

Alzheimer's Preclinical Efficacy Database (AlzPED): A New Data Resource for Improving the Rigor, Transparency, Reproducibility and Translation of Drug Efficacy in Animal Models of Alzheimer's Disease

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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. Several 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 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:

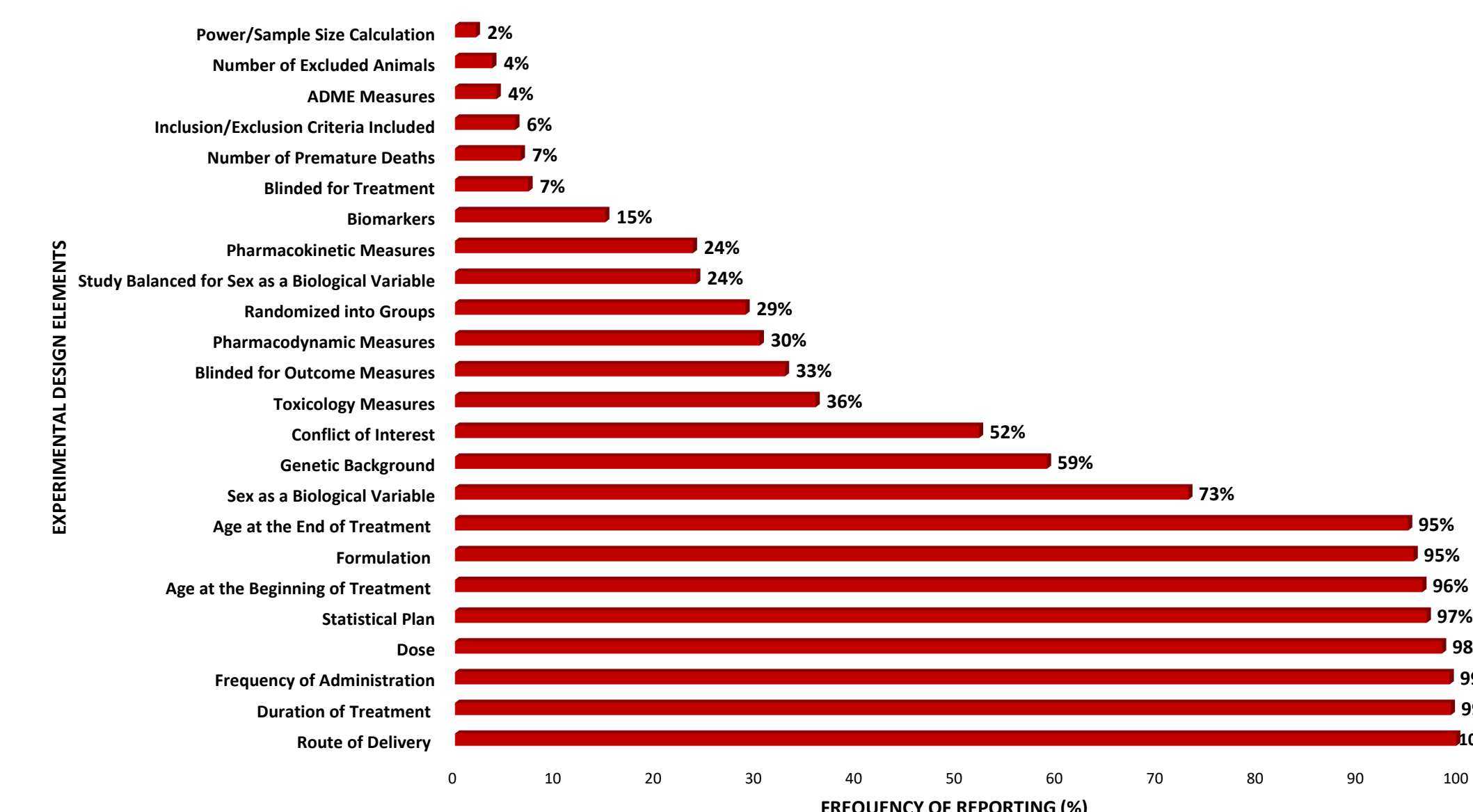
- Provides researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the elements of rigorous study design and requirements for transparent reporting.
- Currently hosts curated summaries from **917** preclinical 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
 - Therapeutic Agent
 - Therapeutic Target
 - Animal Model
 - Principal Investigator
 - Funding Source
 - Related Publications ([PubMed.gov](#))
 - Therapeutic Agents ([PubChem.gov](#) and [DrugBank.ca](#))
 - 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: EXAMPLE OF RIGOROUS STUDY DESIGN

