Improving the Rigor, Reproducibility and Translatability of Preclinical Research for Alzheimer’s Disease:

The Alzheimer’s Disease Preclinical Efficacy Database – AlzPED

The AlzPED Team
National Institute on Aging
What is preclinical research?

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

**Preclinical Research**
- Target identification/validation
- Lead identification/optimization
  - PKPD/ADME
- Toxicity in Rodents, Canines, NHP
- *Drug Efficacy in a Disease Model*

**Clinical Trials**
Safety and
Efficacy in Humans
What are the Needs to be Addressed?

The Failure Of AD Therapies in the Clinic

• The extremely high rate of attrition of drugs in Phase II (92%) and Phase III (98%) with more than half failing due to issues of efficacy.

• During the decade 2002-2012 -244 compounds were tested in 413 clinical trials (Ph I-Ph III) and one (memantine) was advanced to the FDA and approved for marketing, giving an approval rate of 0.4% (>99% attrition).

Cummings et al. Alzheimer's Research & Therapy 2014, 6:37
Status of AD Drugs in the Clinic

Failure due to lack of efficacy or toxicity

Table 1
Current status of selected anti-Alzheimer's drugs in clinical trials.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Clinical stage</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN-1792</td>
<td>Anti-AB vaccine</td>
<td>Phase II</td>
<td>Discontinued</td>
</tr>
<tr>
<td>CAD106</td>
<td>Anti-AB vaccine</td>
<td>Phase II</td>
<td>Terminated</td>
</tr>
<tr>
<td>ACC-001</td>
<td>Anti-AB vaccine</td>
<td>Phase II</td>
<td>Terminated</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Humanized monoclonal anti-AB antibody</td>
<td>Phase III and II/III</td>
<td>Discontinued</td>
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<tr>
<td>Solanezumab</td>
<td>Humanized monoclonal anti-AB antibody</td>
<td>Phase II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Humanized monoclonal anti-AB antibody</td>
<td>Phase II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Humanized monoclonal anti-AB antibody</td>
<td>Phase II</td>
<td>Ongoing</td>
</tr>
<tr>
<td>IVIG</td>
<td>Human polyclonal anti-AB antibody</td>
<td>Phase III</td>
<td>Ongoing</td>
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<td>GSK933776</td>
<td>Humanized monoclonal anti-AB antibody</td>
<td>Phase I</td>
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<tr>
<td>BAN-21</td>
<td>Humanized monoclonal anti-AB antibody</td>
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<td>Ongoing</td>
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<td>AADVac1</td>
<td>Anti-tau vaccine</td>
<td>Phase II</td>
<td>Discontinued</td>
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<tr>
<td>ACI-35</td>
<td>Anti-tau vaccine</td>
<td>Phase I</td>
<td>Ongoing</td>
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<td>Semagacestat</td>
<td>γ-Secretase inhibitor</td>
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<td>γ-Secretase modulator</td>
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<td>Begacestat</td>
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Total of 85 just since 2008
Has Stanford University found a cure for Alzheimer's disease?

The Telegraph

New Alzheimer's treatment fully restores memory function

Mouse study hints at possible Alzheimer's cure

Time

This Alzheimer's Breakthrough Could Be a Game Changer

There is no lack of successful drug treatment trials in AD mouse models.
Problem: Preclinical Drug Efficacy has Not Translated to the Clinic

• 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.

