AlzPED: Optimizing the Predictive Power of Drug Efficacy Studies in Alzheimer's Disease Animal Models

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BACKGROUND

A major challenge to the successful development of therapies for Alzheimer's disease (AD) is the poor translation of preclinical efficacy from animal models to the clinic. Key contributing factors to the unsuccessful translation of therapeutic efficacy include:

- the failure of animal models to fully recapitulate human AD,
- poor rigor in study design, methodology and data analysis,
- 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 and under reporting negative findings.

To address key factors contributing to poor translation of preclinical efficacy from animal models to the clinic in AD therapy development, 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 Disease 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 methods relating to the preclinical testing of candidate therapeutic agents in AD animal models.
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 **1172** preclinical efficacy studies published between 1996 and 2019.
- 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 (16 therapy types)
  - Therapeutic Agent (1019 agents)
  - Therapeutic Target (225 targets)
  - Animal Model (195 models)
  - Principal Investigator
  - Funding Source
  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and DrugBank)
  - 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**.

AlzPED CURATED RECORD

EXAMPLE OF RIGOROUS STUDY DESIGN

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

Bibliographic

Year of Publication: 2019
Contact PI Name: Michal Schwartz
Contact PI Affiliation:
Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel.
Co-Authors:
Neta Rosenzweig, Raz Dvir-Szternfeld, Afroditi Tsitsou-Kampeli, Hadas Keren-Shaul, Hila Ben-Yehuda, Pierre Weill-Raynal, Liora Cahalon, Alex Kertser, Kuti Baruch, Ido Amit, Assaf Weiner
Primary Reference (PubMED ID): 30692527
Funding Source:
EU Seventh Framework Program
Israel Science Foundation (ISF)
ISF-Legacy Heritage Biomedical Science Partnership-research grant
Advanced European Research Council
Study Goal and Principal Findings:
Alzheimer's disease (AD) is a heterogeneous disorder with multiple etiologies. Harnessing the immune system by blocking the programmed cell death receptor (PD)-1 pathway in an amyloid beta mouse model was shown to evoke a sequence of immune responses that lead to disease modification. Here, blocking PD-L1, a PD-1 ligand, was found to have similar efficacy to that of PD-1 blocking in disease modification, in both animal models of AD and of tauopathy. Targeting PD-L1 in a tau-driven disease model resulted in increased immunomodulatory monocyte-derived macrophages within the brain parenchyma. Single cell RNA-seq revealed that the homing macrophages expressed unique scavenger molecules including macrophage scavenger receptor 1 (MSR1), which was shown here to be required for the effect of PD-L1 blockade in disease modification. Overall, our results demonstrate that immune checkpoint blockade targeting the PD-1/PD-L1 pathway leads to modification of common factors that go awry in AD and dementia, and thus can potentially provide an immunotherapy to help combat these diseases.

Therapeutic Agent

Therapeutic Information:

Therapy Type: Biologic - Immunotherapy(passive)
Therapeutic Agent: anti-PD-1 Antibody
PubMed PubChem ClinicalTrials Patent
Therapeutic Target: Programmed Cell Death Protein 1 (PD-1)
Open Targets Pharos

Therapy Type: Biologic - Immunotherapy(passive)
Therapeutic Agent: anti-PD-L1 Antibody
PubMed PubChem ClinicalTrials Patent
Therapeutic Target: Programmed Death-Ligand 1 (PD-L1)
Open Targets Pharos

Animal Model

Model Information:

Species: Mouse
Model Type: APPsPS1
Model Name: 5xFAD ALZFORUM
Strain/Genetic Background: C57BL/6 x SJL

Species: Mouse
Model Type: Tau
Model Name: DM-hTAU PubMed
Strain/Genetic Background: BALBc-C57/BL6

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	• Radial Arm Water Maze • T Maze • Y Maze
Histopathology	• Neuronal Loss • Colocalization-astrocytes/microglia/amyloid plaques • Activated Microglia • beta amyloid deposits • beta amyloid load
Biochemical	• Glial Fibrillary Acidic Protein (GFAP) • IL-10 mRNA • IL-12p40 mRNA • Tumor Necrosis Factor alpha (TNF alpha) • IL-6 mRNA • IL-1 beta mRNA • Ionized Calcium Binding Adaptor Molecule 1 (Iba1)
Immunochemistry	• Neuronal Marker NeuN • Caspase 3 • Glial Fibrillary Acidic Protein (GFAP) • Amyloid Plaques • Synaptophysin • IL-1 beta • Ionized Calcium Binding Adaptor Molecule 1 (Iba1) • phospho-Tau • Tau Protein • Macrophage scavenger receptor 1 (MSR1)
Microscopy	• Cell Survival • Cell Viability
Omics	• Whole Transcriptome Analysis

CRITICAL ELEMENTS OF EXPERIMENTAL DESIGN

Experimental Design *Rigor Report Card*

Is the following information reported in the study?:

