A conversation with Dr. Bruce Miller, April 28, 2015

Participants

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

Summary

The Open Philanthropy Project spoke with Dr. Miller of UCSF as part of its investigation into Alzheimer's disease (AD). Conversation topics included challenges facing this field, as well as underfunded and potentially promising areas of research.

Background

Basic information on Alzheimer's disease can be found here: http://files.givewell.org/files/conversations/Melanie%20Smith%202-17-15%20(public).pdf

Degenerative brain disease is sometimes preventable

Approximately one third of cases of degenerative brain disease are likely preventable.

- Lifestyle factors – Degenerative brain disease is associated with hypertension and low activity. Improving diet and exercise may help prevent it.
- Head trauma – Although the relationship between head trauma and degenerative brain disease is complex, head trauma is certainly a large risk factor for degenerative disease. Football players are the most publicized cases, but head trauma likely plays a broader role in the development of dementia.
- Socioeconomic factors – Socioeconomic factors also play a role in degenerative brain diseases, with poor and underserved populations less likely to be reached by interventions. Research suggests that the socially isolated elderly suffer more from these diseases than those with robust social networks.

Progress in Alzheimer's research has been slow

Beyond prevention, progress in understanding and treating Alzheimer's disease has been limited for several reasons.

A new field with limited funding

In contrast to cancer and HIV, which are well-established research areas and have historically received high levels of funding, Alzheimer's research is relatively new and underfunded. The research budget for AD at the National Institutes of Health (NIH) is approximately $500 million per year. Although there has recently been a push to increase it to $1 billion, it has been static for the last five years.

Oversimplification

Dr. Miller believes that progress has also been hindered because researchers in both academia and the pharmaceutical industry have oversimplified the disease. Since the 1970s, researchers have been describing individuals as suffering from "Alzheimer's disease" when they are likely suffering from a variety of cognitive impairments, including Parkinson's disease, frontotemporal dementia (FTD), and atherosclerosis- related dementia. This is also a view embraced by the pharmaceutical industry. A large population suffering from one disease treatable by a single therapy (rather than several smaller populations with different degenerative diseases all requiring different treatments) means a larger, more lucrative market for an Alzheimer's drug.

In addition, researchers have simplified the clinical problem by focusing on amyloid as the causative molecule in Alzheimer's. Researchers know that the brains of individuals with AD have accumulations of improperly formed proteins called amyloid plaques. The field has focused almost exclusively on treatments that reduce amyloid plaques. Although this may be effective in the right populations using the right treatment, it is a strategy that has not been very successful overall.

Studying the wrong populations

The oversimplification of dementia as one disease affects the quality of Alzheimer's studies, which often include the wrong populations. Most research focuses on individuals over the age of 75, but these patients almost always show a mix of pathologies (this is frequently confirmed by autopsy). Many of these elderly patients have multi-system neurodegeneration, but they are still included in studies of Alzheimer's disease.

Following one study on the reduction of amyloid plaques, researchers tried to determine what percentage of subjects in the study actually had amyloid plaques in their brain. Although they were all suffering from dementia that had been labeled Alzheimer's disease, one third of the participants in the study did not have amyloid plaques in their brains. Studying the wrong people can make it very difficult for researchers to identify effective treatments.

Improving the field

More early-onset studies of well-defined populations

Focus on early-onset Alzheimer's disease

Early-onset Alzheimer's disease (an inherited form of AD that appears before the age of 65) is an underfunded area of research. Because these individuals are less likely to suffer from multiple types of neurodegeneration, they allow researchers to study the pathology of 'pure' Alzheimer's. Conducting in-depth studies of families with a strong history of early-onset Alzheimer's disease would allow researchers to focus on a single gene or constellation of genes responsible for family members' propensity to develop dementia.

Work in this area has shown that the anatomy of early-onset patients with a specific genetic variation called APoE4 differs from that of patients without APoE4, with different parts of the brain affected by the disease. This variation is found in approximately half of all early-onset cases.

Although these early-onset family studies are difficult, they are incredibly important because they will allow researchers to identify other genes/proteins involved in pathogenesis and potentially identify new drug targets.

Include international populations

Expanding the scope of studies to include international populations is important for two reasons:

- Focusing on very well defined populations is essential, but narrowing the target population can make it difficult to find enough individuals to study. Expanding the scope to include international populations can help ensure researchers have access to individuals with specific genetics.
- Even in developing countries with large scientific fields (like India and China), researchers have sometimes not yet been able to identify populations within the country who have genetic mutations of interest to researchers. The field would benefit from helping global populations to organize their research and locate these individuals. Because social norms regarding sharing personal information outside of the family differ across cultures, this can sometimes be difficult, requiring researchers to develop strong relationships with the families they wish to study.