• Evidence of the Poor Translational Validity of Drug Trials in AD Animal Models
Key Factors Contributing to the Poor Translation of Efficacy Studies in AD Animal Models

- 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
Common Critical Elements of Clinical Trial Study Design

1. Power Analysis and Sample Size Calculation

2. Randomization

3. Blinding (treatment allocation and outcome measures)

4. Balancing for Sex/Gender

5. Age Matching

6. Eligibility Criteria (inclusion and exclusion criteria)

7. Use of Biomarkers as Key Outcome Measures

van der Worp et al. PLoS, 2010
Relationship Between Use of Critical Design Elements and Estimates of Preclinical Efficacy

It’s a inverse relationship

Sena et al, Trends in Neurosciences, 2007
Review of the Neuroscience Literature Reveals that the Majority of Animal Studies Lack Rigor in Study Design


<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Publications</th>
<th>Masked Assessment of Outcome (%)</th>
<th>Random Allocation to Group (%)</th>
<th>Allocation Concealment (%)</th>
<th>Sample Size Calculation (%)</th>
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<td>40 (16)</td>
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<td>Focal ischemia</td>
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<td>NXY 059 13</td>
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<td>4 (44)</td>
<td>3 (33)</td>
<td>5 (56)</td>
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<td>Hypothermia 12</td>
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<td>Tirilazad 34</td>
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<td>tPA 14</td>
<td>113</td>
<td>24 (21)</td>
<td>42 (37)</td>
<td>23 (20)</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>

NA, not applicable; tPA, tissue plasminogen activator.
Preclinical Studies Published in Leading Scientific Journals Lack Scientific Rigor in Study Design

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

- 76 articles in 7 leading scientific journals (e.g., Nature, Science, Cell, Neuron etc)
- Published between 1980-2000

DG Hackam, JAMA, 296:1731-2, 2006
Should clinicians care about preclinical animal research?
Poorly conducted preclinical efficacy studies can lead to failure in the clinic.

Minocycline Slows Disease Progression in a Mouse Model of Amyotrophic Lateral Sclerosis

Jasna Kriz, Minh Dang Nguyen, and Jean-Pierre Julien
Centre for Research in Neurosciences, McGill University, Research Institute of the McGill University Health Centre, Montreal, Quebec, H3C 1A4, Canada

Minocycline inhibits cytochrome c release and delays progression of amyotrophic lateral sclerosis in mice


Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial

Nan Gorton, Beth M. Moore, Robert G. Miller, Julianet N. Brown, Joseph J. Verhagen, Carolyn Kiechle, Joost F. Hilson, G. Mark Smith, Robert J. Pendl, Robert J. Basran, Reg Tisdale, for the Westen ALS Study Group*

Summary
Background: Minocycline has anti-apoptotic and anti-inflammatory effects in vitro and studies in animal models of some neurological conditions. Several trials are planned or are in progress to assess whether minocycline slows human neurodegeneration. We aimed to test the efficacy of minocycline as a treatment for amyotrophic lateral sclerosis (ALS).

Methods: We did a multicentre, randomised placebo-controlled phase III trial. After a 4-month lead-in phase, 412 patients were randomly assigned to receive placebo or minocycline in escalating doses of up to 400 mg/day for 9 months. The primary outcome measure was the difference in rate of change in the revised ALS functional rating scale (ALSFRS-R). Secondary outcomes measures were forced vital capacity (FVC), maximal muscle testing (MMT), quality of life, survival, and safety. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00047723.

Findings: ALSFRS-R score deterioration was faster in the minocycline group than in the placebo group (−1.04 units/month, 95% CI for difference −1.58 to −0.50; p < 0.001). Patients on minocycline also had non-significant tendencies towards faster decline in FVC (−3.48 units/month, −6.01 to −0.95; p = 0.095). Patients on minocycline also had non-significant tendencies towards faster decline in FVC (−3.48 to −0.95; p = 0.095). Minimal muscle testing (MMT) score (−0.30 to −0.26, p = 0.08 to 0.03; p = 0.03), and greater mortality during the 9-month treatment phase (hazard ratio 1.32; 95% CI 0.83 to 2.05; p = 0.22) than did patients on placebo. Non-serious gastrointestinal and neurological adverse events were more common in the minocycline group than in the placebo group, but these events were not significantly related to the decline in ALSFRS-R score.

