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PERSPECTIVE

Meeting report of the annual workshop on Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease research

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Abstract

Introduction: The second annual 5-day workshop on Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease Research was held October 7–11, 2019, at The Jackson Laboratory in Bar Harbor, Maine, USA, and included didactic lectures and hands-on training. Participants represented a broad range of research across the Alzheimer's disease (AD) field, and varied in career stages from trainees and early stage investigators to established faculty, with attendance from the United States, Europe, and Asia.

Methods: In line with the National Institutes of Health (NIH) initiative on rigor and reproducibility, the workshop aimed to address training gaps in preclinical drug screening by providing participants with the skills and knowledge required to perform pharmacokinetic, pharmacodynamics, and preclinical efficacy experiments.

Results: This innovative and comprehensive workshop provided training in fundamental skill sets for executing in vivo preclinical translational studies.

Discussion: The success of this workship is expected to translate into practical skills that will enable the goals of improving preclinical to clinical translational studies for AD.

KEYWORDS
Alzheimer's disease, best practices, mouse models, preclinical translation, rigor and reproducibility, training

HIGHLIGHTS

- Nearly all preclinical studies in animal models have failed to translate to successful efficacious medicines for Alzheimer's disease (AD) patients.
- While a wide variety of potential causes of these failures have been proposed,deficiencies in knowledge and best practices for translational research are not being sufficiently addressed by common training practices.

- Here we present proceedings from an annual NIA–sponsored workshop focused specifically on preclinical testing paradigms for AD translational research in animal models aimed at enabling improved preclinical to clinical translation for AD.

1 | INTRODUCTION

Preclinical testing in animal models is critical for informng clinical trial design and understanding the potential for efficacy and safety of therapeutic interventions. Unfortunately, although hundreds of interventions have been demonstrated to have efficacy in animal models of Alzheimer's disease (AD) and these studies ultimately led to clinical trials, poor preclinical to clinical translation has resulted in an exorbitant failure rate for AD therapeutics.[1–3] Although a wide variety of potential causes of these failures have been proposed, deficiencies in the experimental design, execution, and rigor of preclinical translational experiments are not being sufficiently addressed by common training practices across research laboratories.[1–4]

Preclinical translation is not typically a course of study available to researchers at their academic institutions; thus it is not surprising that methods for design and study execution are often based on individual knowledge and experiences rather than a vetted curriculum with specific training criteria.[5,6] Although the pharmaceutical industry employs rigorous best practices that align with clinical study design, this knowledge is not typically available as an instructional course, and neither are the hands-on training components that allow for development of fundamental skillsets needed for proficient execution of in vivo studies, specific to enable translation. In order to address gaps in training deficiencies in preclinical translational studies for AD, we developed a workshop with the following specific aims: (1) train participants in the rigorous design, experimental execution, analysis, and reporting of data in line with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines for preclinical testing of AD therapies; (2) provide participants with the practical laboratory tools and skills to perform rigorous, reproducible preclinical tests on mouse models of AD; and (3) promote honest open discussion to address challenges in the research field to achieving rigorous translational studies that apply best practices. This workshop focused specifically on preclinical testing paradigms for AD translational research that encompassed comprehensive hands-on sessions, didactic lectures, and discussions, in the practices of performing rigorous, reproducible preclinical experiments to enable improved preclinical to clinical translation for AD. As a key component of this workshop, which was presented at The Jackson Laboratory in Bar Harbor, Maine (JAX), participants were exposed to discussion forums on historical practices that have led to gaps in preclinical translation to date, new resources and infrastructure now available to better enable improved translation, and standard operating procedures (SOPs) and best practices used for in vivo screening of potential therapeutic agents for Alzheimer's research. The ultimate goal of this workshop was to enable trainees of this generation of scientists and future generations to accelerate the pace of bringing treatments to patients.