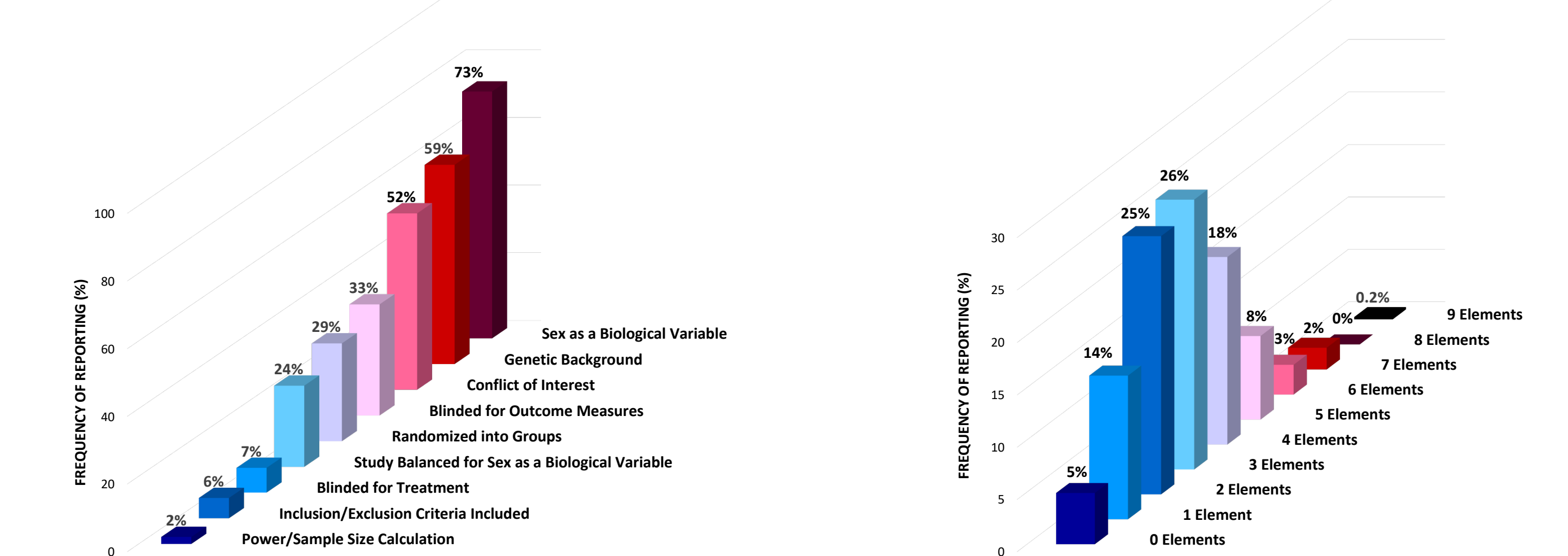
BIBLIOGRAPHIC	THERAPEUTIC AGENT	ANIMAL MODEL	EXPERIMENTAL DESIGN	OUTCOMES														
<p>Bibliographic</p> <p>Year of Publication: 2019</p> <p>Contact PI Name: Michal Schwartz</p> <p>Contact PI Affiliation: Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel.</p> <p>Co-Author: Neta Rosenczweig, Raz Dvir-Szternfeld, Afroditi Tatsou-Kampelli, Hadass Keren-Shaul, Hilla Ben-Yehuda, Pierre Well-Raynal, Liora Cahalon, Alex Kertesz, Kobi Baruch, Idit Amit, Assaf Weiner</p> <p>Primary Reference (PubMed ID): 30692527#</p> <p>Funding Source: EU Seventh Framework Program, Israel Science Foundation (ISF), ISF-Legacy Heritage Biomedical Science Partnership-research grant, Advanced European Research Council</p> <p>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.</p>	<p>Therapeutic Agent</p> <p>Therapeutic Information:</p> <p>Therapy Type: Biologic - Immunotherapy(passive)</p> <p>Therapeutic Agent: anti-PD-1 Antibody</p> <p>PubMed# PubChem# ClinicalTrials# Patent#</p> <p>Therapeutic Target: Programmed Cell Death Protein 1 (PD-1)</p> <p>Open Targets# Pharos#</p> <p>Therapy Type: Biologic - Immunotherapy(passive)</p> <p>Therapeutic Agent: anti-PD-L1 Antibody</p> <p>PubMed# PubChem# ClinicalTrials# Patent#</p> <p>Therapeutic Target: Programmed Death-Ligand 1 (PD-L1)</p> <p>Open Targets# Pharos#</p>	<p>Animal Model</p> <p>Model Information:</p> <p>Species: Mouse</p> <p>Model Type: APP/PS1</p> <p>Model Name: Sx/FAD ALZFORUM#</p> <p>Strain/Genetic Background: C57BL/6 x SJL</p> <p>Species: Mouse</p> <p>Model Type: Tau</p> <p>Model Name: DM-hTAU</p> <p>Strain/Genetic Background: BALB/c-C57/BL6</p>	<p>Experimental Design</p> <p>Is the following information reported in the study?</p> <ul style="list-style-type: none"> ✓ Power/Sample Size Calculation ✓ Blinded for Treatment ✗ Pharmacokinetic Measures ✗ Toxicology Measures ✗ Biomarkers ✓ Formulation ✓ Duration of Treatment ✓ 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 ✓ Blinded for Outcome Measures ✗ Pharmacodynamic Measures ✗ ADME Measures ✓ Dose ✓ Route of Delivery ✓ Frequency of Administration ✓ 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 	<p>Outcomes</p> <table border="1"> <thead> <tr> <th>Outcome Measured</th> <th>Outcome Parameters</th> </tr> </thead> <tbody> <tr> <td>Behavioral</td> <td>• Radial Arm Water Maze • T-Maze • Y-Maze</td> </tr> <tr> <td>Histopathology</td> <td>• Neuronal Loss • Colocalization-astrocytes/microglia/amyloid plaques • Activated Microglia • beta amyloid deposits • beta amyloid load</td> </tr> <tr> <td>Biochemical</td> <td>• 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)</td> </tr> <tr> <td>Immunohistochemistry</td> <td>• 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)</td> </tr> <tr> <td>Microscopy</td> <td>• Cell Survival • Cell Viability</td> </tr> <tr> <td>Omics</td> <td>• Whole Transcriptome Analysis</td> </tr> </tbody> </table>	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)	Immunohistochemistry	• 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
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KEY ELEMENTS OF RIGOROUS EXPERIMENTAL DESIGN



