Bob's Last Marathon
Living the Alzheimer's Journey

TRANSCRIPT

Beyond Plaques and Tangles—Looking Ahead

Dr. Arnold: Alzheimer's disease and other neurodegenerative disease dementias are complicated with a lot of other factors driving the loss of synapses and the death of brain cells. We're rapidly learning how other factors contribute to dementia, and there are many already available and safe drugs that target these factors in other diseases. Could they be helpful in Alzheimer's disease? Will drugs that attack inflammation in diseases like rheumatoid arthritis or psoriasis also reduce brain inflammation in Alzheimer's disease? Will drugs that are used to improve blood flow in people with heart failure help people with Alzheimer's disease? How about drugs we use to improve cell metabolism in diabetes? This is called drug repurposing, taking a medicine that has been shown to be safe and effective for one condition and trying it in another where the biology of the disease suggests that it may respond. We may already have better treatments for Alzheimer's disease in hand, but we don't know it because they haven't been tested in clinical trials yet to see.

Overall, there's been an increase in the number of investigational drugs in registered late-phase clinical trials for Alzheimer's disease over the last five years. Back in 2016, there were 70 different drugs in research trials and now there are over 100. For the medicines designed to modify Alzheimer's disease, over half were focused on amyloid in 2016, and now two thirds of them focus on other factors. There's also a significant pickup in the number of trials of repurposed drugs, and this is a big interest of ours at my institution, Mass General.

One of the biggest challenges in research is, how do we know whether a drug is actually working? Do we really have to wait a few years to see whether the disease progresses or can we get an indication early on? And so the development of biomarkers that can tell us whether synapses are changing, whether they're being preserved or not, is really important.

Timing is really critical because different things that happen in Alzheimer's disease may have different effects at different times during the disease. And this is really important and speaks to the importance of having good biomarker tests to know what is happening in the brain in a given person at any given time.

We need to be able to treat the right person with the right drug at the right time. Yale has been a real leader in PET imaging, especially PET scanning of synapses and many types of synaptic receptors. At Mass General at Harvard a big interest of ours has been in the fluid biomarkers, measuring levels of different proteins in spinal fluid and blood. And I think the huge advances in biomarkers, whether with neuroimaging or with bio fluids, is another reason for optimism. In one sample of spinal fluid or blood, we can measure thousands of different protein molecules involved in inflammation and metabolism, cell stress, along with amyloid, tau, and more recently, synaptic proteins.

With these biomarkers, we're seeing that people also can vary a lot in how much amyloid or tau or synaptic degeneration they have, how much blood vessel disease or inflammation they may have. One of the things that we're recognizing is that Alzheimer's is heterogeneous. Your Alzheimer's disease isn't necessarily the same as my Alzheimer's disease. We should be able to use this information to select the right drug or possibly the right combination of drugs and then be able to measure how effective those drugs are with these biomarkers.

I'd love to hear some of your thoughts about that approach in terms of profiling folks and trying to personalize treatment.

Dr. Strittmatter: There are several very positive aspects. One is Alzheimer's may really be composed of multiple diseases. And if we want to get the right treatments for the right people, we need detailed biomarker profiling of individuals because some drugs may work better for one group than another group, one point. Another is

that we provide much more learning data from any one trial if we have biomarker evidence of what's really going on.

One of the things that you touched on earlier was about drug repurposing, and I wanted to say a few words about that. I think that has great potential because developing a completely new drug from scratch is a very slow process. Whereas a drug that's used for some other indication shortens the process and lets us get to meaningful trials much more quickly with drugs that we know at least are safe in some situation.

We've had some experience with that, and the NIH has recognized that this is really a very promising way to speed drug development. The sub-institute within the NIH called NCATS has an entire program where they collected drugs that were on the shelves of various pharmaceutical companies, negotiated terms, and made them available to academic investigators to test new indications. And through that program, we were able to identify a cancer drug which didn't work so well for cancer, but was safe, and we were able to move it into Alzheimer's trials very quickly.

There are some challenges in drug repurposing. Many drugs aren't developed to get into the brain. If we're going to have an effective Alzheimer's drug, we need to know that the drug actually gets into the brain. So there usually is some work to be done to prove that a drug is actually entering the brain if it's been used for some other purpose.

Secondly, Alzheimer's is a slow process. So many drugs are used for other indications, say for cancer, for a month or two at a time, not for years and decades on end the way an effective Alzheimer's drug would be used. So knowing that the drug is safe in the chronic situation is key.

But still, we moved from identifying a drug, testing it in animals, to testing it in humans in a process of two or three years instead of the 8 to 10 to 20 years that it takes for a completely new chemical entity. So I think this holds huge promise to accelerate the process in combination with really robust biomarker profiling. So I think there's again another reason for optimism in the field.

Dr. Arnold: I think there are two types of repurposing. There are huge numbers of medicines that were designed and tested and didn't, for whatever reason, quite make it out of the drug companies. The other aspect of drug repurposing is drugs that are already approved for other conditions. There are medicines that are used chronically in asthma that may have some benefit for brain disorders including Alzheimer's disease. We're in the middle of a clinical trial with an anti-tuberculosis vaccine that seems to have some really remarkable properties in terms of improving the immune system and perhaps decreasing the hyperinflammation that we see in Alzheimer's disease. Even the most common diabetes drugs. There's a big clinical trial based in New York that's going on, testing Metformin.

