	✗ Genetic Background
✗ Inclusion/Exclusion Criteria Included	✗ Conflict of Interest

Outcomes

Outcome Measured	Outcome Parameters
Behavioral	• Contextual Fear Conditioning
Biochemical	• Notch Selectivity • Gamma Secretase Inhibition • Brain-beta amyloid peptide 40 • Brain-beta amyloid peptide 42 • Plasma-beta amyloid peptide 40 • Plasma-beta amyloid peptide 42 • CSF-beta amyloid peptide 40 • CSF-beta amyloid peptide 42
Biomarker	• Plasma-beta amyloid peptide 40 • Plasma-beta amyloid peptide 42 • CSF-beta amyloid peptide 40 • CSF-beta amyloid peptide 42
Pharmacokinetics	• Cmax • Area Under the Curve (AUC) • Brain/Plasma Ratio • PK/PD relationship
Pharmacodynamics	• Target Engagement (reduction beta amyloid peptides-brain)
Toxicology	• Tissue Histopathological Profile • Body Weight • Mortality • Behavior (general)

AlzPED Monitors Rigor in Study Design for Each Curated Study



Experimental Design *Rigor Report Card*

Is the following information reported in the study?:

✓ Power/Sample Size Calculation	✓ Randomized into Groups
✓ Blinded for Treatment	✓ Blinded for Outcome Measures
✗ Pharmacokinetic Measures	✗ Pharmacodynamic Measures
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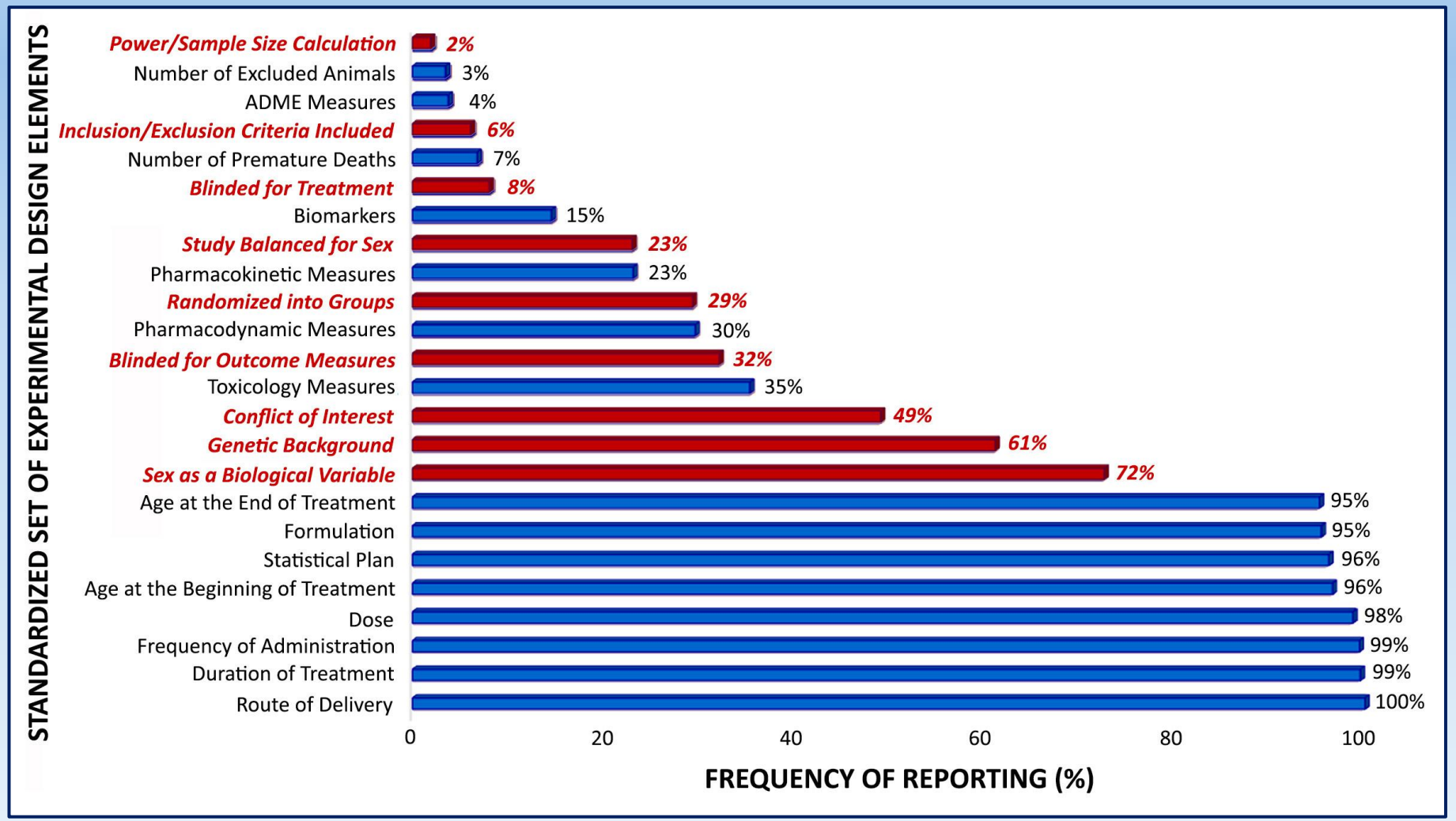
✓ Inclusion/Exclusion Criteria Included	✓ Conflict of Interest

