BIO 282: Argument 1 - Alzheimer's Disease and Proteins

Background

Your friend Ryan was adopted at birth. For their 21st birthday, Ryan's adoptive parents gifted them a 23andme DNA test kit so that they might learn more about their genetic background. After almost two months of waiting, the results came in. Amid all of the fun results on ancestry, earwax type, and the like, one worrying piece of information stood out. The DNA test found a mutation on a gene that codes for something called **"amyloid precursor protein" (APP)**. According to the report, mutations on this gene can greatly increase a person's chances of developing early-onset Alzheimer's disease. Ryan is in a panic and asks you to help them understand the meaning of these results.

You begin by doing some background reading, and learn the following: Alzheimer's is a degenerative disease in which the brain cells gradually lose their connections and die. Increasing memory loss is one of the main symptoms. This memory loss eventually becomes so severe that the person forgets how to do many basic tasks. Years of worsening symptoms inevitably lead to death. According to the Centers for Disease Control And Prevention (CDC), Alzheimer's was the sixth leading cause of death in the US in 2016. Most cases of Alzheimer's are diagnosed in people over the age of 65; the disease is considered early-onset if diagnosed before 65. While age is the most important risk factor for Alzheimer's, there are some genetic mutations that can increase a person's risk for developing the disease.

The exact cause and mechanism of Alzheimer's is not yet fully understood. However, the "beta-amyloid hypothesis" has long been the leading explanation for how brain degeneration occurs in people with this disease. APP (mentioned above) is a large protein that is normally found in the cell membrane of neurons in the brain (**Figure 1**). An enzyme called **beta-secretase** normally cuts APP into smaller peptides, such as **beta-amyloid** (**Figure 2**). Sometimes, the beta-amyloid protein can become misfolded. Misfolded beta-amyloid proteins "stick" to each other and to other large molecules, forming plaques (**Figure 3**). Biomedical researchers hypothesize that these beta-amyloid plaques trigger an immune reaction that causes inflammation in the brain. This inflammation then causes neurons to gradually die off. One mutation that can occur in the APP gene can lead to changes in the amino acid sequence of APP and, by extension, beta-amyloid. The change in APP can lead to beta secretase cutting APP in a way that creates a misfolded beta amyloid (Note - this is not evidence, this is just part of the background).

Note: Figures 1 - 3 are on the next page.

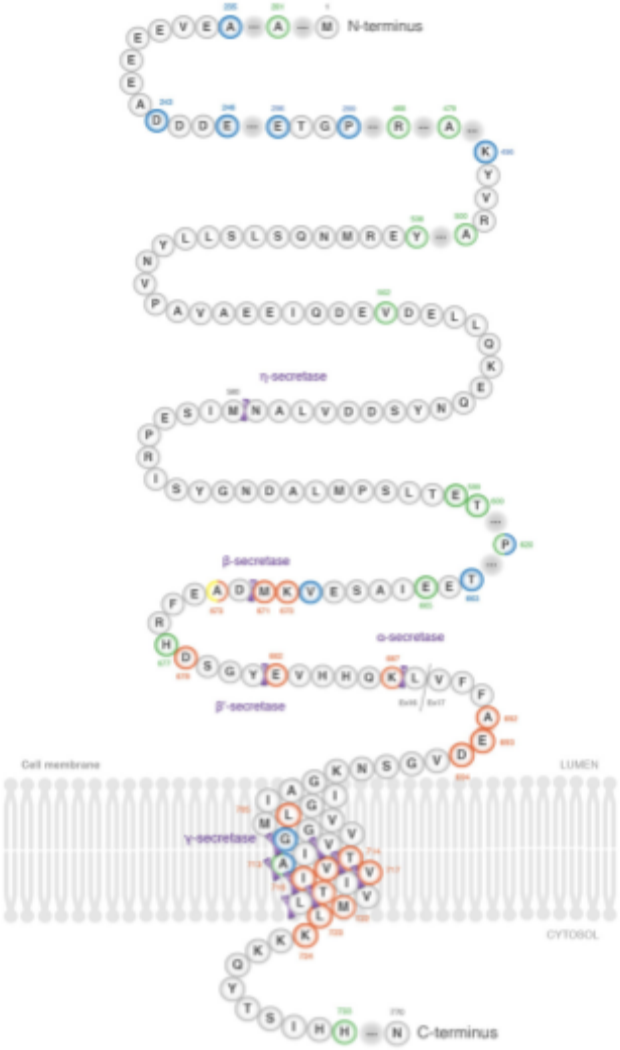

Figure 1. APP molecule with amino acid monomers shown.