1.1 | Gaps in historical preclinical studies for AD

Poor translation of preclinical efficacy data in animal models to effective therapies for patients remains a significant roadblock for advancing interventions through clinical trials and US Food and Drug Administration (FDA) approval.[1–4] Dr. Suzana Petanceska (Director of the Office for Strategic Development and Partnerships, Division of Neuroscience, National Institute on Aging) emphasized a number of key factors including: (1) the failure of the animal models to recapitulate the spectrum of human AD; (2) poor rigor in study design and data analysis; (3) insufficient attention toward best practices; (4) failure to match outcome measures with those of clinical studies; (5) poor reproducibility of published data; and (6) publication bias in favor of reporting positive findings.[7] Dr. Petanceska described efforts to address these gaps by the development of a publicly available data repository curated by the National Institute on Aging and National Institutes of Health (NIH): Alzheimer's Preclinical Efficacy Database (AlzPED; https://alzped.nia.nih.gov/).[7] AlzPED is a searchable web portal that houses information on preclinical studies including animal models descriptors, key elements of the study design, information related to the therapeutic target and therapeutic agent, principal findings, and information related to funding source(s) and financial conflict of interest.[7] A long-term goal for AlzPED is to provide a platform for reporting unpublished studies in order to mitigate the publication bias that favors the reporting of positive findings. Dr. Stacey Rizzo (University of Pittsburgh) provided an overview of the drug-discovery process and provided insight into how traditional cognitive behavioral tests in rodents have failed to translate to cognitive improvement in the clinic.[8] These include the most frequently reported assays for assessing the potential of AD therapeutics including fear conditioning, novel object recognition, and water maze assays.[8] Dr. Rizzo emphasized the lack of rigorous experimental design inclusive of lack of vehicle-treated controls, unknown drug-exposure relationships, absence of dose response, and misinterpretation of data due to confounding variables including hyperactivity and visual impairments related to background strain.[1,2,8] Dr. Michael Sasner (JAX) discussed the challenges and limitations of historical mouse models that have been used frequently to evaluate therapeutics as a factor in poor translation.[3] These include the concern that existing animal models have focused on early-onset AD (EOAD) genetics while the primary patient population are those with the late-onset sporadic form of AD (LOAD); that mice do not spontaneously present with amyloid beta (Aβ)

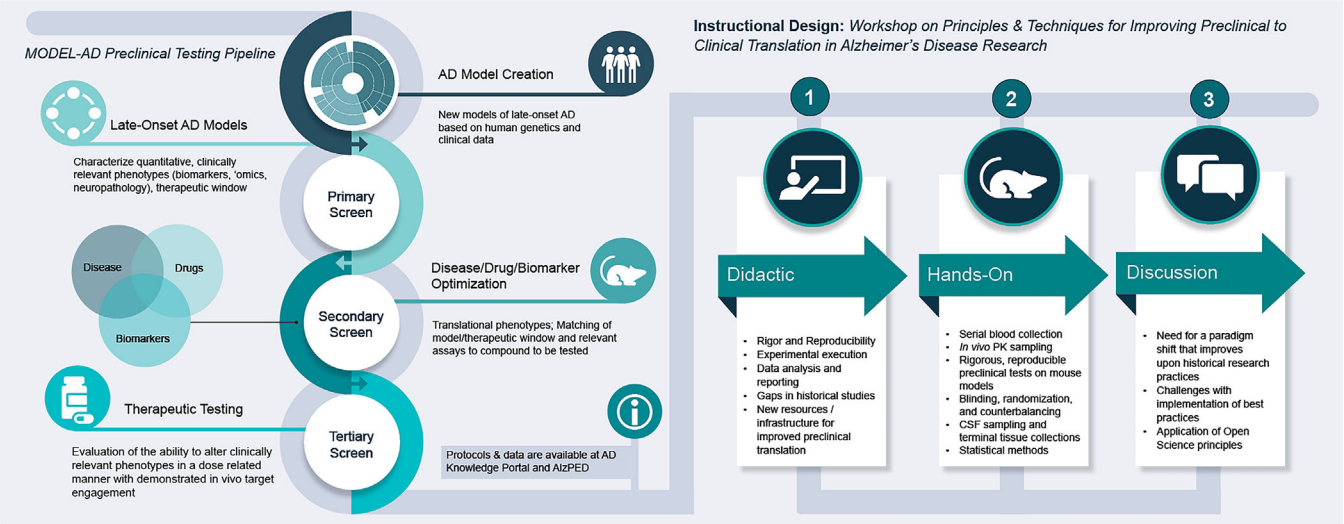

FIGURE 1 The annual workshop on Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease Research provides participants with the skills and knowledge required to perform pharmacokinetics, pharmacodynamics, and preclinical efficacy experiments by leveraging the rigorous best practices and approaches of the MODEL-AD preclinical testing core. This innovative and comprehensive workshop provides training in fundamental skill sets for executing in vivo preclinical translational studies with the goal of improving preclinical to clinical translational studies for AD. AD, Alzheimer's disease; MODEL-AD, Model Organism Development for the Evaluation of Late Onset Alzheimer's Disease.

or tau pathology unless genetically modified, and that no single AD model exhibits both Aβ and tau pathology robustly, and nor do most models recapitulate the extensive neurodegeneration observed in AD patients; that most existing models demonstrate significant ectopic overexpression of a transgene that introduces non-physiologic effects unrelated to AD; issues with models being generated on hybrid genetic backgrounds and not maintained on congenic and genetically stable backgrounds; issues of legal restrictions, preventing use of many models by for-profit companies for preclinical translational studies; and perhaps most importantly, insufficient attention paid to selection of the appropriate model for a specific combination of drug and physiological readout.[3,9–12]