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

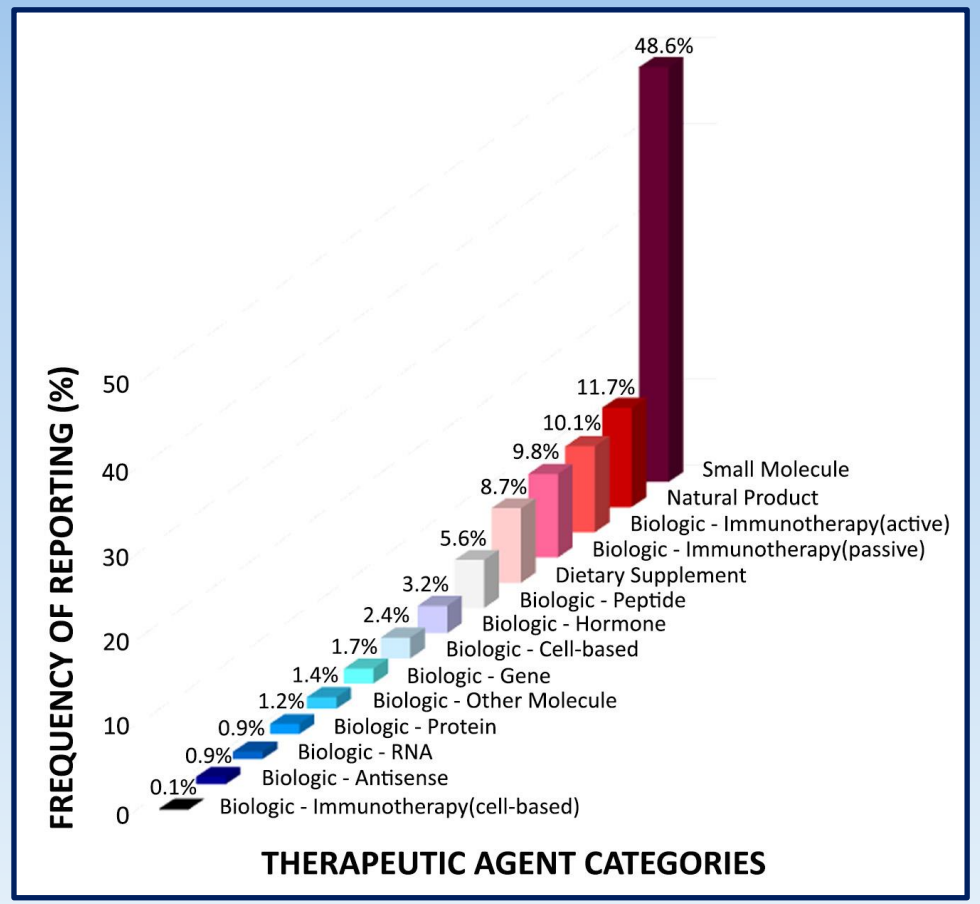
Critical Elements of Experimental Design are Under-Reported

