Aging and Debilitation: The Grave Reality, and Hopeful Future, of Treating Neurodegenerative Disease

**Introduction:**

At the start of the new year, during a time usually associated with resolution and new promises, two major pharmaceutical companies, Pfizer and Axovant, both announced the discontinuation of their campaigns to uncover drugs to treat Alzheimer’s disease and Parkinson’s disease, two progressive and debilitating neurodegenerative diseases that stunt cognitive function and deprive individuals of the ability to complete the most rudimentary physical and mental tasks.1 The stagnation of research related to these diseases is especially relevant in contemporary times given the aging of our population, which will experience a strong shift towards older age in the coming years. Current projections suggest that by 2060, Americans 65 and older may reach 98 million persons, a more than two-fold increase from the current 46 million individuals currently in this age bracket.2 Old age is almost inextricable from decay of the brain and neurodegenerative disease. Thus, an understanding of current research, which hopes to find remedies for these diseases, is pertinent to understanding the innovations and intricacies of science necessary to slow down, and perhaps rescue us from the encroaching grasp of diseases of the brain.

**A Brief Historical Aside:**

Understanding how far our understanding of neurodegenerative disease has progressed is tied to recognizing how rudimentary knowledge of treatments was only a few decades ago. As Anne B. Young notes in a review of the evolution of medicine pertaining to neurological disorders over the past 40 years, the concept of neurology centered on the diagnosis of these diseases and less on how to treat them.3 The brain is an organ protected by the blood-brain barrier and so was hard to access for diagnostic purposes before the emergence of CT, PET, and MRI scans.3 Many neurodegenerative diseases have no definitive cause; paired with the inaccessibility of the brain, this has made diagnostic and treatment approaches relatively difficult. Progress, however, has been made.

The study of neurodegenerative disease gained momentum with the discovery of methods to study the connections between nerve fibers, including one that utilized horseradish peroxidase as a tracer to study axonal pathways, and with the eventual invention and proliferation of novel imaging techniques.4,5 The rise of new imaging platforms as well as the accessibility of thorough genomic data has spurred more targeted research and the creation of effective transgenic mouse models.3 However, in general effective therapies and cures remain elusive. Between 2002 and 2012, there were only 413 drug trials for Alzheimer’s drugs with only a 0.4% success rate.6 To put this in perspective, the *New York Times* published an article in August 2017 with the headline: “A Cancer Conundrum: Too Many Drugs Trials, Too Few Patients.” The article described the difficulty to fill the 1,000 trials for immunotherapy drugs that are currently underway.7

**So What Research Have We Done?**

While it is clear that neurodegenerative disease research requires continued investment of time and resources, the strides that scientists have already made in this field are noteworthy and should be elucidated. The following is a sketch of some common neurodegenerative diseases and possible exciting innovations.

**Alzheimer’s Disease:**

Alzheimer’s Disease, named after Dr. Alois Alzheimer, who discovered the disease in 1906, is the most common form of dementia in older people; estimates put it as the third highest cause of death in older individuals, behind heart disease and cancer.8 Two hallmarks of the disease are the accumulation of plaque deposits consisting of the beta-amyloid protein and tangles consisting of the microtubule-binding protein tau; the disease is also associated with neuron loss and synapse loss.9 Beta-amyloid and tau were discovered in 1984 and 1986, respectively, leading to the first drug trial in 1987, conducted by Pfizer. Currently, there are five FDA-approved drugs to treat Alzheimer’s, though none is significantly effective in reversing or even slowing the progression of the disease.10

However, certain research studies have excited the scientific community. Immunotherapy provides one angle. Some studies suggest that the immune system can be equipped to target beta-amyloid plaques in the hopes of alleviating an individual of this protein, associated with the pathogenesis of the disease.11 Although recent trials have not been successful, clinical trials based on both the humoral (relating to B cells) and cell-mediated (relating to cytotoxic T cells) still remain viable options for future research.

In addition, a recent study in February 2018 showed that inhibiting the BACE1 enzyme through the deletion of the gene that encodes it led to a loss of plaques and improved cognitive function; deleting the gene after early development stages rendered the mice free of any side effects, circumventing the malignancy that deleting genes can often cause.12 Although the transition between mouse models and human subjects is an extrapolation that must be made with caution, hope remains high for the viability of a treatment based on this mechanism. In general, these two examples serve as a microcosm of the unique and exciting science aimed at combatting Alzheimer’s Disease.

**Parkinson’s Disease:**

Parkinson’s Disease, discovered by James Parkinson in 1817, is another relatively common neurological disorder that effects around one million individuals in the United States and five million worldwide. What frustrates scientists and patients alike is that there is no known cause of the disease; rather, it seems as though a confluence of genetic and environmental factors lead to its emergence and progression in individuals.13 The most characteristic symptom of the disease is a tremor in the hands as well as rigidity of movement.13 Just like Alzheimer’s, Parkinson’s disease progressively robs people of their most basic functions. And just like Alzheimer’s as well, Parkinson’s disease is associated with protein aggregates, these ones called lewy bodies, which contain the presynaptic neuronal protein alpha-synuclein. Researchers believe these proteins disrupt synaptic function, leading to the pathogenesis of the disease.14 Currently, treatments are directed towards easing symptoms but do nothing to erase them or significantly slow them down.

