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Comparing Effectiveness of Two Antibodies (Aducanumab and Gantenerumab) on Reducing Amyloid-Beta Plaques

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3d molecular designs

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PDB File: 6CO3 (Aducanumab) & 5CSZ (Gantenerumab)

Primary Citation:

6CO3: Arndt, J. W., Qian, F., Smith, B. A., Quan, C., Kilambi, K. P., Bush, M. W., Walz, T., Pepinsky, R. B., Bussière, T., Hamann, S., Cameron, T. O., & Weinreb, P. H. (2018). Structural and kinetic basis for the selectivity of aducanumab for aggregated forms of amyloid-β. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-24501-0

5CSZ: Tolar, M., Abushakra, S., Hey, J. A., Porsteinsson, A., & Sabbagh, M. (2020). Aducanumab, gantenerumab, BAN2401, and alz-801—the first wave of amyloid-targeting drugs for alzheimer's disease with potential for near term approval. Alzheimer's Research & Therapy, 12(1). https://doi.org/10.1186/s13195-020-00663-w

Description:

Alzheimer's disease is a degenerative neurological disorder that destroys memory and other important cognitive functions. As time progresses, brain cell connections as well as the brain cells themselves atrophy and die. The disease is caused by a missense mutation in the amyloid-beta peptide within the amyloid precursor protein (APP). The mutation results in glutamine being replaced with glutamic acid. Within the brain, the amyloid precursor protein is a transmembrane protein that traditionally functions to regulate synaptogenesis in the nervous system. Synaptogenesis is the process of forming synapses between neurons in the nervous system which allows neurons to effectively communicate, thereby directly improving learning and memory. The mutation of the amyloid-beta peptide in the amyloid precursor protein results in the formation of insoluble and soluble amyloid-beta oligomers, thus preventing normal synaptogenesis. Previously conducted studies showed that mutated forms of the amyloid-beta peptide fragment have a greater tendency to stick together and form protein clumps or aggregates. The abnormal build-up of aggregates in and around brain cells has been found to be strongly associated with the development of Alzheimer's disease, therefore, it appeared crucial to study the methods that reduce these build-ups.

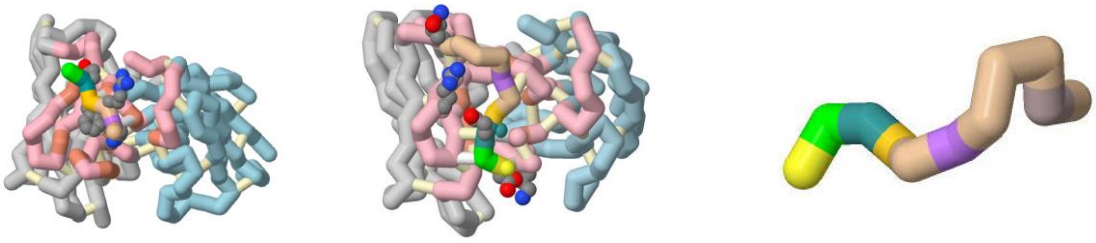
Attempts to treat this disease have produced antibodies that bind to the mutated amyloid-beta peptide and clear the aggregated amyloid precursor protein out of the brain. While multiple antibodies are undergoing testing, Aducanumab, has been fast-tracked by the U.S. Food and Drug Administration. On the other hand, Gantenerumab is still undergoing testing in order to ensure safety and efficacy. The overall goal of the project is to use protein models to show the interactions leading to efficacy variation between Aducanumab and Gantenerumab.

Specific Model Details:

Aducanumab was modeled along with the amyloid-beta peptide (residues 3-7). The light chain of the antibody is shown in light blue and the heavy chain is shown in light gray. Amino acids that are within 10 Angstroms of the amyloid-beta peptide are shown in pink. The hydrophobic pocket of the antibody consists of Y32, Y59, Y92, T94, I102, G103, R105, and P108, and is shown in a dark salmon color. The hydrogen bonds are shown in white between His6 and Tyr92 as well as Phe4 and Thr94.

Gantenerumab was modeled along with amyloid-beta peptide (residues 1-11). Similar to the Aducanumab model, the light chain of the antibody is shown in light blue and the heavy chain is shown in light gray. The amino acids that are within 10 Angstroms of the amyloid-beta peptide are shown in pink. The hydrophobic pocket of the antibody consists of A33, I92, M95, and V110, and is also shown in a dark salmon color. The hydrogen bonds are also shown in white, however, they exist between Glu3 and Val110, Ala2 and Ala53, as well as Tyr10 and Asp7. Within this antibody, the salt bridges exist between Glu3 and Arg57, Asp1 and Lys100, as well as Glu11 and Lys65. To depict these, the negative side chains are depicted in red and the positive side chains are depicted in blue.

Aducanumab: **Gantenerumab:** **Amyloid-Beta Peptide:**



Aducanumab Interactions:

Amyloid-Beta Peptide Amino Acid	Color	Interaction
His6	[204,128,255]	H-bond: Y92 Hydrophobic: Y32, I102, G103, R105, P108
Phe4	[255,209,35]	H-bond: T94 Hydrophobic: R105, T94, Y59, Y92, W52, P108

Gantenerumab Interactions:

Amyloid-Beta Peptide Amino Acid	Color	Interaction
Glu3	[59,158,158]	H-bond: V110 Salt-Bridge: R57 Hydrophobic: V110, I92, M95, A33
Ala2	[0,255,0]	H-bond: A53 Hydrophobic: A33, V110
Asp1	[255,255,48]	Salt-Bridge: K100 Hydrophobic: V110 & A33

Additional References:

Crespi, G. A., Hermans, S. J., Parker, M. W., & Miles, L. A. (2015). Molecular basis for mid-region amyloid-β capture by leading Alzheimer's disease immunotherapies. *Scientific Reports*, *5*(1). https://doi.org/10.1038/srep09649