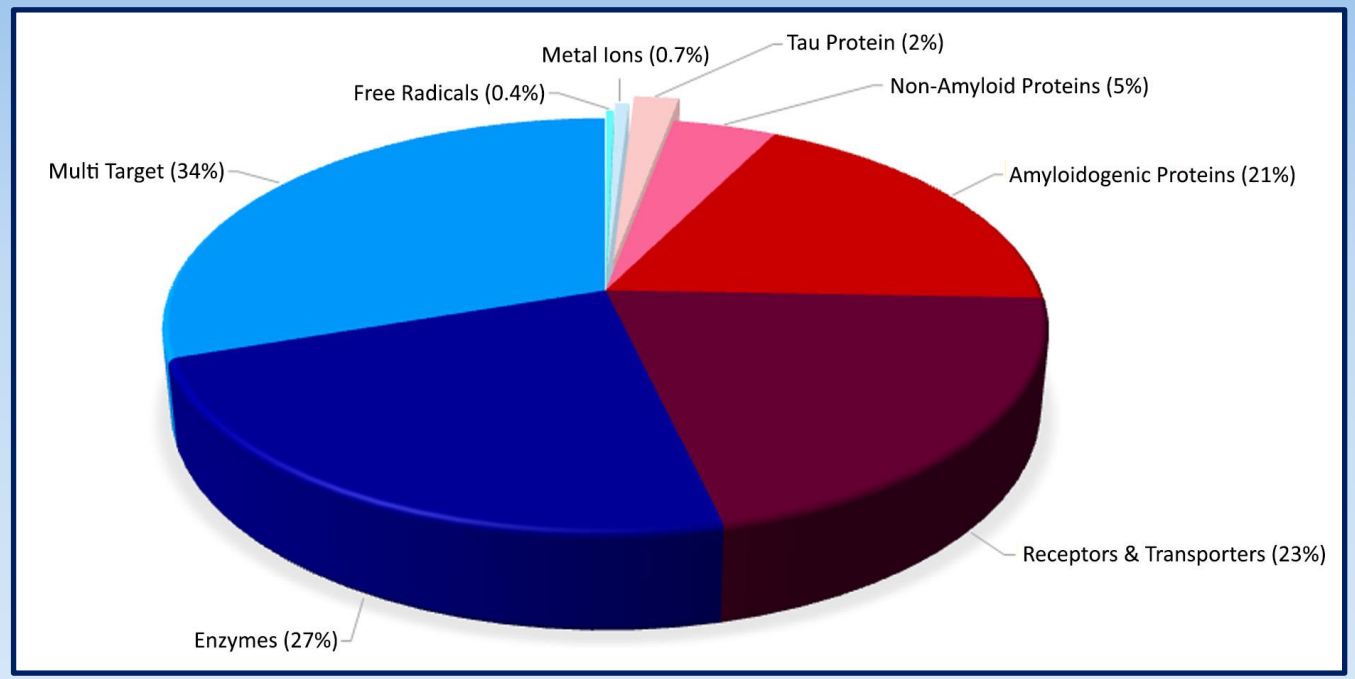


Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements. The red bars represent the 9 core design elements critical for scientific rigor and reproducibility. Data presented as percentage reported, calculated from 1030 published preclinical studies curated to AlzPED.

Detailed Analytics Summary is available on the AlzPED Analytics page

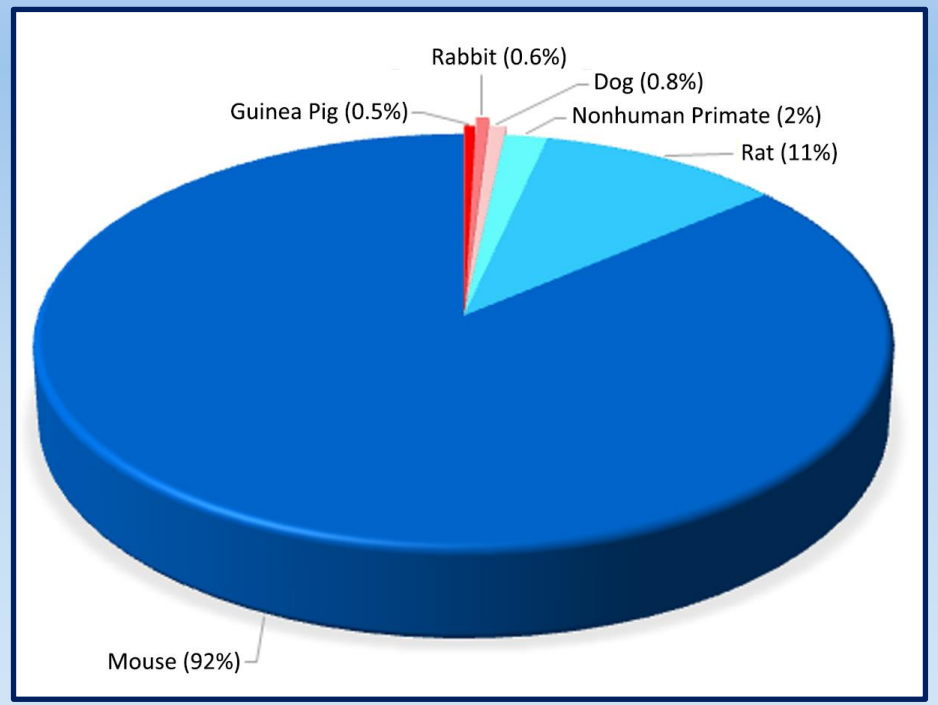
AlzPED Catalogues 890 Therapeutic Agents and 173 Therapeutic Targets



