HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 1 (2022)

# Different Therapeutic Approaches to Alzheimer's Disease

Thomas Magee[1] and Yana Zubarev[1#]

[1]Bellingham High School
[#]Advisor

## ABSTRACT

Amyloid precursor protein is the precursor to the biochemical markers for Alzheimer's disease. ([1–5]) There has been much research in the field of biochemistry to attempt to understand how these proteins interact with each other, both on a biochemical level and on a neurological level. This research has led scientists to conclusions about these proteins' substrates, structure, and functionality outside of the formation of Alzheimer's disease. Amyloid-Beta, for example, is the main biochemical marker for Alzheimer's disease, however, many of Amyloid-Beta's precursors have many substrates outside of APP that are key in overall homeostasis and molecular functionality. ([4,6–12]) There have been many attempts to restrict, increase, and alter the expression of these proteins in hope of treating Alzheimer's. ([2,9,11,13–16]) Here, we break down the core proteins responsible for these interactions and give an overview of current therapeutic approaches to Alzheimer's.

## Introduction

Amyloid Precursor Protein (APP) is a protein that is expressed by a gene located on chromosome 21 and serves as a precursor to the creation of multiple proteins whose goal is to hydrogen-bond with a variety of substrates. ([17,18]) APP, prior to being cleaved by a number of other proteins, operates as a neuron pathway exemplifier whose job is to aid in synapse formation, synaptic transmission, and memory consolidation. ([3,19–21]) Beta- Secretase is one of the varieties of proteins that cleaves APP which results in the creation of sAPPß.([22–24]) After this interaction sAPPß hydrogen bonds to a number of substrates. ([25]) APP is cleaved by beta-secretase results in C99 as the by-product after sAPPß is released. ([2,14,26–29]) C99 comprises AICD and Aß(Amoylid - beta), beta-amyloid is a 42 residue beta peptide that is the biochemical marker for Alzheimer's disease. ([30–35]) C99 is then cleaved by gamma-secretase, which releases Aß.([7,10,12,25,30,36]) Beta-amyloid hydrogen bonds to itself if there is enough present. ([13,37–40]) This causes the creation of oligomers in the brain which slow brain function, resulting in Alzheimer's disease. ([13,37–39]) ADAM is a family of transmembrane and secreted proteins that have a variety of responsibilities. ([3,5]) Alpha Secretase is a member of this family and is more officially known as ADAM10. ([3,5]) Alpha Secretase interacts with APP in a similar way that beta-secretase does. ([3,5,10,12,19,20,25,36]) Alpha secretase cleaves APP lower in the protein which releases sAPPα and leaves C83 which comprises AICD and P3. ([4,5,14,37,39,40]) When C83 is cut by gamma-secretase and AICD is released p3 is leftover instead of Aß.([4,5,14,37,39,40]) The difference is that p3 does not create oligomers. ([13,37,37,38])

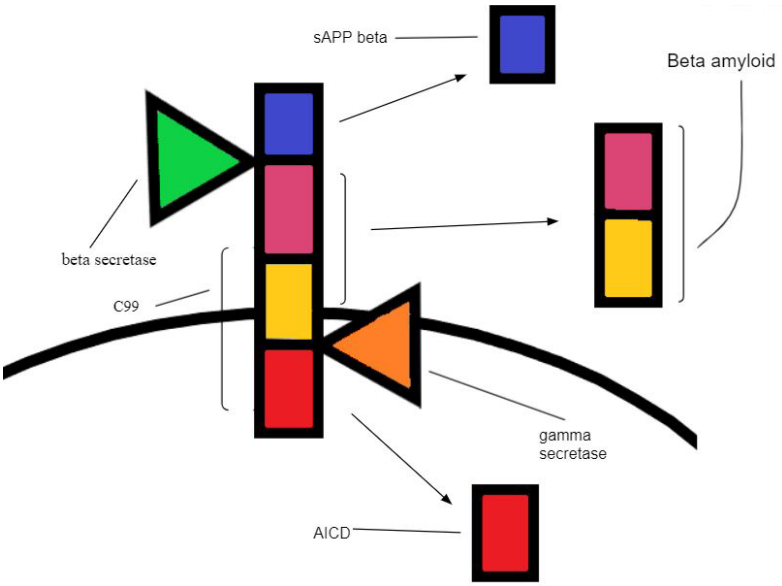


**Figure 1.** As beta-secretase interacts with amyloid precursor protein, sAPPß is released. After this interaction gamma-secretase interacts with the membrane-bound portion of the protein, C99, releasing AICD. After AICD is released the remaining portion of the protein, beta-amyloid, is then also released.