Phenotyping

There should also be a stronger effort around phenotyping, or understanding how the genetic mutations associated with early-onset Alzheimer's disease are expressed in patients. Researchers have access to tools including tau and amyloid imaging and a variety of cerebrospinal fluid (CSF) biomarkers and should be working to better characterize what AD looks like in these early-onset populations.

Therapies are needed

The development of an even mildly effective therapy for AD patients with a specific genetic mutation like APoE4 would drastically change the field. It would allow for the childhood screening of that particular marker, possibly leading to early

diagnosis and intervention. This will not be possible until an intervention beyond symptomatic therapy is available, and that will require a change in the way researchers approach the disease.

More research on tau

Better tau biomarkers are needed

Most Alzheimer's research focuses on amyloid plaques, but more attention should be paid to tau, a protein that is essential to the function of healthy brains but that under some circumstances forms tangles that can kill neurons and disrupt brain function. These tangles are often found in the brains of AD patients.

Right now, researchers have good tools for identifying amyloid plaque depositions, but lack biomarkers that would allow them to reliably differentiate between hyperphosphorylated tau (the kind that forms tangles) and the form of tau the brain needs to function. While these biomarkers are better for patients with early-onset AD, they still need improvement. There are no reliable CSF biomarkers for tau.

Without sensitive and specific biomarkers, it is difficult to screen for the right populations to include in studies. Better biomarkers would allow researchers to do much smaller clinical trials with better-defined genetic populations, but there has so far been insufficient investment in their development.

Initial tau research is promising

There is some promising research being done on tau, and although it's in the early stages, the tau data from research in mice is more promising than the data we have seen thus far with amyloid. When tau levels are lowered in mice with genetic mutations that cause them to have features of AD, they still get amyloid plaques, but they don't show symptoms of AD.

If a tau-lowering agent were available for humans, there are imaging techniques available that would help researchers measure its effectiveness. Researchers could use an imaging technique called positron emission tomography (PET) within weeks of therapy to see if tau were being reduced in the brain or measure peripheral tau levels to try to identify a sink where tau is being pulled out of the brain.

Reforming funding structures

The current funding and incentive structures for researchers are not conducive to finding a cure for a complex disease like Alzheimer's. Funders should consider prioritizing:

Manhattan Project-style working groups

Funders should consider funding Manhattan Project-style working groups in addition to individual scientists. One model for an alternate funding structure is the Tau Consortium, a group funded by a family that has a tauopathy and is interested in finding a cure for degenerative brain diseases related to tau. They brought together the best translational scientists from around the world (including clinicians,

structural biologists, biochemists, and neurologists) and provide approximately $14 million per year.

This structure facilitates interaction with the people the scientists are working to cure. That personal connection provides a sense of urgency often lacking for university scientists, who are under pressure to publish high-impact papers, but not to follow their research all the way down to the human level. Dr. Miller believes this group has made more progress than he has seen elsewhere.

Young researchers

It would also be useful to fund young researchers. Dr. Miller believes these scientists display the most creativity and are often not yet exposed to the groupthink that plagues AD researchers.

Promising areas of research

Connectivity mapping

One promising research area that needs more funding is connectivity mapping, which uses magnetic resonance imaging (MRI) to follow the trajectory of a degenerative disease, looking at the progressive loss of a single circuit within the brain.

By following patients longitudinally, Professor Bill Seeley at UCSF has shown that the best statistical model for the progression of many degenerative diseases is a prion-like mechanism (prions are infectious misfolded proteins that damage the brain) in which dysfunction expands out from a hub along a specific network.

He has shown that degenerative brain diseases follow specific anatomical progressions and have different connectivity deficits: Alzheimer's disease causes degeneration in a hippocampal-posterior-parietal network called the default network, FTD effects a frontal network known as the salience network, and a type of temporal degeneration that causes aphasia effects a knowledge network.

This technique may allow researchers to study a single individual with greater precision, and perhaps lead to selective therapies for different individuals. Pharmaceutical companies are currently focused on large trials conducted over a relatively short period of time, but this would allow single-person pharmaceutical trials in which individuals who receive treatment are compared to their expected trajectories over longer periods of time.

Induced pluripotent stem cells

Another promising technique Dr. Miller believes is worth investing in is induced pluripotent stem (IPS) cells. IPS cells are generated directly from adult cells and can come from specific patients, negating the need for model organisms. Although expensive, this technique allows the researcher to work with human cells while bypassing the difficulty of accessing live neurons from a particular patient.

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