



# AlzPED: A New Data Resource for Improving the Rigor, Transparency, Reproducibility and Translation of Alzheimer's Disease Preclinical Research

Lorenzo M Refolo, PhD<sup>1</sup>, Shreaya Chakroborty, PhD<sup>1</sup>, Zane Martin, PhD<sup>1</sup>, Cindy Sheffield, MBA<sup>2</sup> and Suzana Petanceska, PhD<sup>1</sup>

<sup>1</sup>National Institute on Aging, Bethesda, MD, USA, <sup>2</sup>National Institutes of Health Library, Bethesda, MD, USA

## BACKGROUND

One of the major challenges to the successful development of therapies for Alzheimer's disease (AD) is the poor translation of preclinical efficacy from animal models to the clinic. A number of key factors have been identified as contributors to the unsuccessful translation of therapeutic efficacy, these include:

- the failure of the models to fully recapitulate human AD,
- poor rigor, study design and data analysis, insufficient attention given to using a standard set of "best practices",
- failure to match outcome measures used in preclinical animal studies and clinical studies,
- poor reproducibility of published data, and
- publication bias in favor of reporting positive findings.

To address this challenge and ameliorate some of the factors contributing to the preclinical to clinical gap in the development of AD therapies, several advisory meetings and workshops including the National Institutes of Health (NIH) AD Summits in 2012 and 2015 were held. In response to expert recommendations from these meetings, the National Institute on Aging (NIA) and the NIH Library have created an open science knowledge portal – the **Alzheimer's Preclinical Efficacy Database** or **AlzPED**. Through the following capabilities, AlzPED is intended to guide the development and implementation of strategies and recommendations for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics:

**1**

Publicly available database of preclinical efficacy studies that houses experimental designs and analyses of **positive and negative data** to overcome publication bias.

**2**

Knowledge platform for data sharing, mining and analysis of experimental details, designs, data and methodology missing from studies, making them susceptible to misinterpretation and reducing their reproducibility and translational value.

**3**

Database identifying critical experimental design elements and methodology missing from studies, making them susceptible to misinterpretation and reducing their reproducibility and translational value.

## CAPABILITIES AND SCOPE

AlzPED has the following capabilities:

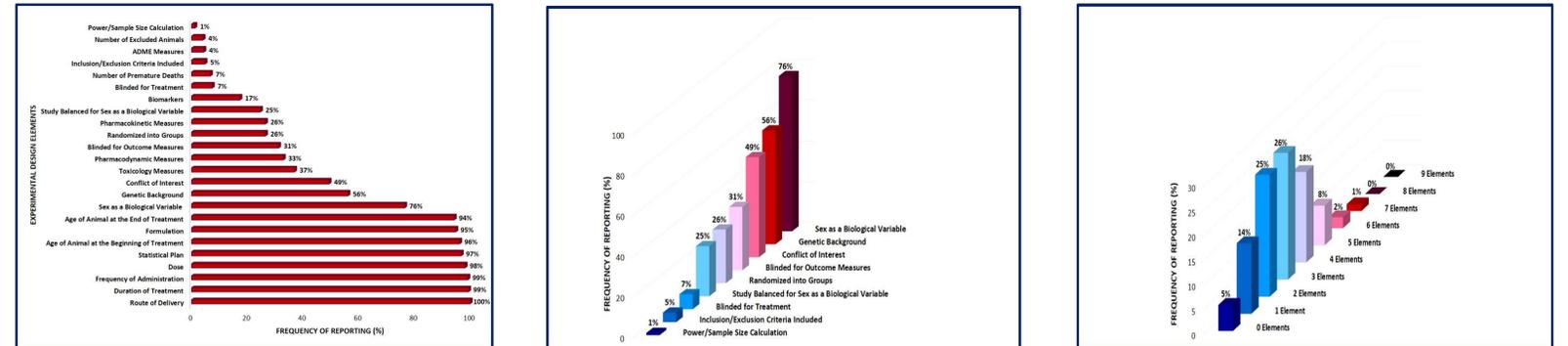
- Provides researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the elements of rigorous study design and requirements for transparent reporting.
- Currently hosts curated summaries from **720** preclinical efficacy studies published between 2000 and 2018.
- Influences the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.
- Provides search capability across relevant translational criteria data sets and external databases:
  - Therapy Type
  - Therapeutic Agent
  - Therapeutic Target
  - Animal Model
  - 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 [USTPO](#))
- Provides funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.
- Provides a platform for creating [citable reports/preprints of unpublished studies](#), including studies with **negative data**.
- **Reports on the rigor of each study by summarizing the elements of experimental design.**