Interpretation: Our finding that minocycline has a harmful effect in patients with ALS has implications for trials of minocycline in patients with other neurological disorders, and for potential neuroprotective agents are screened for use in patients with ALS.
Advisory Meetings and Workshops examining the causes of the poor predictive power/translatability of animal models preclinical efficacy studies:

- **National Institute on Aging**
  - Advisory Meeting: “Advancing AD Therapy Development” 2010
  - NIH AD Summits 2012 & 2015

- **Alzheimer’s Drug Discovery Foundation**
  - Advisory Panel 2010

- **National Institute of Neurological Disorders and Stroke**
  - Workshop 2012

- **Institute of Medicine**
  - Workshop 2012
Recommendations Aimed at Increasing Predictive Power of Drug Efficacy in AD Animal Models:

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

2. The database should be a knowledge platform for data sharing, mining and analysis relating to the preclinical testing of candidate therapeutic agents in AD animal models.

3. The database should help identify critical experimental design elements and methodology missing from studies, reducing their rigor, reproducibility and translational value.
Recommendations: Best Practices and Study Design Guidelines for Preclinical Animal Studies

- Power Analysis/Sample Size
- Statistical Analysis Plan
- Inclusion, Exclusion Criteria
- Randomization
- Blinding (treatment allocation and outcome measures)
- Balance for Sex as a Biological Variable
- Report Age of Animals
- Report Genetic Background
- Dose, Frequency of Administration, Route of Delivery
- Employ Translatable Biomarkers
- Use PK/PD, ADME to Characterize Candidate Therapeutic Agents
- Report Toxicology Measures
- Report Potential Conflicts of Interest
Responding to the Recommendations:
Alzheimer’s Disease Preclinical Efficacy Database

Launched Jan 2016
Overview of Scope:

- 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.
- Provide search capability across relevant translational criteria data sets:
  - Therapy Type
  - Therapeutic Agent
  - Therapeutic Target
  - Animal Model
  - PI Name
  - Funding source
- Influence the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics.
- Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.
Data Sources:

- Published data is extracted from the scientific literature and curated.

- In collaboration with Sage Bionetworks Unpublished (positive and negative data) data is obtained directly from researchers.
AlzPED Data Submission Portal

Submit Your Data (Select "published" or "unpublished" below prior to entering your study information.)

1. Bibliographic
2. Therapeutic
3. Animal Model
4. Experimental Design
5. Outcomes

Year of Publication
The year when the Study was published (if applicable)

Title of Study *

Contact PI Last Name *
Contact PI First Name *
Contact PI Middle Initial

Contact PI Affiliation

Co-Authors

Primary Reference (PubMed ID)

Show special characters.

Contact PI Last Name
Contact PI First Name
Contact PI Middle Initial

Contact PI Affiliation

Co-Authors

Primary Reference (DOI)

Funding Source:
Enter or Select (if necessary)

Conflict of Interest

Published
Unpublished
The AlzPED and Sage Bionetworks partnership aims at enabling the curating unpublished preclinical efficacy studies and creating searchable online reports that are available in a pdf format. Submitting PIs will receive a citable DOI.
Submit unpublished preclinical efficacy study to AlzPED Unpublished Data Submission Portal

Submitted study reviewed by two NIA experts in Alzheimer’s Disease

Accepted study published on SYNAPSE-SAGE BIONETWORKS Open Science Knowledge Portal

Citable DOI generated for accepted submitted study

Searchable online report of study in pdf format
### AlzPED Search Functions

**Bibliographic Info**

- **Study type**
  - All

- **Funding Source**
  - Select Option(s)

- **Full Text Search**
  - Full Text Search

- **PI Name**
  - PI Name

- **Title**
  - Title

- **Primary Reference ID**
  - Primary Reference ID

**Therapeutic Agent**

- **Therapeutic Agent**
  - Select Option(s)

- **Therapy Type**
  - Select Option(s)

- **Therapeutic Target**
  - Select Option(s)

**Animal Model**

- **Model Name**
  - Select Option(s)

