Energy and Commerce Health Subcommittee
The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases
July 29, 2021

Good morning Chairwoman Eshoo, Ranking Member Guthrie, and Members of the Health Subcommittee. My name is Cartier Esham, and I am the Chief Scientific Officer at the Biotechnology Innovation Organization, or BIO. Thank you for the opportunity to share our insights on the state of innovation for medicines to treat neurodegenerative diseases.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations in the United States and over 30 nations. Our mission is to advance biotechnology innovation by promoting sound public policy and fostering collaboration, both locally and globally. Our members range from entrepreneurial companies developing their first product to Fortune 500 multinational companies.

BIO regularly publishes reports that help us assess the health of the biopharmaceutical pipeline across different diseases so that we can identify and remove barriers to providing next generation cures and treatments to patients and their families. I will highlight three such analyses with a focus on neurology clinical development programs (pipeline, investment and clinical trial success rates) with the goal of providing helpful insights to this important conversation. Later I will do a deeper dive into Alzheimer's Disease as an example of the state of innovation for neurodegenerative diseases.

Neurology: Clinical Development Pipeline and FDA Approval Trends

Currently there are 6,476 clinical development programs in the pipeline (Phase 1-NDA/BLA). In 2021 we counted 653 clinical development programs for medicines to treat neurological diseases 43% of which are for neurodegenerative medicines.[1,2] In the neurodegenerative subcategory of neurology, there are 279 clinical development programs with the majority designed to treat Alzheimer's Disease (104), Parkinson's Disease (66), Multiple Sclerosis (34) and Amyotrophic Lateral Sclerosis (34). There are also 17 programs designed to treat Dementia and 13 for Huntington's Disease. The majority of neurological clinical development programs are in Phase 1 and 2 (81%). By comparison there are 2,798 oncology clinical development programs (40% for rare oncology diseases).

There has only been a total of 39 FDA approvals for neurologic treatments in the last decade compared to 123 approved treatments for oncology. This year marked the first-ever FDA approval of a disease modifying treatment for Alzheimer's Disease.

Neurology: Investment and Financial Trends

Analysis of fiscal trends provides us with tremendous insights as to whether incentives are misaligned or there are other scientific or developmental barriers in any given disease area that need to be resolved.

[1] https://www.bio.org/fda-approvals-clinical-development-pipeline
[2] NOTE: Neurology includes treatments for general, headache, insomnia, movement disorders, neurodegenerative, neurodevelopment disorders, neurotoxicity, pain, seizure disorders, pain, stroke and other.

We focus most of our fiscal analyses on emerging companies as they are responsible alone or in partnership with larger biopharmaceutical companies for over 77% of the clinical development pipeline.

Over the past 5 years (2017 – 2021) we have seen an increase of investment in neurology, surpassing $1.5 billion in 2018 and setting a record of $1.7 billion in 2020, a four-fold increase from 2012. While an improvement, it is important to put these numbers into context. In 2020, venture capital invested $18 billion in U.S. emerging biopharmaceutical companies with approximately $7 billion going to emerging companies working on treatments for oncology.

The amount of investment dollars generated by emerging neurology companies going public has also increased in recent years. There was not a single neurologic company that went public in 2012. There was a peak of 7 and 11 U.S. IPOs in 2014 and 2015 raising $419 and $1.5 billion respectively, largely for companies with clinical development programs in Phase 2 and 3. Over the past 5 years, 18 U.S. emerging neurology companies went public with about half in the pre-clinical and Phase 1 stages. For example, in 2019, 5 U.S. IPOs generated $611 million with $443 million attributed to emerging neurology companies in the pre-clinical or Phase 1 stages. Again, to provide context, over the past 5 years (2017-2021) there were 200 U.S. IPOs, 75 of which were U.S. emerging oncology companies raising a low of $766 million in 2017 and a high of $5.1 billion in 2020.[3]

Thus, while neurology is currently ranked the second highest disease category in terms of raising venture capital investment, it is not at the level we would like to see to develop and provide next generation medicines for patients suffering from neurological diseases.