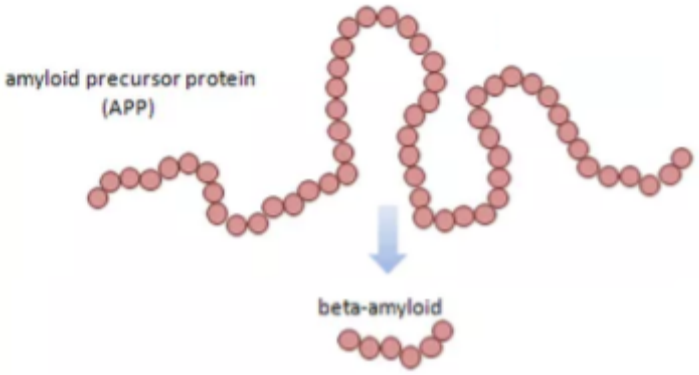

Figure 2. Beta-secretase cuts amyloid precursor protein" (APP) into smaller pieces forming beta-amyloid.

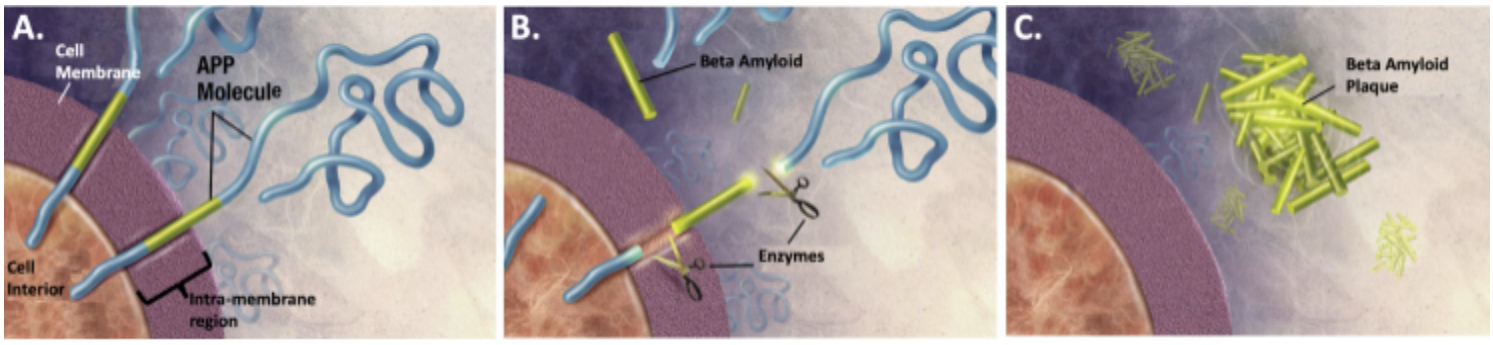

Figure 3. (A) App molecule spans the cellular membrane. (B) Beta-secretase enzymes cleave APP resulting in the creation of beta-amyloids. (C) beta-amyloids build up creating a plaque.
Image: derivative work: Garrondo (talk) Amyloid_01big1.jpg: ADEAR: "Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging."

During your research for Ryan, you came across an article online about how scientists are working to develop drugs to treat Alzheimer's Disease. According to this article, the Alzheimer's drug **verubecestat** is supposed to work by binding to the active site of beta-secretase. Specifically, the article suggests that verubecestat forms hydrogen bonds with the Asp^{32} and Asp^{228} in the beta secretase enzyme (**Figure 4**). *Note - the numbers in superscript above the Asp amino acids represent the positions of those amino acids in the protein beta secretase.*

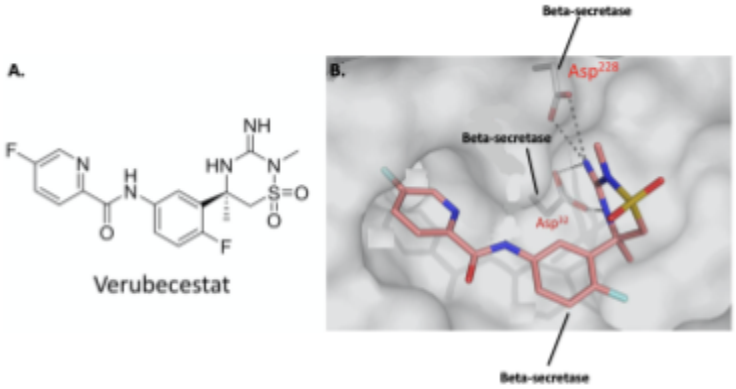

Figure 4. (A) Structural formula of the drug, verubecestat. (B) Illustration of bond formation between verubecestat and beta-secretase.