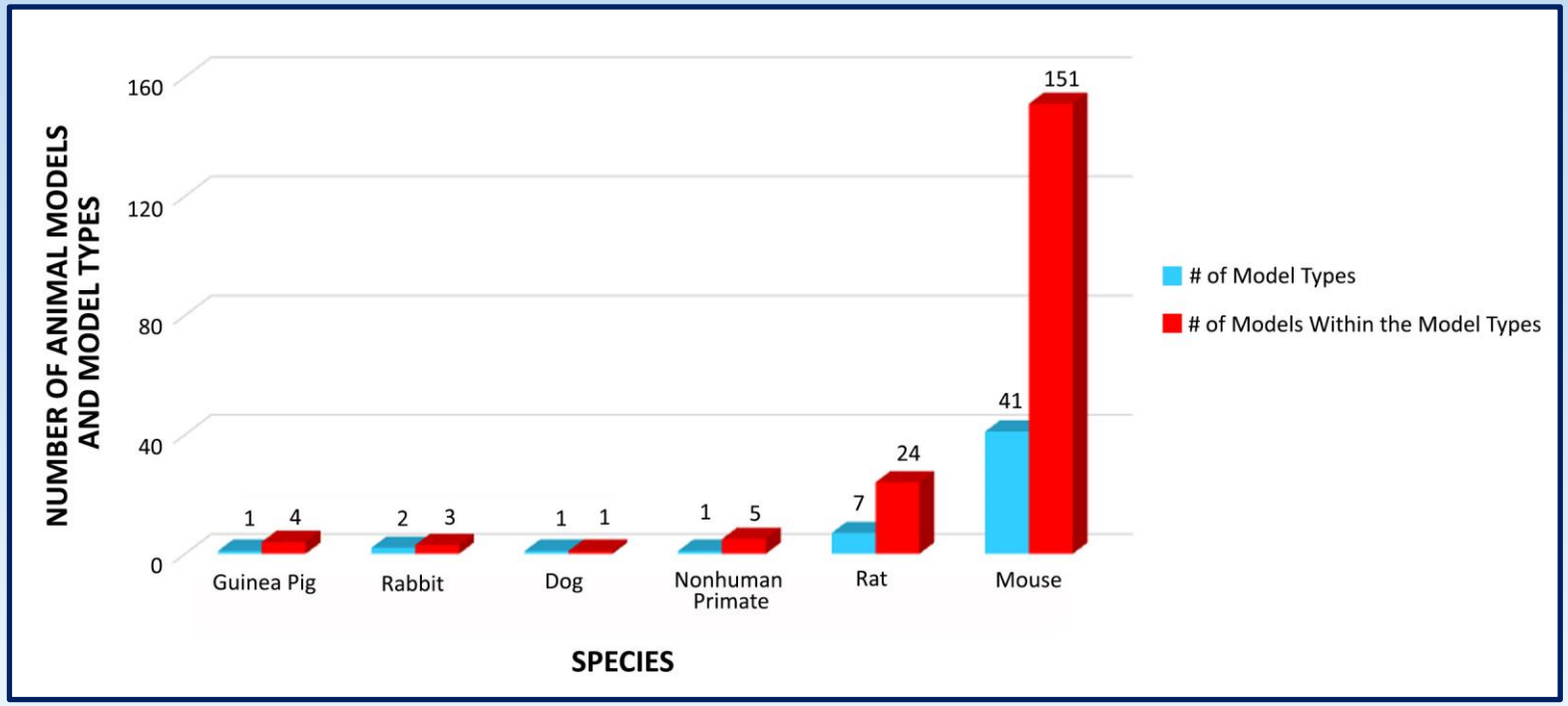


Graphs show the diverse types of therapeutic agents and therapeutic targets tested. Data presented as percentages from 1030 published preclinical studies curated to AlzPED.