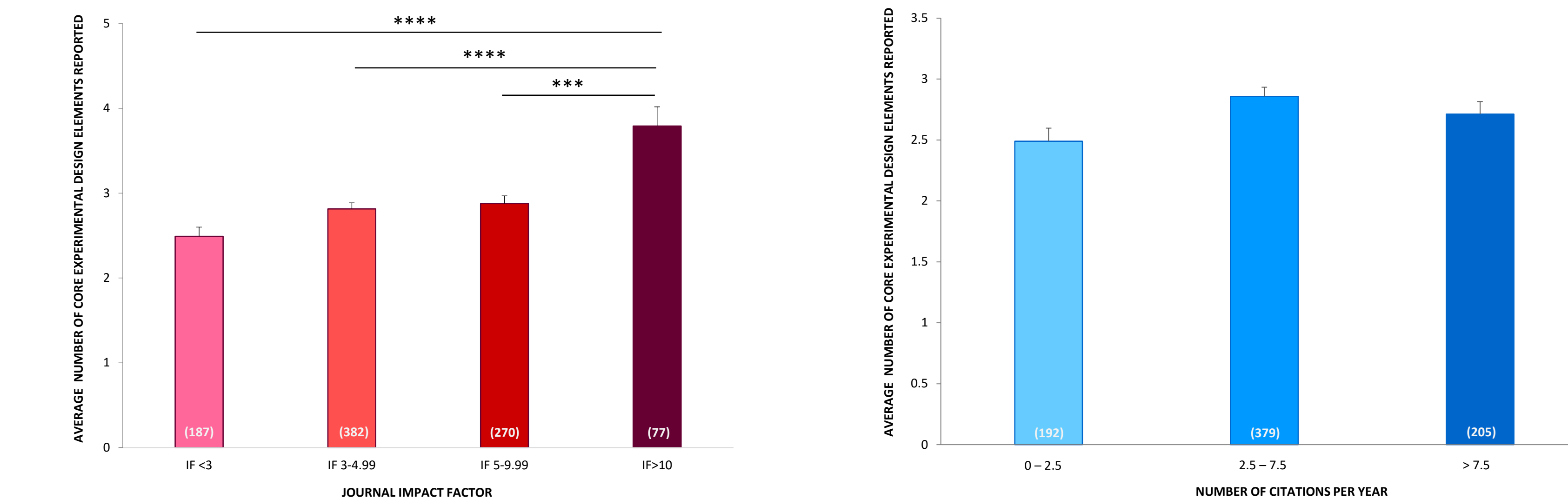
There is considerable variation in the frequency of reporting the 24 recommended elements of experimental design that improve the reproducibility and translational value of preclinical efficacy research. Data are presented as percentages calculated from 917 published preclinical efficacy studies published between 1996 and 2019 and curated in AlzPED.