In their study, the authors tested the effect of verubecestat in monkeys by orally administering either a **placebo**, 3mg/kg of the drug or 10mg/kg of the drug. The researchers then measured the amount of beta amyloid in the **cerebral spinal fluid** (CSF) and in the brains of monkeys over time (**Figure 5a**). Additionally, they calculated the percentage of beta-amyloid protein relative to the placebo treatment present in the CSF and in the cortex of the brain of monkeys (**Figure 5b**). As a follow-up study, they tested verubecestat in healthy humans who did not have Alzheimer's disease. In this follow-up study, they orally administered either a placebo, 20 mg/kg, 100 mg/kg, or 550 mg/kg of the drug. The researchers then measured how the amount of beta amyloid protein in the CSF changed over time (**Figure 6**).

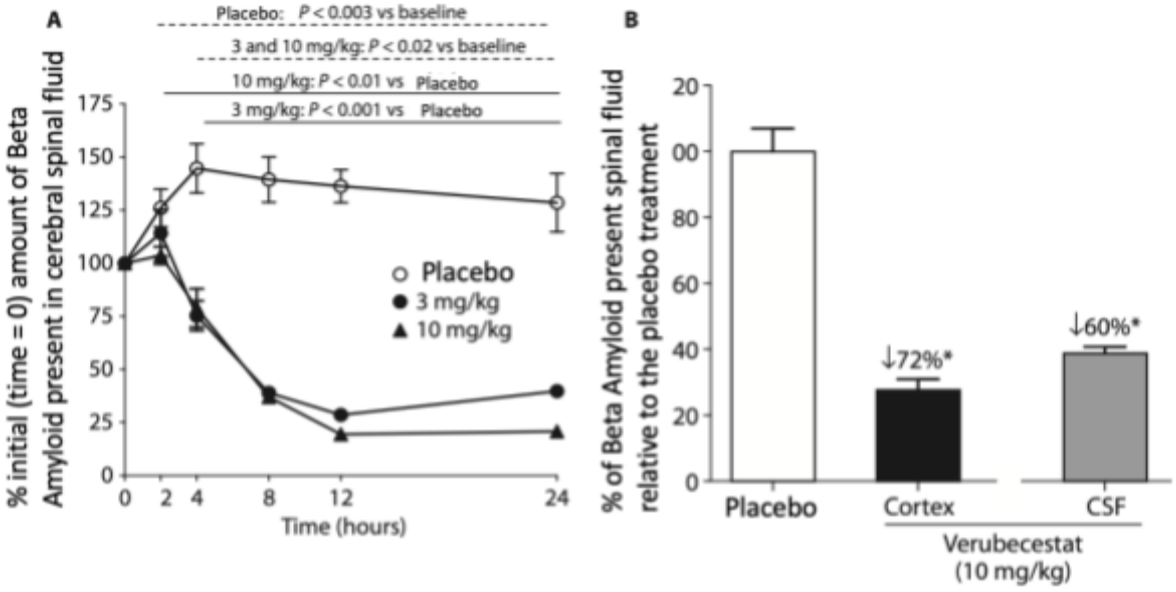

Figure 5. (A) Monkeys were given a placebo, 3mg/kg verubecestat, or 10 mg/kg verubecestat. The percent of the the original amount of beta-amyloid present at time = 0 in the monkey's cerebral spinal fluid was measured at 2, 4, 8, 12, and 24 hrs after administration of the oral medication or placebo. (B) The percent of amyloid-beta present in the cortex of the brain and cerebral spinal fluid were compared between a placebo group of monkeys and a group receiving the verubecestat.