Dr. Strittmatter: Since you brought up Metformin, you might comment on one of these questions in the Q&A.

Dr. Arnold: We've been doing work in this area for a long time. And it taps into what I was saying before about the metabolic activity of cells. Some people started noticing that there were higher rates of Alzheimer's-type dementia in people with long-standing diabetes. And so we wanted to know, what is the main feature of type 2 diabetes? It's insulin resistance. Our cells are resistant to the hormone insulin, which helps absorb glucose and enhance the metabolic activity of cells. And so we started looking for evidence of insulin resistance in brain cells in people with Alzheimer's disease. And we saw a lot of features in brain cells that look like the cells are resistant to the insulin. But the thing is that we saw it not only in diabetics who had Alzheimer's disease, but also people with Alzheimer's disease who didn't have a history of diabetes. So this made us think, "Okay, the brain is different than the rest of the body in this regard." And we know that insulin does other things

in the brain than it does in the body. It acts more as a growth factor. It even enhances synaptic growth and maintenance of synapses. So if there were ways to use drugs that can enhance insulin sensitivity and if they get into the brain, do they have beneficial effects on brain cells? Can we see this? So that's a very, very lively area of research now. There are a number of clinical trials.

Lena: There are several questions related to diet and supplements. Would you like to answer some of these, Dr. Strittmatter?

Dr. Strittmatter: I'll just say a general statement about supplements is, they may be beneficial, but there is not proof that they're beneficial that's risen to the level that's accepted in the medical community. There's not the kind of standard of proof that we accept in medical practice that these are beneficial.

Dr. Arnold: Many of them do work in mice with Alzheimer's disease. They work in cell cultures that kind of mimic Alzheimer's disease. And some of us like to say now, "It's a great time to have Alzheimer's disease if you're a mouse," because we can prevent it or even cure your Alzheimer's disease if you're a mouse. But how many of them actually work in humans?

And the big frustration is that it's hard to move these things into bona fide rigorous clinical trials. A lot of that is financially based. Some of them do look as good as some of the most promising new chemical entities that we create to drive amyloid down, improve inflammation, enhance metabolism, improve blood flow to the brain and the like.

Lena: Dr. Strittmatter, what are the most encouraging biomarkers now being studied that you think might correlate with Alzheimer's disease and progression?

Dr. Strittmatter: The type of assay that's attracted the most attention recently is using plasma samples to look at specific species of tau. This has been shown in research studies to be highly correlated with the presence of Alzheimer's disease as proven by PET scans. It also correlates with progression and it requires a simple plasma test. These aren't widely available in clinical practice. It's still a research tool at this point, but I think that's going to really make it much easier to diagnose the disease and also track the progression of disease. At least so far, some of these plasma phospho tau biomarkers have the best data around them in terms of changing the way we run clinical trials.

Lena: So then, Dr. Strittmatter, what's your best guess of when a new class of therapeutics might be available to the patient?

Dr. Strittmatter: Realistically, because Alzheimer's is a slow disease, anything that's going to be newly registered as part of standard practice is going to require these large Phase III trials that monitor people over 12 to 18 months. To get to that endpoint is a several-year process. But I guess it would be hard to say that something's going to be there in the next two years, but two to five years is plausible and 2 to 10 years is a safer number to say.

Lena: There's a very interesting question about the rates of Alzheimer's disease crossing different countries and cultures. Have you observed any of these cultural differences?

Dr. Arnold: This does tap into one of the things I talked about before with heterogeneity, that there are a lot of different risk factors that can affect the onset and the course of Alzheimer's disease. Certainly genetics is one thing that affects it. The occurrence of cardiovascular disease or metabolic diseases, high blood pressure, diabetes, high cholesterol, heart disease, these are all things that can increase the rates of occurrence and perhaps the progression of Alzheimer's disease. Depression, stress, environmental stresses, these are also factors that can affect the occurrence of Alzheimer's disease and dementia. Each of these different risk factors may translate into its own biological changes and biomarker changes that we can see in the brain—heterogeneity we actually use to better personalize a treatment program for people.

TRANSCRIPT Beyond Plaques and Tangles—Looking Ahead

Dr. Strittmatter: This is something I think that the research community and the NIH in particular has very much recognized, that differences are likely to exist. There's now a lot of research going on about differences across cultures, across lifestyles, and really trying to nail down, what are the important factors and how big are they? Different aspects of culture, lifestyles and socioeconomic status, race, etc.

Steven E. Arnold, MD

Professor of Neurology
Harvard Medical School
Managing Director
Interdisciplinary Brain Center, Massachusetts General Hospital

www.actru.org

Stephen M. Strittmatter, MD, PhD

Vincent Coates Professor of Neurology
Professor of Neuroscience
Director of Cellular Neuroscience, Neurodegeneration and Repair Program
Yale School of Medicine

https://medicine.yale.edu/cnnr/