Again, possibilities in treatment and cures remain high. In improving the methods to improve the diagnosis of Parkinson’s Disease, researchers have used CRISPR, the novel gene-editing technique that has been used for a wide variety of scientific purposes. Scientists at the University of Central Florida have used CRISPR to attach a reporter gene, a NanoLuciferase, to alpha-synuclein, generating an effective way to visualize the progression of Parkinson’s Disease.15 This would allow researchers to use an early diagnosis to begin treating the disease in its early stages, a strategy important in combating any progressive disease. In addition, because Parkinson’s disease leads to the destruction of dopamine producing neurons, scientists have attempted to create these cells in primate models with great success.16 The use of iPSCs circumvents ethical concerns while also providing a viable option to combat Parkinson’s disease by restoring the brain’s ability to generate dopamine.

**Amyotrophic Lateral Sclerosis:**

Amyotrophic Lateral Sclerosis, or ALS, rose to the national stage when Yankee legend Lou Gehrig was diagnosed with the disease and passed away shortly thereafter. The disease is characterized by progressive muscle wasting and a loss in the ability to control voluntary movement. Muscle weakness is followed by muscle twitching, which in turn is followed by muscle atrophy.17

Research has been slower for ALS, but huge social movements have enabled momentum to build. The once famous ice bucket challenge and the now prevalent hot pepper challenge are a testament to the societal backing of research. In 1994, the drug Riluzole was shown to slow the progression of the disease by targeting the neurotransmitter glutamate that may be involved in its pathogenesis.18 In 2017, the FDA approved Edaravone, a drug that reduces the oxidative stress of ALS.19

**Some Final Thoughts:**

Neurodegenerative disease is wide in its breadth and devastating in its effects. However, Pfizer and Axovant’s discontinuations of their neurodegenerative disease treatment programs should not be deterrents to the potential of biomedical research to solve the mechanisms behind these diseases. Science has already made great leaps, and it is important for policy makers and scientists to work together to develop therapies. In a sign that this synergy is possible, FDA director Dr. Scott Gottlieb announced in February 2018 that he supports a “broader, programmatic focus on advancing treatments for neurological disorders that aren’t adequately addressed by available therapies.”20 With continued government support and intellectual initiative from a wide array of scientists, one day we will certainly develop cures for these neurodegenerative diseases.

**Leon ‘21 is a freshman in Weld Hall thinking about concentrated in MCB or Neurobiology, but is ultimately undecided.**

Works Cited

[1] NPR.org. <https://www.npr.org/sections/thetwo-way/2018/01/08/576443442/pfizer-halts-research-efforts-into-alzheimers-and-parkinsons-treatments> (accessed February 18, 2018).

[2] Population Reference Bureau. <http://www.prb.org/Publications/Media-Guides/2016/aging-unitedstates-fact-sheet.aspx> (accessed February 18, 2018).

[3] Young, Anne B. *J. Neurosci.* 2012, *29*, 12722–28.

[4] Graybiel, A. M., and M. Devor. *Brain Res.* 1974, *68*, 167–73.

[5] Jack, Clifford R., *et al*. *Alzheimer’s Assoc.* 2015, *11*, 740–56.

[6] Cummings, Jeffrey L., Travis Morstorf, and Kate Zhong. *Alzheimer’s Res. & Ther.* 2014, *37*

[7] Kolata, G. New York Times. https://www.nytimes.com/2017/08/12/health/cancer-drug-trials-encounter-a-problem-too-few-patients.html (accessed February 18, 2018).

[8] “Alzheimer’s Disease Fact Sheet.” https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet (accessed February 18, 2018).

[9] Murphy, M. Paul, and Harry LeVine. *J Alzheimer’s Dis.* 2010, *19*, 311.

[10] Alzheimer’s Association. //www.alz.org/research/science/alzheimers\_disease\_treatments.asp. (accessed February 18, 2018).

[11] Weiner, Howard L., and Dan Frenkel. *Nature Rev Immunol*,2006 6, 404–16.

[12] Hu, Xiangyou, Brati Das, Hailong Hou, Wanxia He, and Riqiang Yan. *J. Exp. Med.* 2018.

[13] The Michael J. Fox Foundation for Parkinson’s Research. https://www.michaeljfox.org/understanding-parkinsons/living-with-pd/topic.php?causes&navid=causes (accessed February 18, 2018).

[14] Stefanis, Leonidas. *Cold Spring Harb Perspect Med*. 2012, *2*.

[15] Basu, Sambuddha, Levi Adams, Subhrangshu Guhathakurta, and Yoon-Seong Kim. *Sci. Rep.* 2017, *7*.

[16] Kikuchi, Tetsuhiro, Asuka Morizane, Daisuke Doi, Hiroaki Magotani, Hirotaka Onoe, Takuya Hayashi, Hiroshi Mizuma, et al. *Nature.* 2017, *548*, 592–96.

[17] National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet (accessed February 19, 2018).

[18] Bensimon, G., L. Lacomblez, V. Meininger, and the ALS/Riluzole Study Group. *N Engl J Med.* 330, 1994, *9*, 585–91.

[19] Sawada, Hideyuki. *Expert Op. Pharm.* 2017, *18,* 735-738.

[20] Commissioner, Office of the. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596897.htm (accessed February 19, 2018).