## Prevention of APP Cleavage by beta-secretase, by means of restriction of beta-secretase

The prevention of APP cleavage by means of a reduction of beta-secretase is a popular hypothesis among scientists. The idea behind this hypothesis is that a restriction of beta-secretase would result in fewer interactions with APP, thus preventing gamma-secretase (**γ**-secretase) from cleaving APP and preventing beta-amyloid from creating oligomers in the brain.([13,14,24,37–39,41]) This solution is attractive if not for beta-secretase's other substrates that contribute to overall well-being. ([42]) There are many types of beta-secretase, however, the specific beta-secretase that is important for the treatment of Alzheimer's is BACE1. ([42–45]) BACE1 is a glycoprotein that cleaves APP at its peptide bond located at Met671 and Asp672. ([22,24,45,46]) The cleavage site of beta-secretase is located in the 10s loop, which is located in the S3 binding pocket of its structure. ([22]) In the 10sp loop are aspartic acid(asp) - 32 and asp-228, which are both the main contributors to the cleavage of APP.([22]) (The 10s loop of beta-secretase also includes Trp76, Ser35, The 231, and AZD 3839)([47]) Beta - Secretase increases the activity of 116 different proteins, 43 of which are non-membrane bound. ([42]) This means that there are a variety of substrates that are important for beta-secretase to hydrogen bond to, which means the limitation of beta-secretase, only for restriction of the release of beta-amyloid is destructive to the other substrates. ([42]) Beta-Secretase's substrates other than APP include, but are not limited to [Transmembrane Protein 132A; Disintegrin and Metalloproteinase domain-containing protein 10; Desmoglein; Glypican-3]. ([42]) Tumor necrosis factor receptor superfamily member 21 for example, is a protein that promotes apoptosis within cancer-causing cells and is another substrate of beta-secretase. ([40,48,49]) If there was a restriction of beta-secretase then tumor necrosis factor receptor superfamily member 21 would not be able to inspire apoptosis within cancer-causing cells resulting in the creation of tumors. ([48,49]) This is one of the problems scientists face when trying to restrict beta-secretase.

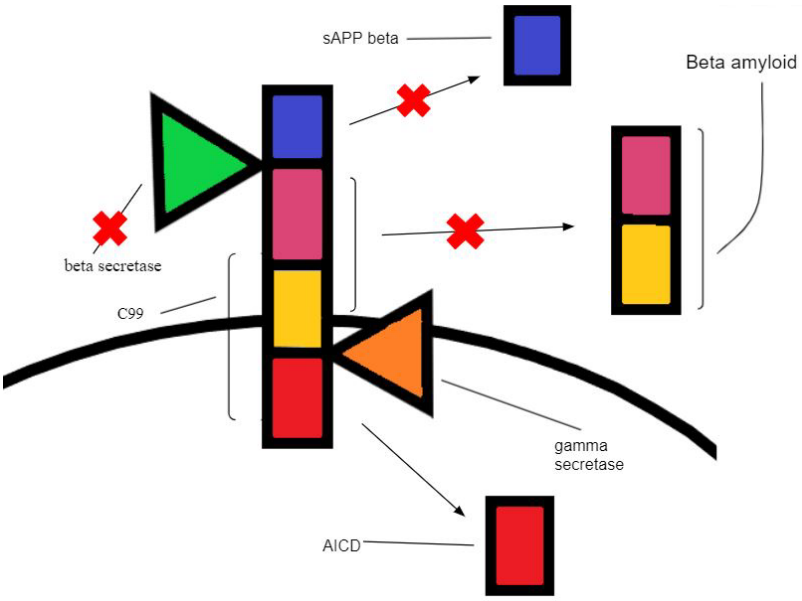


**Figure 2.** Restriction of beta-secretase prevents aAPPß from being released, which prevents gamma-secretase from interacting with C99 and releasing beta-amyloid.