Neurology: Clinical Trial Success Rates

The BIO Industry Analysis Research team, in partnership with Pharma Intelligence and Quantitative Life Sciences, recently published a report examining clinical development success rates and contribution factors for the years 2011-2020.[4] The study examined 9,704 clinical drug programs from 1,779 biopharmaceutical companies. The overall success rate from Phase 1 to approval is 7.9% with an average timeline of 10.5 years. There are important and informative differences in success rates when you look at modalities and disease categories. For example:

- New molecular entities, biologics and vaccines have a success rate of 6.8% compared to 14.7% for non-novel therapies.
- New molecular entities have a 5.7% success rate compared to 9.1% for novel biologics.
- CART-T and siRNA/RNAi programs have success rates of 17.3% and 13.5% compared to small molecule programs which have a 7.5% success rate.
- Immuno-oncology therapies have a success rate of 12.4% compared to 5.3% for all oncology programs.

[3] https://www.bio.org/emerging-therapeutic-company-investment-and-deal-trends
[4] https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_ga=2.93040989.1759484495.1627399346-1071669468.1611082403

- Development programs with patient preselection biomarkers have a two-fold higher success rate of 15.9%.
- Chronic, high prevalence disease therapies have an overall success rate of 5.9% compared to a 17.0% success rate for rare diseases.
- The biggest hurdle is advancing from Phase 2 to Phase 3 (28.9% probability of success).
- Neurology clinical development programs have a 5.9% success rate taking approximately 11 years from Phase 1 to approval.
- The top contributing factors toward phase success are disease indication, target, modality, and drug novelty.

The success rate for neurological programs transitioning from Phase 2 to Phase 3 is 26.8%, which ranks 11th out of the 16 disease categories we analyzed in our report. When we look at the chance of success for transitioning from Phase 3 to submission, they rank 14th out the 16 categories, dragging down the overall Phase I to approval success rate for this disease category to 5.9%.

The state of science and precedence for neurological clinical development is important to note as there is not an abundance of approved medicines. For example, clinical development programs for neurodegenerative diseases are often designed to find adequate justification from biomarker data to progress into late-stage trials, without having a clinical proof-of-concept on clinically validated endpoints. It is also important to note that high prevalent chronic diseases do not have many of the characteristics that are contributing factors to the higher clinical trial success rates we see for rare disease clinical programs such as the ability to target molecularly defined causes of the disease.

Alzheimer's Disease: The State of Innovation

In 2019 we published a report, *The State of Innovation in Highly Prevalent Chronic Diseases, Vol. IV: Alzheimer's Disease Therapeutics*.[5] This was the fourth report in a series on the innovation landscape of high prevalent, chronic diseases. We published this series because we wanted to better understand the state of emerging company investment for high prevalent chronic disease development which appears to have been declining and/or low relative to total patient population and need to improve care.

Alzheimer's Disease comprises up to 80% of all diagnosed dementia, which affects 5.7 million people in the U.S. alone and costs the U.S. healthcare system $277 billion annually, with Medicare and Medicaid shouldering $186 billion (67%) of the total. The growing Alzheimer's disease epidemic is expected to affect more than 13.8 million people in the U.S. by 2050 and cost well over $1 trillion annually. [6] Global estimates for dementia by 2050 suggest close to 152 million people with a cost at over $2 trillion annually.[7]

Alzheimer's is a complex chronic disease. The progressive decline in cognition and memory are a result of the accumulation of extracellular protein plaques, neurofibrillary protein tangles, a loss of functional

[5] http://go.bio.org/rs/490-EHZ-999/images/BIO_HPCD4_ALZHEIMERS.pdf?_ga=2.68943441.1759484495.1627399346-1071669468.1611082403
[6] https://www.alz.org/alzheimers-dementia/facts-figures
[7] Alzheimer's disease International. World Alzheimer Report 2018. https://www.alz.co.uk/research/world-report (accessed March 2019)

synaptic connections, and eventually the complete loss of neurons.[8,9] It is also complex in that while most cases of Alzheimer's are diagnosed later in life (over 65 years of age) there is a form of early-on-set Alzheimer's that can appear as early as 40. In each case there is a further categorization of disease progression including a pre-symptomatic phase, a mild cognitive impairment stage and a severe dementia stage.[10]

Scientists have identified more than two dozen genes known to correlate with increased risk of Alzheimer's. These genes have functional roles in pathways currently targeted for drug development, such as amyloid and /or tau clearance. Another well-known gene mutation associated with late-onset Alzheimer's is the ApoE gene variant, ApoE4. ApoE4 gene carriers have impaired lipid and protein trafficking that are correlated to rapid cognitive decline. However, despite the identification of gene mutations associated with Alzheimer's Disease, many unknowns remain. For example, there are individuals who do not have Alzheimer's associated gene mutations that still develop the disease. Conversely, other individuals may have clinical outcomes such as fibrillary tangles but do not exhibit dementia.