## ANALYTICS

### A CURATED RECORD IN AlzPED

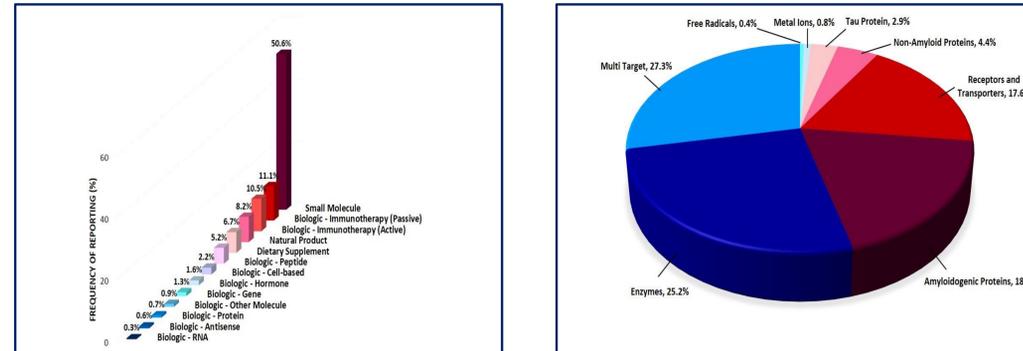
BIBLIOGRAPHIC	THERAPEUTIC AGENT	ANIMAL MODEL	EXPERIMENTAL DESIGN	OUTCOMES																																						
<p><b>Bibliographic</b></p> <p>Year of Publication: 2018</p> <p>Contact PI Name: Lennart Mucke</p> <p>Contact PI Affiliation: Gladstone Institute of Neurological Disease, San Francisco, CA, USA</p> <p>Co-Author: Anna G. Ori, Iris Lo, Heike Schumacher, Kathryn Ho, Michael Gill, Weikun Guo, Daniel H. Kim, Anthony Knox, Takashi Saito, Takao M. Saito, Jeffrey Simms, Carlee Toddes, Xin Wang, Gui-Qiu Yu</p> <p>Primary Reference (PubMed ID): 29109987</p> <p>Funding Source: Alan Kagranov Scholarship, Dotby Family, MetLife Foundation, National Center for Research Resources (NCRR), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Aging (NIA), S.D. Bachtel, Jr. Foundation</p> <p><b>Study Goal and Principal Findings:</b> Adenosine A2A receptors are putative therapeutic targets for neurological disorders. The adenosine A2A receptor antagonist istradefylline is approved in Japan for Parkinson's disease and is being tested in clinical trials for this condition elsewhere. A2A receptors on neurons and astrocytes may contribute to Alzheimer's disease (AD) by impairing memory. However, it is not known whether istradefylline enhances cognitive function in aging animals with AD-like amyloid plaque pathology. Here, we show that elevated levels of Aβ<sub>1-42</sub> C-terminal fragments of the amyloid precursor protein (APP), or amyloid plaques, but not overexpression of APP per se, increase astrocytic A2A receptor levels in the hippocampus and neocortex of aging mice. Moreover, in amyloid plaque-bearing mice, low-dose istradefylline treatment enhanced spatial memory and habituation, supporting the conclusion that, within a well-defined dose range, A2A receptor blockers might help counteract memory problems in patients with Alzheimer's disease.</p>	<p><b>Therapeutic Agent</b></p> <p>Therapeutic Information:</p> <p>Therapy Type: Small Molecule</p> <p>Therapeutic Agent: Istradefylline</p> <p>PubMed# PubChem# DrugBank# ClinicalTrials# Patents#</p> <p>Therapeutic Target: Adenosine A2A Receptor</p> <p>Open Targets# Pharos#</p>	<p><b>Animal Model</b></p> <p>Model Information:</p> <p>Species: Mouse</p> <p>Model Type: APP</p> <p>Model Name: PDGF-APP (WT) (line 15) ALZFORUM#</p> <p>Strain/Genetic Background: C57BL/6</p>	<p><b>Experimental Design</b></p> <p>Is the following information reported in the study?</p> <table border="0"> <tr> <td>✓ Power/Sample Size Calculation</td> <td>✓ Randomized into Groups</td> </tr> <tr> <td>✓ Blinded for Treatment</td> <td>✓ Blinded for Outcome Measures</td> </tr> <tr> <td>✓ Pharmacokinetic Measures</td> <td>✓ Pharmacodynamic Measures</td> </tr> <tr> <td>✓ Toxicology Measures</td> <td>✓ ADME Measures</td> </tr> <tr> <td>✓ Biomarkers</td> <td>✓ Dose</td> </tr> <tr> <td>✓ Formulation</td> <td>✓ Route of Delivery</td> </tr> <tr> <td>✓ Duration of Treatment</td> <td>✓ Frequency of Administration</td> </tr> <tr> <td>✓ Age of Animal at the Beginning of Treatment</td> <td>✓ Age of Animal at the End of Treatment</td> </tr> <tr> <td>✓ Sex as a Biological Variable</td> <td>✓ Study Balanced for Sex as a Biological Variable</td> </tr> <tr> <td>✓ Number of Premature Deaths</td> <td>✓ Number of Excluded Animals</td> </tr> <tr> <td>✓ Statistical Plan</td> <td>✓ Genetic Background</td> </tr> <tr> <td>✓ Inclusion/Exclusion Criteria Included</td> <td>✓ Conflict of Interest</td> </tr> </table>	✓ 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	<table border="1"> <thead> <tr> <th>Outcome Measured</th> <th>Outcome