Telocyte Newsletter
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TELOCYTE
A FUTURE BEYOND ALZHEIMER'S

The number of people dying from age-related dementias continues to climb. Why? Within the US alone, the CDC points out that the incidence of death from dementias has more than doubled since the turn of the century and now accounts for almost half of all deaths. This is partly due to the gradual improvement in survival from other age-related causes of death – largely cardiovascular disease and cancer – with the result that more of us now live long enough to succumb to dementia, rather than, for example, heart attacks or breast cancer. We live longer, but our risk of dementia rises with our life expectancy. This increase in dementia includes not only Alzheimer's disease, but vascular dementia as well as other unspecified dementias, all of which are age-related. The older we get, the higher our chances of having dementia.

It might be easy to simply shrug our shoulders and leave it at that, with the pessimistic view that we all age and that dementia is inescapable, but it that true? While it's true that the older we are (and as we survive other causes of death), the more likely we are to get Alzheimer's disease, but why can't we intervene? After all, we once thought of other diseases as inevitable as well, yet few of us now die of infectious diseases that were once "inescapable". As we came to understand that microbes caused such diseases, we finally began to cure them. If we come to understand the causes of dementia, can we cure Alzheimer's?

The first problem lies in not having a single viable model for Alzheimer's. Putting it bluntly, most researchers, most pharmaceutical companies, most biotechnology companies, and almost everyone else admits that they don't actually know what causes Alzheimer's disease or, if they do know, then everyone else disagrees with them. We know what it does, but not why it happens. A few months ago, I gave a talk at an Alzheimer's Association meeting in Washington, in which I pointed out that in order to move ahead, we need a single, comprehensive model that explains not only Alzheimer's dementia , but all of the other age-related dementias (including Parkinson's). Moreover, as I noted in my talk, the standard complaint is that "everything works in mice, but nothing works in humans". Any model that can explain human dementias must also be able to explain the same sort of problems that occur in aging animals. In short, we need a systematic model that can consistently explain the age-related cognitive decline seen in humans and animals, Alzheimer's and Parkinson's, those with genetic risks and those without, and a lot more. After the meeting, the audience was in enthusiastic agreement. The Editor-in-Chief of the journal *Alzheimer's & Dementia* asked me to publish such a model and promptly joined our Scientific Advisory Board (see below).

While the absence of a rational and comprehensive model is the first problem, the second stumbling block lies in the inability of investors and others to accept innovation. While almost all venture capital groups, pharmaceutical companies, and entrepreneurs proclaim their interest in innovation, revolutionary technology, and bold new ideas, the reality is that they trudge along in the worn-out path of any previous innovation; they support incremental advances (a marginally improved hot air balloon), but seldom support innovative advances (the Wright brothers). Even when they see the first flight at Kitty Hawk as revolutionary and innovative, they get bogged down in that particular innovation and are unable to go further. It's as though they were awed by the achievement of the Wright brothers and, loudly proclaiming their support for "innovation", they try to perfect a better kind of wood frame, a tougher kind of cloth, a lighter bicycle chain transmission, and a "more advanced" 12 horsepower engine – a 14 horsepower engine? This might make for a longer flight at Kitty Hawk, but it won't result in international passenger jets that carry hundreds of passengers across the Pacific Ocean in a few hours. Incremental improvements are not innovation. Tweaking of existing molecules is not a revolutionary therapy.

For Alzheimer's disease, the result is that not only do we lack an accepted comprehensive model, but most investors are zealously averse to innovation. They prefer spruce wood and bicycle chains to jet engines. The result is the consistent failure of human AD trials as well as useless and exorbitant expense. Biogen alone, in its recent failure with aducanumab, spent more than three quarters of a billion dollars – without a viable intervention or any clear pathway forward. Sailing into the unknown without a map is both heartbreaking and expensive.

To some extent, *although far less than you might imagine*, the FDA itself has dragged its heels with respect to innovation. Ironically, compared to many researchers or to institutional investors, the FDA has actually tried very hard to keep up with the pace of technology – for example, gene therapy – and to foster true innovation. That's not to say that any regulatory system is perfect, but the FDA is an example of a government agency that has shown an honest and largely effective interest in moving ahead with safer, cheaper, and more effective clinical interventions. As Scott Gottlieb, the recent head of the FDA put it, "Without a more agile clinical research enterprise capable of testing more therapies or combinations of therapies … more efficiently and at lower total cost, important therapeutic opportunities may be delayed or discarded because we can't afford to run trials needed to validate them."

Exactly.

Meet our Scientific Advisory Board:

We'd like to welcome our newest board member, Zaven Khachaturian, and to introduce you to this remarkable and well-known researcher in the field of Alzheimer's disease. Dr. Khachaturian is the Editor-in-Chief of *Alzheimer's & Dementia*, as well as a neurophysiologist with a life-long interest in understanding the causes of dementia.


Zaven Khachaturian, PhD
Scientific Advisory Board

Dr. Zaven Khachaturian is the Senior Science Advisor to the *Alzheimer's Association*, Editor-in-Chief of *Alzheimer's & Dementia* (the journal of the *Alzheimer's Association*) as well as President of The Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020). He was the chief architect of the extramural research programs on "Brain aging and Alzheimer's Disease" supported by the NIA/NIH from 1977-1995, then worked with national and international advocacy organizations, governments, and universities on strategic planning, development, and financing signature research programs on brain aging and dementia. His primary scientific contributions include a broad-spectrum approach to integrate basic research, public health research, public policy formulation and bioinformatics to solve the diseases associated with brain aging. As a planner and developer of research programs, he has identified the most important scientific challenges confronting the field, assembled the best research teams to solve these problems, and has developed innovative solutions and resources to enable for rapid breakthroughs. He is the best recruiter of scientific talent for the field of Alzheimer's research and has mentored countless investigators worldwide including many of key opinion leaders in aging-dementia research. He continues to coordinate researchers from a wide spectrum of approaches. His major scientific achievements also include the earliest diagnostic criteria for Alzheimer's disease and the calcium hypothesis. He trained in neurophysiology at Yale (BA), Case Western (PhD) and Columbia (Postdoc).