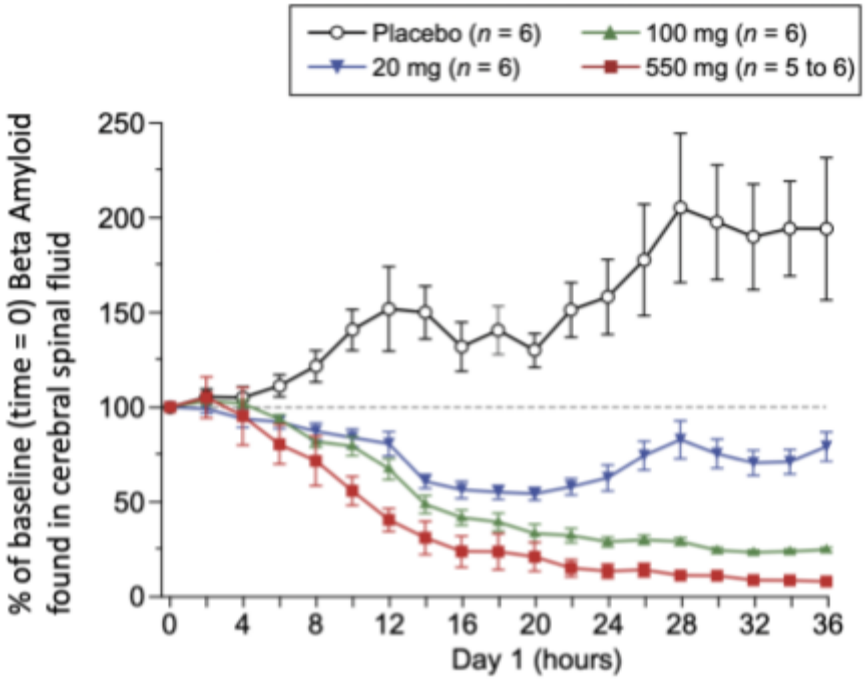

Figure 6. Healthy adult humans without Alzheimer's disease were given a placebo or verubecestat in varying strengths. The percent of amyloid-beta present in the participants' cerebral spinal fluid over the course of 35 hours was calculated with the amount of amyloid-beta present at the beginning of the study used as a baseline.

DIRECTIONS

You've told Ryan about the basic information about Alzheimers, so now you want to explain to them if this drug could be an effective treatment for Alzheimers and how. Your hope is that providing this information, you will help calm Ryan and assure that there are drugs in development that may treat Alzheimers. Ryan doesn't have a background in biology, so you decide to construct a short and concise email using non-technical jargon so that this information is accessible to them.

In your email, you should construct an argument to Ryan answering the question below. You will **not** need to construct a rebuttal to any counter arguments, as they have not been provided for this assignment. Based on the information supplied in this case, the information provided in our textbook and or lectures for BIO 282, and your knowledge of biology, construct an argument that addresses the following question:

> **Question:** Is verubecestat a potential treatment for Alzheimer's disease in humans and, if so, how does the drug work?
>
> **Things to think about:** *(1) What is beta secretase's role in the Alzheimers? (2) Think about what would happen to an enzyme if something other than it's target/substrate binds to the active site?*

Audience: Your audience is a friend who does not have expertise in biology. Thus you should be careful not to use too many technical words or jargon. If you must use jargon, make sure to define it briefly.

Due date: The original version of this argument is due by **Friday, February 14th by 11:59pm**

Group work: You are permitted to complete this assignment in groups (**MAXIMUM** three (3) students per group). You can pick your own groups - but they must be students in this class. If you would prefer to work in a smaller group (groups of 2) or work by yourself, that is fine too. **For those students working in groups, you only need to submit one assignment per team.** The points earned for the assignment will be applied equally to all members of a group. Group members are responsible for ensuring their name is included on the final document that is submitted and enrolling into the proper Canvas group. Corrections made for enrolling in the incorrect Canvas group will result in a grade deduction. If your name is not on any of the assignments that are submitted, you will receive a zero for the assignment.

Academic Integrity: You are limited to the resources in your textbook, the resources/information presented in the slides in class/lab, and the resources/information presented in this case. No additional outside resources are permitted. You can reference the figures, but you must explain what the evidence is saying and how it supports your claim. As such, you do not need to cite anything in this study. Whether you are working in a group or by yourself, you must write up an argument that is in your OWN words (or your teammates words). This means you cannot copy/paste sentences from this or any other permitted resources. This also means you may not plagiarize off other groups in the course. We will have an active plagiarism checker on, which will compare your submission to your peers as well to other resources. Any individuals and or groups caught plagiarizing will be found in violation of the University's academic integrity policies and will minimally receive a zero for this assignment.

Format:
You must use the following guidelines when constructing your case.

- Names of each team member should be at the top of the submitted assignment.
- Provide a word count for the argument (names do not count as part of word count) below the names of the team members.
- Write in full sentences and using paragraph format.
- Do not include copies of the table / figures in your response.
- Do not use direct quotes.
- Use 11pt font, Time New Roman
- Single spacing; Margins: 1 inch margins all around

- Your argument is limited to 500 words or less
- SUBMIT the final version by copying the template below and submitting as PDF
- Label the Claim, Evidence, Reasoning, and Explanation in your argument by placing a (C) for claim, (Ev) for evidence, or (R) for reasoning at the beginning of the corresponding sentences. For example, your claim would be written as “(C) Yellow is the best color for increasing people's moods.

Template:

Name of group member:
Name of group member:
Name of group member:

Enter your argument word count here:_____

Argument written in paragraph format. The order that you place the claim, evidence, and reasoning.

(C) Write your claim here. **(EV)**Write your evidence here. **(EV)** Be sure to label all evidence sentences.**(R)** Write your reasoning here**. (R)** Be sure to label all reasoning.