1.2 | New resources for supporting preclinical translational studies of AD

As highlighted by Dr. Petanceska, significant investment in infrastructure and resources for AD have been made by the NIA over the last several years in order to move the field forward in line with the National Alzheimer's Project Act to identify a treatment by 2025. These include many new funding opportunities such as that which led to the establishment of the Model Organism Development for the Evaluation of Late Onset Alzheimer's Disease (MODEL-AD) Precision Medicine Consortium.[1,3] Dr. Sasner provide an overview of MODEL-AD as a resource for generating and comprehensively characterizing up to 50 new mouse models focused on genetic variants of LOAD that are available without restrictions to the research community. Details of variant selection and the characterization pipelines with a focus on best practices were highlighted by Drs. Greg Carter and Gareth Howell (JAX). These models are ultimately being created to be used to evaluate potential therapeutics. Dr. Kelly Dakin (AlzForum) provided a tutorial on how to navigate the AlzForum website, a public resource that curates information on historical and new mouse models from MODEL-AD that researchers can access for the most updated information in the field.[13] In addition, Dr. Kristen Onos (JAX) highlighted work on genetically diverse mouse strains and their utility as improved models for AD over traditional inbred strains.[14] Finally, Dr. Paul Territo (Indiana University) and Dr. Rizzo described the Preclinical Testing Core of MODEL-AD and the best practices established for preclinical screening of compounds that prioritizes translational pharmacokinetics (PK) and pharmacodynamics (PD) measures including positron emission tomography/magnetic resonance (PET/MR), 'omics, neuropathology, and biomarkers over traditional cognitive assessments in rodents as part of the preclinical screening pipeline. In addition, methods for training of staff including proficiency metrics to ensure rigor and reliability were discussed.[1,3]

1.3 | Hands-on practicums for the development of fundamental skill sets for in vivo studies

Following an Animal Welfare orientation requirement, participants were approved by the Institutional Animal Care and Use Committee (IACUC) at JAX to conduct approved procedures on mice. Training over the course of multiple hands-on sessions included serial blood collections using established protocols for in vivo PK sampling studies;

practicums on methods for blinding, randomization, and counterbalancing of samples in real-time; and methods for cerebrospinal fluid (CSF) sampling and terminal tissue collections. The trainer to trainee ratio was 1:2. At the conclusion of the hands-on training, Dr. Sara Quinney (Indiana University) described how to interpret bioanalytical data from in vivo PK sampling and the importance of PK/PD modeling. Finally, Dr. Vivek Philip (JAX) provided a statistical practicum including methods and resources for conducting power analyses and the development of an appropriate experimental design for rigorous preclinical translational studies. This session also provided the opportunity for participants to get assistance with experimental designs for upcoming studies in their respective laboratories.

2 | DISCUSSION

This workshop was developed with the overall goal to provide much needed training in screening strategies in vivo for researchers engaged in translational studies with a focus on development of fundamental hands-on skills in executing rigorous preclinical studies. This format also provided an opportunity for participants to discuss challenges with implementing these types of rigorous best practices in their laboratories. A common concern voiced among trainees was the lack of resources and/or funding to be able to conduct rigorous, well-powered studies, as well as concerns of pressure from their superiors, either perceived or real, toward biasing their experimental design or data manipulation toward a positive result. However, trainees were also optimistic that as they transition to their own independent laboratories that this workshop provided them with the essential hands-on skills and knowledge to enable improved translational studies and train the next generation of researchers. In closing, this workshop provided unique instructional strategies with training aimed to improve rigor in preclinical drug-screening experiments and ultimately accelerate the pace of bringing treatments to patients (Figure 1). This hands-on workshop is planned as an annual event at The Jackson Laboratory in Bar Harbor, Maine. The course is open to trainees, experienced researchers, and clinicians at all levels, across academia and industry. Those researchers new to the field are also highly encouraged to register and attend. Course details and registration information can be found at The Jackson Laboratory Courses & Workshop website.

AUTHOR CONTRIBUTIONS

Michael Sasner, Paul R. Territo, and Stacey J. Sukoff Rizzo are course directors, designed the workshop content, and wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

Michael Sasner is a full-time employee of The Jackson Laboratory. Paul R. Territo is a full-time employee of Indiana University School of Medicine. Stacey J. Sukoff Rizzo is a full-time employee of The University of Pittsburgh School of Medicine. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the meeting. The MODEL-AD SOPs provided during the hands-on workshop are available through the AD Knowledge Portal: adknowledgeportal.synapse.org

CONSENT STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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