Parameters</th> </tr> </thead> <tbody> <tr> <td>Behavioral</td> <td> <ul style="list-style-type: none"> <li>Cued Task</li> <li>Elevated Plus Maze</li> <li>Exploratory Activity</li> <li>Habituation Learning</li> <li>Hidden Platform Task</li> <li>Morris Water Maze</li> <li>Open Field Test</li> <li>Rearing</li> <li>Spontaneous Activity</li> <li>Visible Platform</li> </ul> </td> </tr> <tr> <td>Motor Function</td> <td> <ul style="list-style-type: none"> <li>Locomotor Activity</li> <li>Rotarod Test</li> <li>Path Length</li> <li>Swimming Speed</li> </ul> </td> </tr> <tr> <td>Histopathology</td> <td> <ul style="list-style-type: none"> <li>Activated Astrocytes</li> <li>beta amyloid deposits</li> </ul> </td> </tr> <tr> <td>Immunohistochemistry</td> <td> <ul style="list-style-type: none"> <li>Adenosine A2A Receptor</li> <li>Brain beta amyloid deposits</li> <li>Glial Fibrillary Acidic Protein (GFAP)</li> </ul> </td> </tr> <tr> <td>Pharmacokinetics</td> <td> <ul style="list-style-type: none"> <li>Drug Concentration-Brain</li> <li>Drug Concentration-Plasma</li> </ul> </td> </tr> <tr> <td>Toxicology</td> <td> <ul style="list-style-type: none"> <li>Body Weight</li> <li>Food Intake</li> <li>Water Consumption</li> </ul> </td> </tr> </tbody> </table>	Outcome Measured	Outcome Parameters	Behavioral	<ul style="list-style-type: none"> <li>Cued Task</li> <li>Elevated Plus Maze</li> <li>Exploratory Activity</li> <li>Habituation Learning</li> <li>Hidden Platform Task</li> <li>Morris Water Maze</li> <li>Open Field Test</li> <li>Rearing</li> <li>Spontaneous Activity</li> <li>Visible Platform</li> </ul>	Motor Function	<ul style="list-style-type: none"> <li>Locomotor Activity</li> <li>Rotarod Test</li> <li>Path Length</li> <li>Swimming Speed</li> </ul>	Histopathology	<ul style="list-style-type: none"> <li>Activated Astrocytes</li> <li>beta amyloid deposits</li> </ul>	Immunohistochemistry	<ul style="list-style-type: none"> <li>Adenosine A2A Receptor</li> <li>Brain beta amyloid deposits</li> <li>Glial Fibrillary Acidic Protein (GFAP)</li> </ul>	Pharmacokinetics	<ul style="list-style-type: none"> <li>Drug Concentration-Brain</li> <li>Drug Concentration-Plasma</li> </ul>	Toxicology	<ul style="list-style-type: none"> <li>Body Weight</li> <li>Food Intake</li> <li>Water Consumption</li> </ul>
✓ 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																																									
Outcome Measured	Outcome Parameters																																									
Behavioral	<ul style="list-style-type: none"> <li>Cued Task</li> <li>Elevated Plus Maze</li> <li>Exploratory Activity</li> <li>Habituation Learning</li> <li>Hidden Platform Task</li> <li>Morris Water Maze</li> <li>Open Field Test</li> <li>Rearing</li> <li>Spontaneous Activity</li> <li>Visible Platform</li> </ul>																																									
Motor Function	<ul style="list-style-type: none"> <li>Locomotor Activity</li> <li>Rotarod Test</li> <li>Path Length</li> <li>Swimming Speed</li> </ul>																																									
Histopathology	<ul style="list-style-type: none"> <li>Activated Astrocytes</li> <li>beta amyloid deposits</li> </ul>																																									
Immunohistochemistry	<ul style="list-style-type: none"> <li>Adenosine A2A Receptor</li> <li>Brain beta amyloid deposits</li> <li>Glial Fibrillary Acidic Protein (GFAP)</li> </ul>																																									
Pharmacokinetics	<ul style="list-style-type: none"> <li>Drug Concentration-Brain</li> <li>Drug Concentration-Plasma</li> </ul>																																									
Toxicology	<ul style="list-style-type: none"> <li>Body Weight</li> <li>Food Intake</li> <li>Water Consumption</li> </ul>																																									

