

A conversation with Dr. Diana Shineman, June 8, 2015

Participants

- Diana Shineman, Ph.D. – Director for Scientific Affairs, Alzheimer’s Drug Discovery Foundation
- Nick Beckstead, Ph.D. – Research Analyst, Open Philanthropy Project
- Lily Kim, Ph.D. – Science Advisor, Open Philanthropy Project

Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. Diana Shineman.

Summary

The Open Philanthropy Project spoke with Dr. Shineman of the Alzheimer’s Drug Discovery Foundation (ADDF) as part of its investigation into Alzheimer’s disease. Conversation topics included the ADDF’s research priorities, challenges and opportunities in the Alzheimer’s disease funding space, and the importance of biomarker development, as well as a number of other issues facing the field.

The Alzheimer’s Drug Discovery Foundation

The Alzheimer’s Drug Discovery Foundation (ADDF) was founded in 1998 to focus on direct discovery and development of Alzheimer’s disease therapies. It operates using a venture philanthropy model (most similar to that used by the Michael J. Fox Foundation), negotiating a return if the projects or companies it funds are successful. Initially the organization acted as a seed funder, working to de-risk promising treatments until they were likely to be supported by more risk-averse funders.

Since then, the funding landscape has shifted. Although most funders focus on basic research and consortium building, including clinical trial networks and biomarker initiatives, more funders are investing in drug discovery. At the same time, other funders have begun investing even later in the research pipeline, so the ADDF now funds later stage research than it did originally in order to fill gaps created by this shift.

The ADDF sometimes partners with other foundations (including Alzheimer’s Society in the UK) to support some of its larger projects.

Research priorities

The ADDF’s annual research budget is \$10 million. Like most AD funders, the ADDF only funds research on existing targets. It focuses primarily on topics it believes are underrepresented among other funders, including:

- **ApoE** – The ADDF is the largest funder of research on ApoE, an allele strongly associated with late-onset Alzheimer’s disease. It sometimes supports

contradictory approaches (the ADDF funds research on some drugs that increase ApoE and others that decrease it) to more efficiently test hypotheses about the role of ApoE in AD.

- **Tau** – Alzheimer’s disease is associated with two mis-folded proteins in the brain: amyloid and tau. The ADDF is no longer funding amyloid targeting therapies, which are widely supported by pharmaceutical companies and other funders. Instead, it has made tau a priority, because although there is broad interest in tau from government funders, there is still a shortage of funding.
- **Pathways that degenerate with age** – Aging is the greatest risk factor for Alzheimer’s disease. The general homeostatic mechanisms that support the brain tend to dysfunction with age, so the ADDF supports research that targets these pathways., including **neuroinflammation** and **mitochondrial dysfunction**

The ADDF also funds some areas that overlap more with others funders, including clinical trials, biomarker projects, and early detection research (between 15 and 20 percent of the ADDF’s funding portfolio is related to early detection). ADDF’s main interest in funding early detection is to accelerate clinical development by being able to better choose patients for clinical trials and track response to investigational treatments.

Funding for Alzheimer’s disease research

Although it affects a large share of the population, Alzheimer’s disease receives very little money compared to cancer or heart disease. The National Institute on Aging (NIA), one of the largest funders of AD research, only funds 3% of the grant proposals it receives. This lack of funding is one of the biggest challenges facing AD researchers.

More funding for basic research

Most government funding supports translational research and larger initiatives and consortia, leaving basic research particularly underfunded. One of the biggest consequences of such limited funding is that researchers who are unable to obtain funding often shift their focus to another disease, leaving fewer talented researchers in the field. More support for basic research could help retain these scientists.

In particular, Dr. Shineman believes the field needs more basic research on neuroinflammation, lipoproteins (molecules that contain both fat and protein and play an important role in the development of AD), ApoE, and the pathways in the brain that deteriorate with age, especially inflammation. Neuroinflammation is a challenging area of research because it is difficult to study in humans and very dissimilar in animal models, but a great deal of research (including what researchers

know about the genetics of AD) points to neuroinflammation as playing an important role in AD.

Alternate funding model

Tough competition for very limited funding sometimes means that investigators are focused on appeasing peer reviewers rather than on truly innovative ideas. Recently, this problem manifested in an overabundance of research focused on amyloid with other targets neglected. However, the field is evolving and although Dr. Shineman believes this may still be a problem, the ADDF explicitly focuses on underfunded, innovative and riskier areas of research, so this issue is not a major one for the foundation.

Howard Hughes Medical Institute

A funding model that gave investigators more freedom and stability and was more supportive of younger investigators could bring an element of creativity to the field, allow researchers to take more risks, and open the door to the possibility of more collaborative interdisciplinary research teams.

Dr. Shineman believes that the funding model used by the Howard Hughes Medical Institute (HHMI) is one that could work well in the AD funding space. HHMI provides unrestricted funding to talented investigators and focuses on finding promising people rather than promising projects.

Funding reforms

Several organizations are working to address structural issues related to funding:

- The Alzheimer's Association and the NIA have convened a group of international AD funders that meet annually and use quarterly calls and working groups to address funding challenges in the field.
- The Coalition Against Major Diseases, along with industry and foundation partners, is working with the FDA to incorporate biomarkers into their approval process, expediting clinical trials and making them more cost effective.

Alzheimer's disease biomarkers

Conducting effective clinical trials

There are many hurdles to conducting effective clinical trials for potential Alzheimer's disease therapies, including variability of the disease, challenges measuring cognitive outcomes, and the ability to conduct long-term trials, but the lack of accurate Alzheimer's disease biomarkers (measurable indicators of the progression of a disease or the body's response to a treatment) is widely recognized as one of the biggest barriers.