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✗ Toxicology Measures	✗ ADME Measures
✗ Biomarkers	✓ Dose
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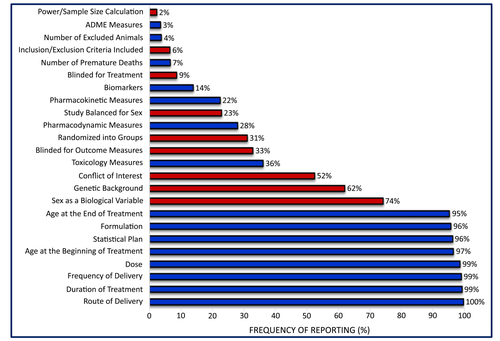
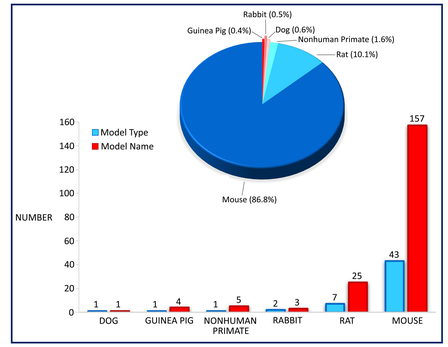


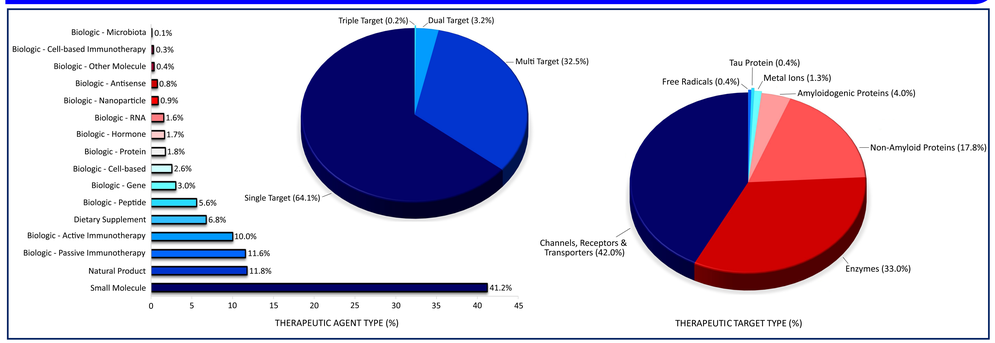
Left: AlzPED is designed to monitor the scientific rigor of curated studies with a **"Rigor Report Card"** consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups. **Right:** Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements. **The red bars represent the 9 core design elements critical for scientific rigor, and reproducibility**. Data is presented as percentage reported, calculated from 1172 published preclinical studies curated to AlzPED.

ANIMAL MODELS



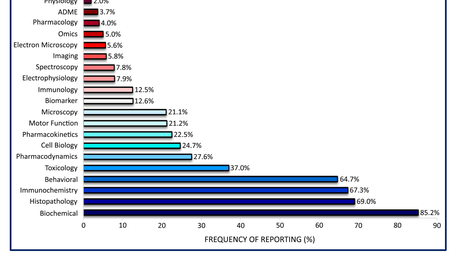
Preclinical efficacy data from 6 animal species, 55 model types and 195 different AD animal models are currently available in AlzPED. Data is presented as percentage reported, calculated from 1172 published preclinical studies curated to AlzPED.

THERAPEUTICS: AGENTS AND TARGETS



A diverse array of therapeutic agents and targets are catalogued in AlzPED. **Left:** The database categorizes 1019 novel therapeutic agents into 16 distinct categories. Therapeutic agents are dual-target, triple-target multi-target or have a single specific target. **Right:** AlzPED stores information on 225 therapeutic targets that are categorized according to function. Data is presented as percentage reported, calculated from 1172 published preclinical studies curated to AlzPED.

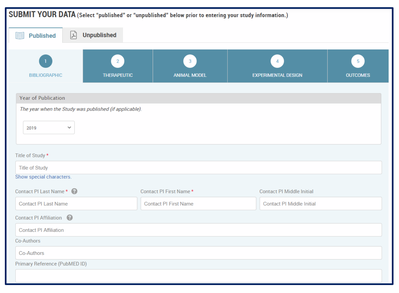
OUTCOME MEASURES

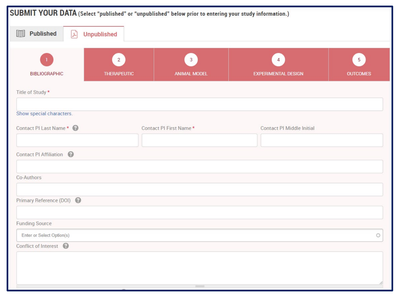


Curated studies provide an individual snapshot of the measures tested and outcomes achieved in response to the therapeutic agent tested. AlzPED defines 22 different outcome measures that are categorized as either functional or descriptive. Data is presented as percentage reported, calculated from 1172 published preclinical studies curated to AlzPED.

PUBLISHED AND UNPUBLISHED DATA SUBMISSION PLATFORM

Left: Published data is extracted from the scientific literature and curated in 5 categories – bibliographic, therapeutic, animal model, experimental design and outcomes. **Right:** 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.





CONCLUSIONS

- Analysis of more than 1100 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
- AlzPED serves as a platform for reporting unpublished negative findings to mitigate publication bias that favors reporting of positive findings.

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Detailed Analytics Summary is available here: AlzPED Analytics