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## 2022 PSBR High School Essay Contest *Finalist*

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I still recall the times I would go to my grandmother's house and play board games with her, be it chess, Pictionary, or Scrabble. I loved the time my sister and I were able to spend with her enjoying what I thought would always remain the same old game night. Everything changed 6 years ago, however, when my parents finally broke the news to me that she had Alzheimer's.

Alzheimer's disease affects over 6 million people in the U.S. alone. It is a neurodegenerative disease commonly linked with dementia caused by a combination of environmental and genetic factors. It was first studied in 1906 when Dr. Alzheimer noticed that an affected woman had several clumps, tangled fibers, and a general reduction in volume throughout her brain. Researchers would later discover that these clumps were plaques composed of excess beta-amyloid protein between neurons and that the tangles were made of tau protein that accumulated inside neurons. They also observed how these two abnormalities led to a host of other issues, such as decreased vascularization and a reduction in synapses.

When my parents first told me about my grandmother's condition, I wasn't exactly as shocked as they expected. Because I had started reading about the nervous system for my school's Science Olympiad program, I already knew a few facts about the disease. After knowing she had it, I was able to draw several connections between what I read and the symptoms I observed. She would often ask me the same exact question over and over again because she never recalled my answer; she constantly wondered if she had forgotten to feed her dog, Maggie; once, she was even unable to remember who my sister was. Although I initially dismissed these events as ones that regularly occur as a person ages, I soon realized that there was a much larger factor at play.

Although the effects of Alzheimer's can be identified throughout the entire brain, regions associated with memory, such as the hippocampus and entorhinal cortex, are the most drastically damaged. This ties back to George Glenner's isolation of amyloid- $\beta$  in 1984 and John Hardy's identification of the first Alzheimer's gene in 1991 and how these two discoveries contributed to the amyloid hypothesis, which states that the accumulation of amyloid- $\beta$  is the primary cause of Alzheimer's and should thus be the main target of therapeutics.

In December of 2021, my grandmother was prescribed one of these targeted therapeutics. Known as aducanumab, it is a monoclonal antibody that was first studied in animal models before being approved for clinical trials. Groundbreaking research began in 2011, when Robert Dunstan and his fellow scientists under Biogen and Neurimmune used transgenic mice as an excellent model organism. After administering aducanumab into the mice, they found that it was able to cross the blood-brain barrier, bind to the amyloid plaques, and gradually remove those plaques with the help of the immune system. Because of this

strong in vivo support for using aducanumab to slow the progression and symptoms of Alzheimer's in human patients, clinical trials began.

Then, in 2016, a group of researchers including Jeff Sevigny again used transgenic mice to model Alzheimer's, but this time found that aducanumab specifically binds to parenchymal amyloid- $\beta$  and reduced levels of both its soluble and insoluble forms. They also showed that when administered intravenously, it reduced these plaques and could thus halt the progression of the disease in a dose-dependent manner. This was another significant piece of evidence supporting human clinical trials, which had the results necessary to receive accelerated FDA approval.

Recently, my grandmother has been receiving her aducanumab via an IV infusion once every 4 weeks. We have already begun to see a slight improvement in her cognitive function and hope to be able to put the joy back into game night. I am grateful for what animal research has offered to millions of patients just like her across the world. Thanks to animal models, not only have we begun testing even more promising treatments such as gene therapy and various chemical compounds, including the PBT2 ionophore, but we have also gained a better understanding of the underlying biological characteristics of Alzheimer's disease. There is still much more to uncover in the mystery behind Alzheimer's, with controversy existing around the Amyloid hypothesis and even the FDA's approval of aducanumab, and animal studies will be the key for that and for the other conditions they have already had a tremendous impact on, ranging from Parkinson's to ACL tear recovery.

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