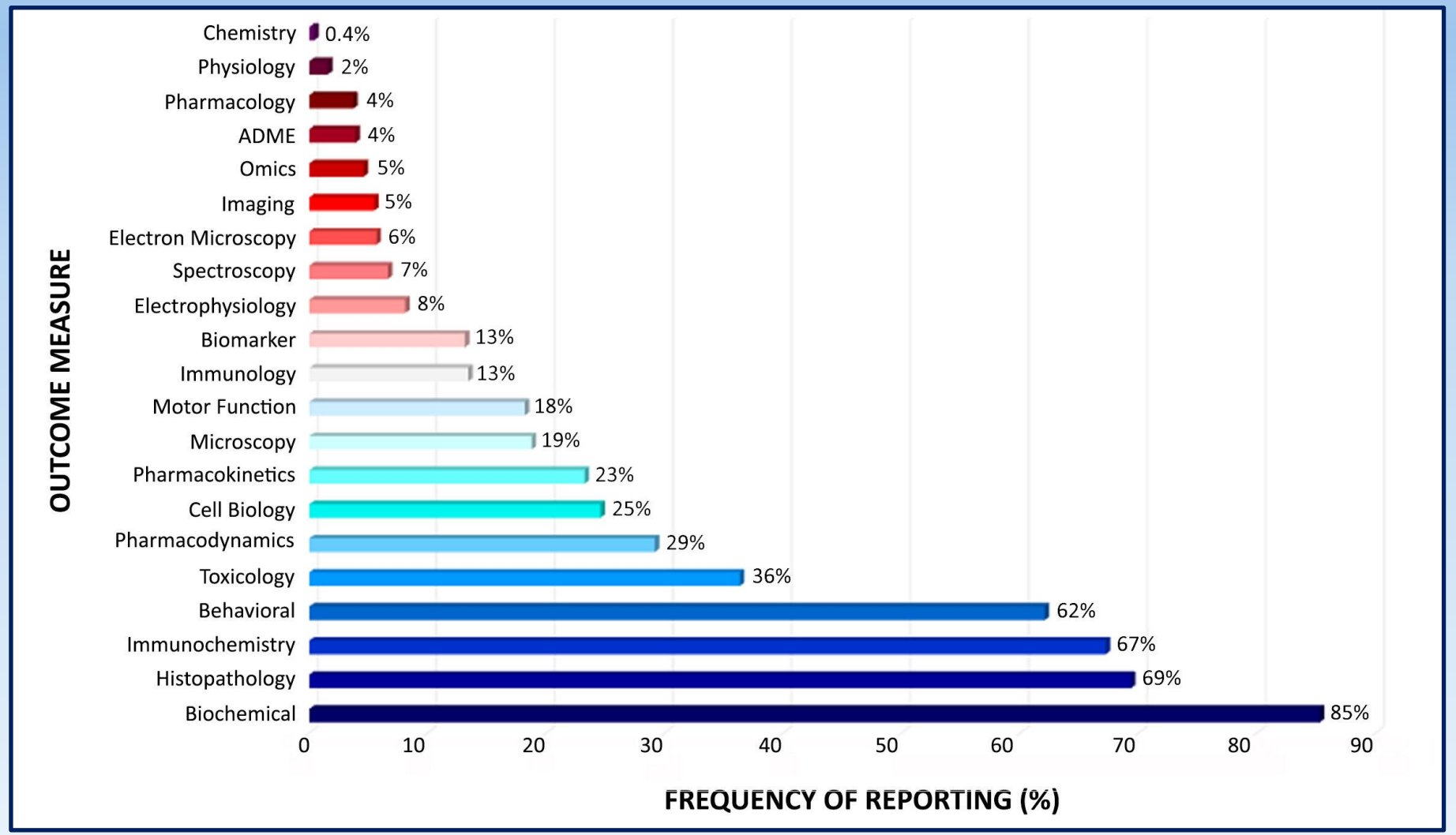
AlzPED Catalogues 188 Animal Models



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.

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 drug testing data 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 both rigorous, transparent and reproducible.

Acknowledgements

NIA

Shreaya Chakroborty
Zane Martin
Suzana Petanceska
Lorenzo Refolo
Ali Sharma
Erika Tarver
Jean Yuan

NIH Library

Bridget Burns
James King

Sage Bionetworks

Kenneth Daily
Mette Peters

Contact Information

alzped.nia.nih.gov
@Alzheimers_NIH
alzped@nih.gov
AlzPED

Partner Organizations