Identifying the right clinical trial patients

The inability to identify and select the right populations is one of the reasons previous trials have been unsuccessful. In some trials, as many as 30 percent of participants had no amyloid in their brains. If researchers had specific biomarkers that allowed them to more accurately identify the patients with the highest chances of responding to a particular therapy and to monitor the effects of that therapy over a shorter time period, they could more easily conduct high quality, cost-effective clinical trials.

Evaluating promising combination therapies

Combination therapies involve multiple drugs that researchers believe may have a synergistic effect when administered together. To evaluate these therapies, researchers need clear indications of target engagement for each individual component of the therapy to assess whether the drugs are effective in combination. As more specific biomarkers are validated, researchers can better understand these therapies without the need for very long trials.

Advancing biomarker research

Researchers are making progress identifying and validating new biomarkers. The Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private partnership that recruits patients and collects samples (which facilitates long-term study of Alzheimer's patients) has helped researchers validate a number of biomarkers.

However, many candidate biomarkers have been developed or tested on very small patient populations. Researchers need access to larger patient populations and additional patient samples so that these markers can be tested and validated. Researchers also need to standardize the investigative procedures they use to measure biomarkers and to better understand how the presence of other diseases can influence AD biomarkers.

Eventually, new biomarkers should be implemented in small clinical trials to assess their performance.

Problems with current imaging techniques

The positron emission topography (PET) imaging techniques available to researchers have had a large impact on clinical trials, but researchers still need to identify and validate more biomarkers. Challenges with PET imaging include:

- **Accessibility** – PET imaging is not always accessible to researchers and when it is, it is very expensive, increasing the costs of clinical trials.
- **Safety** – There are safety concerns with repeated exposure to the radioactivity associated with these scans.
- **Non-amyloid targets** – The most effective PET imaging is amyloid imaging, which is only useful when researchers are studying an amyloid therapy. Researchers need biomarkers for other targets, including tau, inflammation, and synaptic function.

Preventative trials

The A4 study

Funders are investing heavily in preventative therapies targeted at patients with amyloid deposits in their brains, but no or limited cognitive impairment. The largest of these studies (the A4 study) is funded by the NIA and the pharmaceutical industry and focuses on patients who have amyloid plaques in their brains but are not yet exhibiting symptoms of Alzheimer's disease. These participants are treated with immunotherapy that targets amyloid in an effort to prevent additional build-up.

Preventative trials in patients without amyloid in their brains

Dr. Shineman believes that there are challenges with the idea of running preventive trials on patients that have not yet developed amyloid plaques, including:

- **Patient burden** – The treatments being studied are usually delivered via a weekly or monthly IV, a mechanism that is burdensome for patients. Some researchers believe that treatment should ideally begin before symptoms develop, which means that some patients may have to continue treatment for as long as 30 years. Many patients may not be willing to endure frequent IV infusions over such a long period of time.
- **Expense** – Such a long study would be very expensive.
- **Safety** – There are also safety concerns related to targeting amyloid. Amyloid-related imaging abnormalities (ARIA) are asymptomatic side effects that have been found in some participants, but some patients may experience more harmful side effects.
- **Effectiveness** – Some researchers believe that previous trials were unsuccessful because the Alzheimer's patients involved were too advanced and that researchers would have more success with patients who are not yet symptomatic. This hypothesis is still debated in the research community. Dr. Shineman believes if the therapies tested in these trials were eliciting dramatic improvement, they would show some ability to slow disease progression when administered in early symptomatic patients.

Other issues in the field

Data sharing

Researchers need more patient samples and would benefit from the ability to access samples from already-established patient cohorts, but there are challenges related to consent (it is often difficult to locate these patients and obtain their consent once again) and data sharing that make this difficult.

The NIA now emphasizes data sharing, and other funders are collaborating on new language on consent that would allow researchers to more easily share this

information, but many AD researchers lack the expertise needed to make use of the data.

Patient registries

There are a number of efforts underway to try to create patient registries, but the field would benefit more from a single, unified effort.

Public health campaigns

Several organizations, including the ADDF, focus some of their activities on Alzheimer's disease prevention and awareness:

- Studies conducted in the U.K. have suggested that Alzheimer's disease prevalence decreases with increasing awareness of how to improve cardiovascular health.
- The ADDF has created a website (www.cognitivevitality.org) that focuses on prevention and provides scientific assessments of foods, supplements, and drugs that are purported to prevent Alzheimer's disease.
- The Alzheimer's Foundation of America conducts a memory screening day.

Other organizations

Research

Other organizations that fund Alzheimer's disease research include the Cure Alzheimer's Fund the Alzheimer's Association and the Bright Focus Foundation. . ADDF has collaborated with these organizations on various initiatives.

Advocacy

While ADDF is primarily a research funding organization and does not participate in patient advocacy, there have been efforts from numerous other organizations to coordinate advocacy efforts, primarily around increased research funding but also on issues related to caregiver support. Several major foundations are involved in the Leaders Engaged on Alzheimer's Disease (LEAD) coalition, Alzheimer's Association, USAgainstAlzheimer's and the Alzheimer's Foundation of America.

Other people to talk to

- **Heather Snyder, Ph.D.** – Director of Medical and Scientific Operations, Medical and Scientific Relations at the Alzheimer's Association
- **Suzana Petanceska, Ph. D.** – Health Scientist Administrator, Division of Neuroscience at the NIA

All Open Philanthropy Project conversations are available at
<http://www.givewell.org/conversations>