- **Model Type**
  - Select Option(s)
### AlzPED Search Functions

#### Bibliographic Info
- **Study type**
  - All
- **Funding Source**
  - Select Option(s)
- **Full Text Search**
  - Full Text Search
  - Title
  - PI Name
  - Primary Reference ID

#### Therapeutic Agent
- **Therapeutic Agent**
  - Select Option(s)
- **Therapy Type**
  - Select Option(s)
- **Therapeutic Target**
  - *Gamma secretion X*

#### Animal Model
- **Model Name**
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- **Model Type**
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<tr>
<th>APID</th>
<th>Title</th>
<th>Year</th>
<th>PI Name</th>
<th>Therapeutic Agent(s)</th>
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<tbody>
<tr>
<td>9311115</td>
<td>Peptides of presenilin-1 bind the amyloid precursor protein ectodomain and offer a novel and specific therapeutic approach to reduce β-amyloid in Alzheimer’s disease</td>
<td>2015</td>
<td>Dewji N Nazneen</td>
<td>PS-1, NH2-terminal peptides</td>
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<tr>
<td>10761110</td>
<td>Oral treatment with a gamma-secretase inhibitor improves long-term potentiation in a mouse model of Alzheimer’s disease</td>
<td>2010</td>
<td>Townsend Matthew</td>
<td>MRK-560</td>
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<td>10811107</td>
<td>The novel gamma secretase inhibitor N-[cis-4-{[4-chlorophenyl]sulfonyl}]-4-(2,5-difluorophenyl)cyclohexyl]-1,1,1-trifluoromethanesulfonamide (MRK-560) reduces amyloid plaque deposition without evidence of notch-related pathology in the Tg2576 mouse</td>
<td>2007</td>
<td>Best D. Jonathan</td>
<td>MRK-560</td>
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<td>11550510</td>
<td>Chronic treatment with a novel gamma-secretase modulator, JNU-40188777, inhibits amyloid plaque formation in a mouse model of Alzheimer’s disease.</td>
<td>2010</td>
<td>Mercken Marc</td>
<td>JNU-40188777</td>
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Sample of a Curated Record on AlzPED


**Therapeutic Agent**
- **Therapeutic Type:** Small Molecule
- **Therapeutic Agent:** GSI-953 (Begacestat)
- **Therapeutic Target:** Gamma secretase

**Animal Model**
- **Species:** Mouse
- **Model Name:** Tg2576
- **Strain/Genetic Background:** Not Reported

**Outcomes**
- **Outcome Parameters:**
  - Behavioral
  - Biochemical
  - Pharmacokinetics
  - Pharmacodynamics
  - Toxicology

**Experimental Design**
- **Is the following information reported in the study?:**
  - Randomized into Groups
  - Elicited for Treatment
  - Pharmacokinetic Measures
  - Toxicology Measures
  - Biomarkers
  - Formulation
  - Duration of Treatment
  - Sex at the Beginning of Treatment
  - Sex as a Biological Variable
  - Number of Premature Deaths
  - Statistical Plan
  - Inclusion/Exclusion Criteria Included
  - Conflict of Interest


Abstract

The presenilin containing gamma-secretase complex is responsible for the regulated intramembranous proteolysis of the amyloid precursor protein (APP), the Notch receptor, and a multitude of other substrates. Gamma-Secretase catalyzes the final step in the generation of Abeta(40) and Abeta(42) peptides from APP. Amyloid beta-peptides (Abeta peptides) aggregate to form neurotoxic oligomers, senile plaques, and congoophilic angiopathy, some of the cardinal pathologies associated with Alzheimer’s disease. Although inhibition of this protease acting on APP may result in potentially therapeutic reductions of neurotoxic Abeta peptides, nonselective inhibition of the enzyme may cause severe adverse events as a result of impaired Notch receptor processing. Here, we report the preclinical pharmacological profile of GSI-953 (begacestat), a novel thiophene sulfonamide gamma-secretase inhibitor (GSI) that selectively inhibits cleavage of APP over Notch. This GSI inhibits Abeta production with low nanomolar potency in cellular and cell-free assays of gamma-secretase function, and displaces a tritiated analog of GSI-953 from enriched gamma-secretase enzyme complexes with similar potency. Cellular assays of Notch cleavage reveal that this compound is approximately 16-fold selective for the inhibition of APP cleavage. In the human APP-overexpressing Tg2576 transgenic mouse, treatment with this orally active compound results in a robust reduction in brain, plasma, and cerebral spinal fluid Abeta levels, and a reversal of contextual fear-conditioning deficits that are correlated with Abeta load. In healthy human volunteers, oral administration of a single dose of GSI-953 produces dose-dependent changes in plasma Abeta levels, confirming pharmacodynamic activity of GSI-953 in humans.