9 CORE ELEMENTS OF RIGOROUS EXPERIMENTAL DESIGN



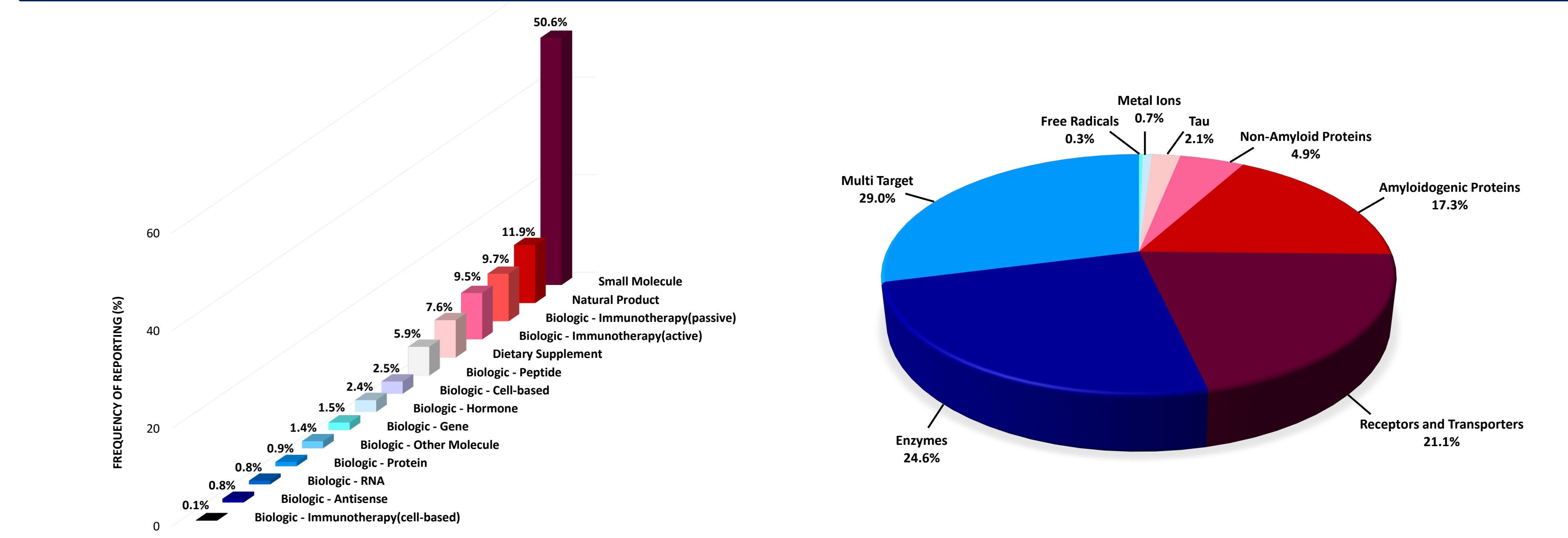
LEFT: 9 **CORE** elements of experimental design that are **critical** for scientific rigor and reproducibility are poorly reported in preclinical research. RIGHT: Few studies report more than 5 core design elements, most reporting only 2-4 core design elements.

