A conversation with Dr. Dena Dubal, March 10, 2015

Participants

- Dr. Dena Dubal – Assistant Professor of Neurology and David Coulter Endowed Chair in Aging and Neurodegenerative Disease at the University of California, San Francisco (UCSF)
- Melanie Smith, PhD – Scientific 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. Dena Dubal.

Summary

The Open Philanthropy Project spoke with Dr. Dubal of UCSF as part of its investigation into Alzheimer's disease (AD). Conversation topics included current scientific understandings of AD, the key unanswered questions, and the importance of supporting creative, non-traditional approaches to AD.

Current Understandings of AD

Early-onset familial AD

Early-onset familial AD is a very aggressive form of AD. It is better understood than sporadic AD.

All animal models of AD are derived from a genetic understanding of AD, which is based on studies of early-onset familial cases. Understanding the genetic basis of familial AD has given researchers some insight into the nature of sporadic AD (i.e., non-familial).

Sporadic AD

Sporadic AD can be considered a chronic disease. There is a gradual onset and progression and on average, patients live for 10 to 15 years after receiving a diagnosis. If treatment options improve, AD will likely become even more of a chronic condition.

The etiology of sporadic AD is not well understood. This is an area of active research.

- The hallmarks of sporadic AD look similar to familial AD, but it is possible it could be a different disease that shares pathological hallmarks.
- Because age and various chronic diseases (e.g., diabetes, heart disease, and vascular disease) are risk factors for sporadic AD, it is possible that sporadic AD is a constellation of different chronic conditions.

Genetics of sporadic AD

Genome wide association studies (GWAS) looking for genetic risk factors of sporadic AD have found only very small effects. It is unlikely that multiple genetic variants might combine to create a synergistic risk for sporadic AD.

GWAS data has mostly identified molecules that confer risk by accelerating the toxicity of Aβ and tau. ApoE4 for example, the largest known genetic risk factor for sporadic AD, accelerates Aβ deposition.

Role of Aβ and tau

Tau and Aβ are the primary molecules that are studied as the etiological factors of AD. Every AD brain has amyloid plaques and tau tangles. However, Aβ and tau also have normal functions in the brain. It might be problematic to get rid of them entirely.

Role of Aβ

All genetic causes of AD are based on a mutation or problem involving Aβ. For example, people with Down syndrome have more because they are born with three copies of chromosome 21, where the gene for the amyloid precursor protein is located. They tend to show signs and symptoms of AD by age 40.

Because Aβ is the strongest causative factor in early-onset familial AD, there is hope that it is also a major contributor to sporadic AD. However, the direct relationship between Aβ and sporadic AD is not well understood. Some elderly people have heavy Aβ deposits and don't show any cognitive deficits. In AD, there does not seem to be a linear correlation between Aβ load and severity of symptoms. It is possible that amyloid plaques are actually a protective mechanism and sequester toxic species.

Oligomers, a form of Aβ that precedes plaque formation, are toxic in models. The amount of oligomers in the brain correlates with severity of AD symptoms.

Role of tau

Neurofibrillary tangles (aggregates of hyperphosphorylated tau) are one of the hallmark findings in the brain of a patient with AD. The presence of tau appears to be necessary for Aβ to be toxic. Tau tangles destabilize microtubules, which affects axonal transport, neuronal excitability, and other cellular functions.

There is no genetic mutation in tau that leads to AD.

There is currently a lot of attention on tau's role in AD. Many animal models have combined Aβ and tau in order to study their joint toxicity. Researchers are beginning to design tau directed therapies, although they are less well developed than Aβ targeted therapies.

- Dr. David Holtzman, of Washington University in St. Louis School of Medicine, is developing antibodies that will target and destroy tau.
- Imaging scientists have developed tau ligands (traceable molecules that bind to tau) that make it possible to map the tau burden in the brain.

Biomarkers

Researchers have developed two biomarkers that can predict AD to some extent, but cannot make a definitive diagnosis:

- The ratio of Aβ to tau in the cerebral spinal fluid.
- Hypometabolism in the temporoparietal regions of the brain identified with a positron emission tomography (PET) scan.

What measures will predict who shows clinical deficits of AD in 20 years? This is a high yield question. Multiple researchers have characterized groups of 5-6 biomarkers that they argue can predict AD when used together, but it is unclear if these will be effective predictors of AD.

There is currently funding for biomarker research. The National Institutes of Health (NIH) values this research. Nearly everyone agrees that biomarkers are necessary to understand when the AD process is beginning. Currently, the available biomarkers are used more in research than in clinical practice.

Clinical trials

All clinical trials of AD, most of which target Aβ, have failed. Antibodies (e.g., Crenezumab) designed to target and destroy Aβ worked in animal models but failed in human trials.

There is now good evidence that these trials may be a case of "too little, too late." The AD process begins in the brain decades before clinical symptoms appear. Giving therapy at the end stage of the disease is like giving a little bit of chemo to a widespread, aggressive cancer in its final stages.