### ELEMENTS OF EXPERIMENTAL DESIGN



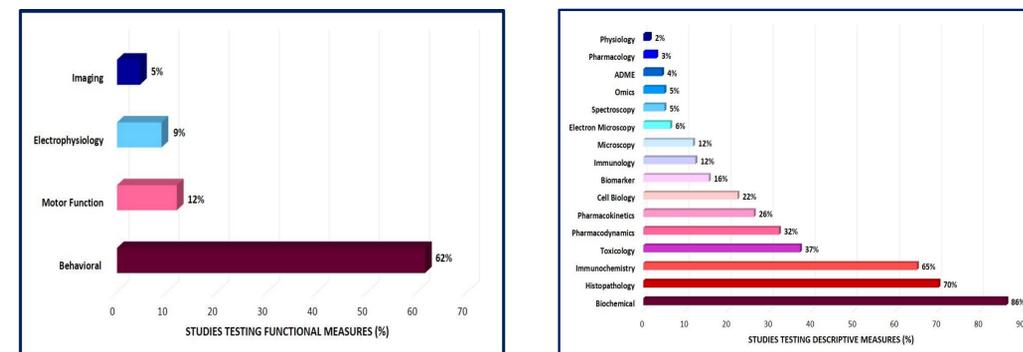
**LEFT:** Frequency of reporting the 24 recommended elements of experimental design that improve the reproducibility and translational value of preclinical efficacy research. **CENTER:** Frequency of reporting the 9 core elements of experimental design that are critical for ensuring scientific rigor of preclinical efficacy research. **RIGHT:** Trends in the reporting of the 9 core elements of experimental design. Data are presented as percentages calculated from 720 published preclinical efficacy studies curated in AlzPED. The studies were published between 2000 and 2018.

## THERAPEUTICS



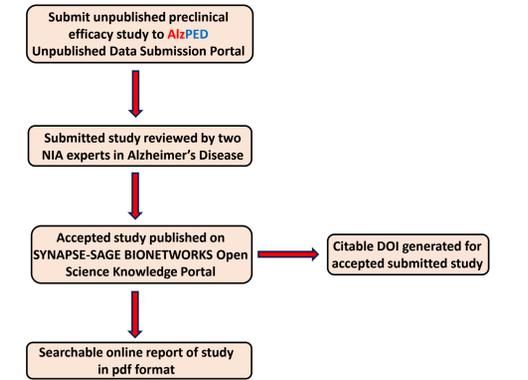
**LEFT:** 640 therapeutic agents are catalogued in 13 categories. **RIGHT:** 145 therapeutic targets are catalogued in 7 categories. Data are presented as percentages calculated from 720 published preclinical efficacy studies curated in AlzPED.

## OUTCOME MEASURES



**LEFT:** Frequency of reporting functional outcome measures. **RIGHT:** Frequency of reporting descriptive outcome measures. Data are presented as percentages calculated from 720 published preclinical efficacy studies curated in AlzPED.

## UNPUBLISHED STUDY SUBMISSION PORTAL



Overview of the submission process for unpublished data. The DOI provided is citable in grant applications and peer-reviewed publications

## SUMMARY

In summary, **AlzPED**:

- Provides free access to information pertaining to experimental designs, AD animal models, therapeutic agents and targets, outcome measures, and principal findings from preclinical studies.
- Serves as a platform for reporting unpublished negative findings to mitigate publication bias that favors reporting of positive findings.
- Is a resource for researchers to survey existing preclinical therapy developments, understand the requirements of rigorous study design, transparent reporting, and plan preclinical intervention studies.
- Provides funding agencies with a tool for the enforcement of requirements for transparent reporting and rigorous study design.