REPORTING TRENDS FOR THE 9 CORE ELEMENTS BASED ON JOURNAL IMPACT FACTOR AND NUMBER OF CITATIONS PER YEAR



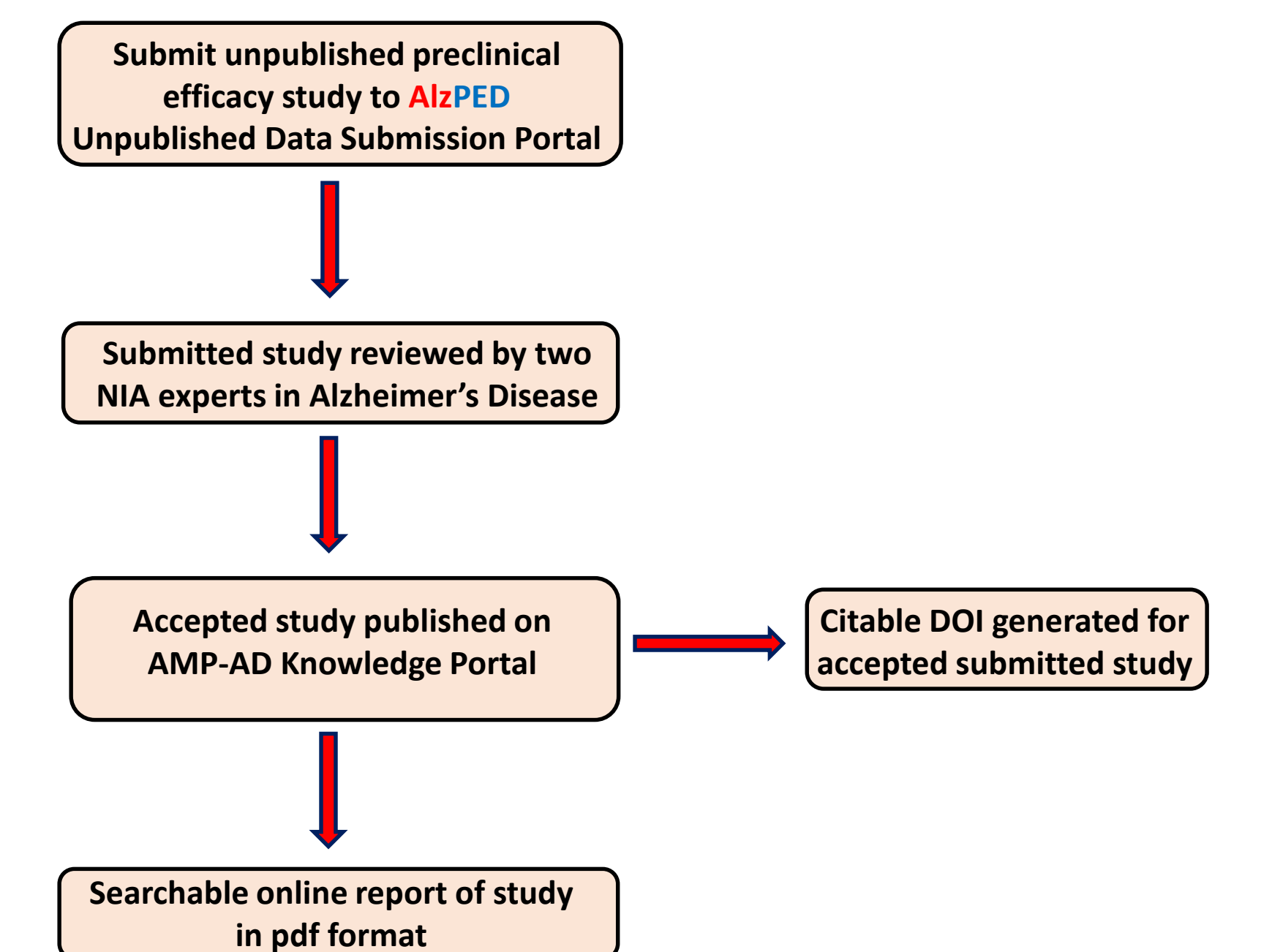
LEFT: Reporting trends for the 9 core design elements based on 2018 journal impact factors. RIGHT: Reporting trends for the 9 core design elements based on number of citations per year from studies published between 1996 and 2017. Note that, while there are statistically significant differences in reporting these elements in publications from high impact journals (IF > 10), overall the data show poor reporting practices irrespective of journal impact factor and number of citations per year. Data are presented as Mean ± SEM and analyzed using t tests, ***p<0.001, ****p<0.0001, samples sizes for each group are listed on the graphs.

THERAPEUTICS



LEFT: 804 therapeutic agents are catalogued in 14 categories. RIGHT: 175 therapeutic targets are catalogued in 8 categories. Data are presented as percentages calculated from 917 published preclinical efficacy studies published between 1996 and 2019 and 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**:

- Analysis of curated studies in AlzPED, demonstrates serious deficiencies in reporting critical elements of methodology such as power calculation, blinding for treatment/outcomes, randomization, sex of animal used and balancing for sex, animal genetic background and others.
- Poor reporting of critical elements of methodology is demonstrated in high impact factor journals as well as highly cited published preclinical research.
- These deficiencies in study design and methodology diminish the scientific rigor, reproducibility and translational value of the preclinical studies.
- It is evident that a standardized set of best practices is required for successful translation of therapeutic efficacy in AD research.