There is now a move to do clinical trials with people with mild cognitive impairment who are just beginning to show signs of AD. However, even at this stage, AD has likely been developing in the brain for years. It may still be too late to see a therapeutic effect.

There is currently an on-going clinical trial in Columbia with a family that carries the genetic mutations that cause early-onset familial AD. The extended family is being treated with an anti-Aβ therapy even before symptoms appear.

Key unanswered questions

The key unanswered questions in the field of AD research are:

1. What is sporadic AD? Is it different from familial AD?
2. How can we predict who will get sporadic AD?
3. What influences AD pathophysiology besides Aβ and tau?

New approaches to AD

There is urgency in the scientific community and the world at large to understand why clinical trials are failing. Dr. Dubal believes that the scientific community, in

part, needs to think about AD more creatively and design new treatments that go beyond Aβ and tau.

Most people continue to argue for disease specific targets, but scientists don't understand AD enough to design effective disease-specific strategies at the moment. Eventually, the cures for AD will emerge out of this research. However, until then, more multifaceted approaches are important.

Approaches that go beyond Aβ and tau include research on:

1. **Lifestyle changes** – A study in 2014 found that lifestyle modifications significantly improved AD clinical symptoms, more so than any pharmaceutical to date. These modifications included a Mediterranean diet, exercise, and mental stimulation (e.g. social networking). Patients who made these changes saw improvements in cognitive and behavioral dysfunction.
2. **Resilience** – Research on how to offer resilience to the brain needs much more funding and support. Increasing resilience in the brain offers resistance against many kinds of toxins. Exercise, sleep and stress reduction all offer resilience to the brain, but there is currently no kind of medicinal treatment that can harness and capture those effects in order to boost brain function and cognition. This research could yield sole treatments or complimentary approaches. Research on resilience may reveal why some elderly people have many amyloid plaques and tau tangles but do not show cognitive problems.
3. **Aging** – There are a lot of great minds in the aging field. It is likely that a lot of interesting approaches and new, effective therapies will emerge from this field.

   These approaches that enhance resilience in the brain would also protect against AD toxins and pathologies that have yet to be fully elucidated or even identified.

Dr. Dubal's Research

Resilience

Dr. Dubal discovered that an endogenous (naturally produced) hormone, klotho, is associated with enhanced cognition. Her study (link here: http://dx.doi.org/10.1016/j.celrep.2014.03.076 or here: http://www.cell.com/cell-reports/abstract/S2211-1247(14)00287-3) has received a lot of press and visibility over the last six to nine months (for example, see http://www.economist.com/news/science-and-technology/21601809-potent-source-genetic-variation-cognitive-ability-has-just-been and http://www.huffingtonpost.com/2014/05/12/longevity-gene-klotho-_n_5309865.html).

She established that a *KLOTHO* gene variant in humans results in higher klotho levels and is associated with a boost in brain function. Mice that are genetically engineered to produce more of the klotho hormone are smarter and are more resistant to Alzheimer-related toxins.

Klotho is pleiotropic, meaning it has multiple effects in the body. In general, klotho is associated with longevity and better aging. Scientists in the kidney field have been excited about klotho for a long time because it is associated with better renal function.

Challenges

Funding

It is hard to find funding for innovative and creative projects such as Dr. Dubal's resilience research.

Overall, there is not enough money for AD related research. Only a small portion of grant applications to the NIH receive funding.

Dr. Dubal wonders when the federal funds allotted to the NIH will increase to match the value of discovery to our lives and the world. If only a limited amount of total funding is available, it might be a good idea to allot a certain percentage for non-traditional projects that are supported with good evidence.

Salary support

Many researchers have to spend a substantial portion of their time—sometimes more than 50%—writing grants. This is sometimes where most of the researcher's salary comes from. If a funder were to invest in creative individuals and provide them with a salary, those researchers could spend their time working on their research and not constantly writing grants that go mostly unfunded. Dr. Dubal was fortunate to have substantial startup funds that allowed her to focus on research when she first started her lab.

Publishing research

It can be particularly difficult to publish translational research that involves both mouse models and human clinical work. It often doesn't go through the peer review process well because basic scientists and clinicians largely have and value disparate sets of tools and approaches to scientific discovery. There is little integration of basic science to the human condition.

People to Talk To

1. **Bruce Miller** – Professor of Neurology, UCSF.
4. **Lennart Mucke** – Director and Senior Investigator, Gladstone Institute of Neurological Disease; Professor of Neurology, UCSF.
5. **Stanley Prusiner** – Director of the Institute for Neurodegenerative Disease and Professor of Neurology, UCSF.
6. **Dale Bredesen** – Director, Mary S. Easton Center for Alzheimer's disease Research at University of California, Los Angeles.
7. **David Holtzman** – Professor and Chairman of Neurology, Washington University in St. Louis.

8. **Randy Bateman** – Professor of Neurology at Washington University School of Medicine.
9. **David Bennett** – Director of Rush Alzheimer's disease Center, Rush University.

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