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COMMENTARY

National Institute on Aging

NIA Commentary: Translational Issues in Alzheimer's Disease Drug Development

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Alzheimer's disease (AD) mainly affects elderly individuals, and because of the aging of populations worldwide, this disorder is reaching epidemic proportions, with an enormous human and economic burden. Effective treatments are urgently needed to treat the cognitive and behavioral symptoms of AD and to slow its progression. The National Institute on Aging (NIA) has developed a number of grant and contract mechanisms to support this effort.

The NIA has an exploratory R21 grant program (http://grants.nih.gov/grants/guide/pa-files/PAS-10-151.html) for early AD drug discovery, in collaboration with the Alzheimer's Drug Discovery Foundation, and a program for preclinical drug development of small molecules, biologics, or other compounds for the treatment of AD, mild cognitive impairment (MCI), and age-related cognitive decline, using the U01 cooperative agreement mechanism (http://grants.nih.gov/grants/guide/pa-files/PAR-08-266.html). Examples of funded grants include studies of small molecule neurotrophin mimetics, novel anti-inflammatory compounds, and τ-aggregation inhibitors. The NIA provides investigational new drug-enabling toxicology services for novel AD therapeutic drugs through a contract, which is open to individual investigators or small companies.

The NIA also participates in many trans-NIH programs including program announcements for drug discovery for nervous system diseases utilizing the R21 and R01 grant mechanisms, Small Business Innovation Research/Small Business Technology Transfer Research grant programs, and translational programs through the NIH Neuroscience Blueprint (http://neuroscienceblueprint.nih.gov/).

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The overall goal of these translational research initiatives is to provide support to investigators from academia and the biotechnology sector to increase the number of drug candidates that can be clinically tested. Clinical development can be done through partnership with industry or through NIA-supported clinical trial programs. These include a program announcement for pilot clinical trials (http://grants.nih.gov/grants/guide/pa-files/PAR-11-100.html), large R01 grant applications, and the Alzheimer's Disease Cooperative Study, an NIA-supported clinical trials consortium. Examples of pilot trials include intranasal insulin in people with AD/MCI, and carvedilol in AD, which is an anti-hypertensive drug that was re-purposed for AD, with support from the U01 program.

Through these programs, the NIA hopes to facilitate the discovery, development, and testing of new therapeutic agents for AD, MCI, and age-related cognitive impairment. There are very few drugs that have been approved by the Food and Drug Administration for the treatment of AD. There have been many recent clinical trials of potential new therapeutic agents, but none has been shown to be effective in providing symptomatic benefit or slowing disease progression. This indicates the critical nature of the NIA/NIH programs in trying to facilitate getting new therapies out to the patients and families who desperately need them.

FUTURE DIRECTIONS

In 2010 PhRMA, the pharmaceutical industry's advocacy group reported 79 new therapies in development for AD (http://www.phrma.org/sites/default/files/422/alzheimers2010.pdf). To date, none of these therapies has been successful in the clinic. There are numerous reasons to explain this high rate of clinical failure, but a major one is the inability of preclinical studies to correctly characterize and identify good clinical candidates.

To address this problem, the NIA convened an advisory workshop, 'Advancing Preclinical Therapy Development for

Alzheimer's Disease.' The following three topics focused on improving the quality of preclinical therapy studies.

Can Systems Biology Rescue AD Drug Discovery?

A major obstacle in developing new treatments for AD is an inadequate understanding of basic biological pathways affected by the disease, and the contributions of these pathways to disease pathophysiology. There is a growing realization that AD is a disorder affecting a large number of neuronal cell types organized into functionally connected networks across many brain regions, and not just a disease of discrete brain lesions isolated in specific brain regions (Liu *et al*, 2010). Many in the AD field now view the disease as a response to a shift from normal to pathological networks, not a response to a pathogenic change in a single target, and this poses a special challenge to the selection of truly disease-relevant therapeutic targets. Furthermore, the focus of AD therapy development has been a target-centric drug discovery, with target selection based on genetic studies and pathological features of the disease, and validated in transgenic mouse models of AD pathology in the absence of any solid biological/physiological validation. Drugs are identified and optimized for activity in target-based *in vitro* screens, and not in truly relevant biological models of the disease. This approach has proven very disappointing. There is a need for a biology-driven or systems-biological approach that will allow a better understanding of disease complexity, specifically, an understanding of the response of a potential therapeutic target within the physiological networks operating in the brains of AD patients.

What are the Causes for the Failed Pre-Clinical to Clinical Translation of AD Therapies?

AD animal models have contributed greatly to our understanding of disease mechanisms. However, the large number of clinical failures, mostly due to lack of efficacy, which have followed successful pre-clinical efficacy studies suggests that their translational value in predicting the effectiveness of therapies in humans is marginal (van der Worp *et al*, 2010). Current AD animal models do not accurately recapitulate the human disease; therefore, these differences contribute to the difficulty of predicting efficacy in humans with AD (Ashe and Zahs, 2010). Also, preclinical studies are not aligned with relevant points along the AD disease continuum, meaning that animals are being treated in what corresponds to the human prodromal stage, prior to appearance of measurable cognitive deficits and pathological lesions, but humans are being treated at the fully-developed stage of AD (Zahs and Ashe, 2010). As they are used now, the pre-clinical animal studies inform only prevention trials or, at best, early MCI; they need to be aligned with all the stages of AD. Also needed is the identification and incorporation of reliable preclinical biomarkers that can be translated to clinical development. In addition, translational failure may be explained by a lack of standardized operating procedures used within and across laboratories. This has led to systematic bias, inadequate collection of data, and incorrect conclusions about animal efficacy. Animal studies must avoid bias by using power analysis, animal randomization, double blinding, and intention-to-treat analysis in the design of preclinical efficacy studies (van der Worp *et al*, 2010).

Finally, publication bias is likely to contribute to the failure, to translate preclinical efficacy to the clinic (Sena *et al*, 2010). Optimally, the decision to assess the effect of novel AD treatments in clinical trials should be based on an appreciation of all the publically reported information from pre-clinical studies. However, if only those pre-clinical studies reporting robust efficacy are published, such a publication bias would lead to overestimation of treatment effects, leading to unreliability in making decisions on which treatments to take to the clinic.

Is a Public–Private Partnership to Promote AD Drug Discovery a Helpful Direction for Positive Change?

Biopharmaceutical companies are currently facing considerable challenges due to high attrition of projects and rising costs of development. These have led government funders and biopharmaceutical companies to consider an alternative model for high-risk drug discovery, driven by the great opportunities for innovation offered by a relatively new entrant into the drug discovery space—academia (Cressey, 2011). Academic research has traditionally been the home of basic research. However, in recent years, universities have become more involved in drug discovery. This change is partly due to a refocus in NIH-funding that has encouraged a significant number of academic researchers to engage in early stage, pre-clinical therapy development. As a result of this trend, biopharmaceutical companies and universities have begun to develop new public–private partnerships. In this model, the universities take on the high-risk, early-stage drug discovery, and early-stage clinical (Phase I) development activities, handing off to the companies' de-risked programs that can be taken through later-stage clinical development (Phase II–III). Public–private collaboration could solve some of the problems of the biopharmaceutical companies. However, there are a number of barriers that must be overcome, including the availability of drug discovery resources and training for academic researchers, the necessity of working in a 'pre-competitive' space, managing intellectual property issues, and the need to show investors a clear path to financial return.

We believe that the NIA/NIH can have a major role in facilitating drug discovery public–private –partnerships as it has done for other areas of neuroscience such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Burton, 2011).

DISCLOSURE

The authors declare no conflict of interest.

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