Case Study 2

Question/Biological Problem

Alzheimer‘s disease (AD) is a neurodegenerative disease that causes deterioration of brain cells in the cortex and is also the main cause for dementia. Some of the most common symptoms of Alzheimer‘s disease are loss of memory, disorientation, and the inability to comprehend learning, speech, and other cognitive skills. The cause of Alzheimer‘s disease by itself is not completely understood; however, researchers strongly believe that there are two main contributors that cause this disease that affects millions of people: the accumulation of insoluble plaques made up of peptides called amyloid beta (Abeta), and the abnormal modification and dissociation of Tau in the microtubules that clump up together which will eventually spread and kill healthy neurons [3]. As of right now, there is no known cure for Alzheimer‘s, but there are treatments and medication that can help alleviate and reduce the symptoms attributed with Alzheimer‘s disease. One example that we will be looking into is the effectiveness of the drug, Aducaumab, which works by targeting amyloid beta and thus reducing plaque buildup.

Aim

To develop a research model in order to investigate and confirm the presence of amyloid beta and misfolded Tau proteins within the brain cortex of mice. Then, we want to analyze how effective the drug Aducaumab is.

Research Model and Plan:

- For our first experiment, we want to be able to detect and confirm the presence of amyloid beta in transgenic mice animal models.
    - Our first challenge is to express human amyloid precursor protein (APP) in our mice models, since compared to humans, wild type mice have different sequence differences that do not allow Abeta aggregation and thus prevent amyloid plaques from forming. [2]
    - Therefore, transgenic mice will be developed to express Swedish, London, Florida APP mutations as well as the $PS1^{M146L}$ and $PS1^{L286V}$ mutations, since the expression of these five FAD mutations will allow our transgenic mice to exhibit Abeta accumulation at 6 weeks, which leads to plaque formations at 2 months. This can be done by performing a ‘knock in’ the combination of desired APP FAD mutations [2].
    - To identify the amyloid fibrils, we will use 19F-MRI with a 9.4-T MR scanner to scan mouse brains injected with (E,E)-1,4-bis(4-trifluoromethoxy)styryl-benzene—which has a Kd binding affinity of 10 $\pm$ 1nM and 8.6$\pm$ 0.2 signal/noise ratio—to identify Abeta plaques [4].
    - For the results, we expect to see in our 19F-MRI images, the Abeta plaques to fluoresce red in our transgenic mice that we prepared and little to no fluorescence activity in normal mice. This will then show that the build up of Abeta plaques is a key contributor to Alzheimer‘s disease.
- For our second experiment, we will now perform a similar procedure to detect Tau protein aggregation.

    - Much like Abeta, the challenge we face here is the ability to express Tau in our mice models since humans and mice only share a sequence homology of 88% for tau.
    - We propose developing mice to express 4R tau with P301L or P301S mutations [2]; however, it should be noted that the results of the experiment may not be accurate or simulate human results due to the fact that mouse tau mutations on their neurofibrillary tangles exhibit some traits that are not seen in human Alzheimer‘s disease.
    - Tau imaging is done by injecting our mice with styryl-benzoxazole derivatives with a 15-18 Anstrom pi-electron-conjugated backbone to detect neurofibrillary tangles. An example of this 19F-MRI probe is Shiga-X35 [4], which we will use.
    - Once Shiga-X35 is injected into the brain, MR imaging with a 7.0-T MR scanner is done on the live mouse to detect Shiga-X35 uptake and thus determine Tau pathology. We expect to see more signals from mice with the Tau mutations compared to healthy mice.
    - As mentioned earlier, there are some limitations to this experiment: the data and results from the experiment may not reflect what we will see in human patients. In addition, according to Yeo et al, unwanted 19F-MRI signals were detected in wild-type mice; this means that the Shiga-X35 probe and its derivatives‘ specificity and sensitivity are not yet up to standard [4].
    - However, this experiment will still better our understanding on the role of Tau in Alzhiemer’s patients.
- Finally, our final objective is to detect the effectiveness of Aducaumab, which is the first FDA approved medication used to treat Alzheimer‘s disease [1].
    - Mice that were prepared to express the human amyloid precursor protein from our first experiment will be used for this experiment as well.
    - Mice starting from 6 weeks old and before 2 months will be given the Aducaumab drug.
    - After 2 months, the mice treated with Aducaumab will then undergo the same 19F-MRI scan using the 9,4-T scanner to scan for amyloid plaques and fibrils.
    - What we expect to see is a significant decrease in fluorescence activity compared to mice that express the FAD mutations and were given no medication.

Works Cited

[1] Center for Drug Evaluation and Research. “Aducanumab (Marketed as Aduhelm) Information.” *U.S. Food and Drug Administration*, FDA, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information.

[2 Drummond, Eleanor, and Thomas Wisniewski. “Alzheimer's Disease: Experimental Models and Reality.” *Acta Neuropathologica*, U.S. National Library of Medicine, Feb. 2017, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5253109/.

[3] Kumar, Anil. “Alzheimer Disease.” *StatPearls [Internet].*, U.S. National Library of Medicine, 11 Aug. 2021, https://www.ncbi.nlm.nih.gov/books/NBK499922/.

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