Given the number of patients impacted and the public health need, the fact that venture capital funding of U.S. companies with lead stage programs in Alzheimer's was 16 times below oncology funding from 2009-2019 is not ideal ($1 billion vs. $16.5 billion).

Clinical development for disease-modifying drug programs for Alzheimer's has been difficult with no disease-modifying drugs moving beyond Phase III to FDA filing until this year and 87 programs suspended during the 2008-2019 time period.

When the report was published in 2019, we identified 74 clinical-stage programs, the majority of which are small molecules (56%), with disease-modifying potential in Alzheimer's disease. The drug candidates in these programs are attempting to stop, prevent, or slow the progression of Alzheimer's disease. We identified 10 strategies involving 30 distinct molecular targets in the pipeline. The dominate strategy are for medicines that target the buildup of nefarious forms of amyloid β or tau protein (60% of the pipeline). The other eight approaches are: neuro-regeneration (n=12), inflammation pathways (n=7), metabolic/energy pathway(n=2), epigenetic (n=3), glucocorticoids/cortisol (n=2), antioxidant (n=1), as well as the more recent, antibacterial (n=1), and the epichaperome (n=1) approaches.

Our report also analyzed the preclinical pipeline to gain insights on what types of strategies are on the horizon. We found that 23 of the 102 preclinical programs listed had unique targets not currently in the clinic, including caspases, different growth receptors, inflammation factors, kinases, and modified blood proteins that may restore or protect neuronal function.

[8] Within the temporal lobe is the entorhinal cortex, the hub connecting the neocortex to the hippocampus. Pathological markers of Alzheimer's disease have been shown to spreads from the entorhinal neocortical area to the hippocampus, and then to other areas of the brain. Querfurth, H., et al. Mechanism of Disease, Alzheimer's Disease. NEJM 362, 4, p.329-344 (2010)
[9] Jalbert, J., et. al. Dementia of the Alzheimer Type. Epidemiologic Reviews, 30 (1) p15–34 (2008)
[10] https://www.brightfocus.org/alzheimers/question/what-are-stages-alzheimers-disease

To deliver on these innovations and overcome historical odds, creative solutions are required during the development lifespan. Coordinated dialogue between stakeholders will help optimize development programs that aim to make meaningful differences in patient's lives. For example, academic and industry findings have helped inform the recent modernization of the FDA's endpoint guidelines in Alzheimer's trials. As our scientific understanding of the disease evolves, so must the way we develop drugs. Policies supporting efficient and effective regulatory environments will encourage investments into new treatments. For example, expanded utilization of biomarkers to stratify patient populations to better predict what treatments work best, and when and for whom they work best, would serve to incentivize innovation and change the paradigm of how we treat this widespread disease.

Meanwhile, more effort upstream is still needed. Continued funding of basic research to advance our understanding of the biology of Alzheimer's disease will arm drug developers with new targets and approaches to attack this complex disease. Although we now have identified multiple players in the etiology of the disease, the exact detailed molecular mechanism behind Alzheimer's remains unknown. Many therapies found to be very effective in animal models, and even some with promising Phase II results, have failed to show significant effects in statistically rigorous trials. To find the right intervention may require more predictive animal models and more advanced biomarkers. Although a few biomarkers for Alzheimer's have been established, such as the CSF measurement for amyloid and tau, or via PET scans with tracer agents, more biomarkers for early-stages of the disease are needed. Lastly, while not discussed in this report, BIO also supports the need to advance development of neurodegenerative medicines focused on neuropsychiatric symptoms (NPS) that provide much needed improved quality of life to patients and their caregivers.

Conclusion

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to helping patients with Alzheimer's disease and other neurodegenerative diseases. Advancements in science, more choices for patients, and a policy environment that stimulates investment in R&D are necessary to achieve this goal.