PMID: 19671883 DOI: 10.1124/jpet.109.152975
AlzPED Tracks Critical Elements of Design for Each Curated Study

### Bibliographic Information


**APIID:** 11261209  
**PI Name:** Jacobsen, J Steven  
**Year of Publication:** 2009

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**Is the following information reported in the study?**

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

- Hosts curated summaries from 720 published preclinical efficacy studies

- Searchable by:
  - Therapeutic Target (146 Therapeutic Targets)
  - Therapeutic Agent (641 Therapeutic Agents)
  - Animal Model (149 Models)
  - Principal Investigator
  - Funding Agency

- Includes links to databases for:
  - Related Publications (PubMed)
  - Therapeutic Targets (Open Targets & Pharos)
  - Therapeutic Agents (PubChem)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Patents (Google Patents)

- Provides a platform for creating citable reports/preprints of unpublished studies, including studies with negative data. Full reports and data hosted on Synapse/AMP-AD Knowledge Portal

- Summarizes Elements of Experimental Design (reports on RIGOR of each study)
AlzPED Identifies 24 Experimental Design Elements that Improve Rigor and Translational Value of Preclinical Studies

Data presented as percentage reported, calculated from 720 curated studies

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<th>EXPERIMENTAL DESIGN ELEMENTS</th>
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<td>99</td>
</tr>
<tr>
<td>Route of Delivery</td>
<td>100</td>
</tr>
</tbody>
</table>
AlzPED Identifies 9 Core Experimental Design Elements that are Essential for Improving Rigor and Translational Value of Preclinical Studies

Data presented as percentage reported, calculated from 720 curated studies
AlzPED Summary: Percentage of Curated Studies Reporting 0-8 Core Experimental Design Elements Essential for Rigor and Reproducibility

DATA PRESENTED AS PERCENTAGE REPORTED, CALCULATED FROM 720 CURATED STUDIES
**AlzPED** Compares the Reporting Trends in 9 Core Experimental Design Elements Between NIH-Funded and Non-NIH Funded Studies

Data presented as percentage reported, calculated from 275 NIH-funded studies and 445 non-NIH funded studies, and analyzed using two-tailed t test; **p=0.0126, ***p=0.0019
Alzheimer’s Disease Preclinical Efficacy Database (AlzPED)

Open Science Knowledge Portal ● Rigor in Research ● Transparency ● Reproducibility ● Translatability ● Lets Connect!

Washington D.C. Metro Area

• Publicly available and searchable data resource designed to improve the reproducibility and translatability of animal model efficacy testing studies for Alzheimer’s Disease and related dementias.

• Hosts curated summaries of published studies and provides easy access to information on study design methods and outcomes, animal models, therapeutic agents, therapeutic targets, patents and related clinical trials.

• Provides a platform for creating citable reports/preprints of unpublished studies, including studies with negative findings.

Join at: linkedin.com/in/alzheimer’s-disease-preclinical-efficacy-database-alzped-13631a177
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Alzheimer's Disease Preclinical Efficacy Database
AlzPED - Transparent, Reproducible, Translatable
AlzPED Contact Information

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