## Prevention of APP cleavage by gamma-secretase, by means of restriction of gamma-secretase

Another popular hypothesis among scientists is to restrict gamma-secretase so that it cannot cleave C99 and release beta-amyloid. ([14,50]) This solution has similar issues to restricting beta-secretase, whereas gamma-secretase has many other substrates that cannot be interfered with if homeostasis is going to be maintained. ([29,51]) Gamma Secretase has around 88 known substrates that cannot be interfered with, other than C99. ([29,52,53]) Gamma-Secretase's structure can be separated by two lobes: a large lobe and a small lobe that can be further specified into four other lobes: BAP large lobe, ECD large lobe, ECD small lobe, and BAP small lobe. ([50,54]) Gamma-Secretase bonds to C99 by means of a binding pocket enclosed by a lid on the gamma-secretase structure, which is located on the BAP large lobe. ([26,50,54]) The binding pocket is made of two zinc ions and the amino acids Glu289 and Tyr293. ([54]) This binding pocket is also used to hydrogen bond to a variety of other substrates as well, these include but are not limited to [Delta 1; Dystroglycan; DCC; EpCAM; NPR-C; Ptprz]. ([29,54]) These substrates must be hydrogen-bonded with gamma-secretase for their specific protein capabilities to be carried out. ([29]) So the restriction of gamma-secretase for the specific reason to prevent the release of beta-amyloid would be catastrophic to the homeostasis that gamma-secretase provides. Dystroglycan, for example, is a protein that is vital in the repair of epithelium and specifically wound repair of the epithelium. ([55]) This means that one of the substrates of gamma-secretase is vital in the repair of skin tissue. ([55]) This is one of the many problems faced while restricting gamma-secretase.

## Prevention of APP cleavage by Beta - Secretase, by means of increasing alpha - secretase

Alpha secretase (ADAM10) interacts with APP in a similar way to beta-secretase, with the only key difference being that alpha-secretase cleaves APP lower in the protein releasing sAPPα and C83 instead of sAPPß and C99. ([3,5,25,45,56]) After gamma-secretase cleaves C99, AICD and p3 are released, the key difference between that p3 does not create the Alzheimer's causing oligomers that beta-amyloid does.([3,5,25,45,57]) The hypothesis when in regards to Alpha - secretase

is to increase the amount of alpha-secretase so that there is more interaction between alpha-secretase and APP, and an increased amount of beta-amyloid will not be released (because of beta-secretase's lack of interaction with APP) and cause oligomer formation. ([5,13,36,40,41]) This hypothesis theoretically works in contradiction to the way that the previous hypotheses theoretically work. Whereas this hypothesis works by increasing an enzyme and the others work by decreasing an enzyme. However, the application of this hypothesis has unintended consequences in the same way that the previous hypotheses have. ADAM10 has many other substrates other than APP, in the same way, that all of APP's substrates do. ([3,58]) These substrates include but are not limited to [VE-cadherin, TNFα, IL6R, CXCL16, CX3CL1]. ([3]) VE-cadherin, for example, is a substrate of APP that promotes proliferation in new cells. ([59]) Theoretically, if there was an increase in ADAM10 then the expression of VE-cadherin would be overexerted and cause an increased likelihood of tumor growth. ([59])

## Prevention of beta-amyloid Bonding by means of decreasing beta-amyloid

Beta-Amyloid is one of the many by-products of interaction between APP, beta-secretase, and gamma-secretase. ([25,60]) As previously stated beta-amyloid is the biochemical marker for the progression of Alzheimer's disease. ([7,25,30,39,61–63]) This is because of beta-amyloid's nature of hydrogen bonding to itself to create oligomers. ([13,64]) This poses the question of preventing beta-amyloid from bonding to itself to prevent the formation of oligomers. Aducanumab, for example, is a medication that was approved by the FDA for use in patients with Alzheimer's**.** ([63,65]) The medication works by binding to oligomers in a patient's brain, which causes the immune system to believe that there is an invader and will then destroy the plaque. ([63,65]) This medication is still very new and has already posed problems in some patients. ([63]) 30% of patients have experienced brain swelling and 10% have experienced brain bleeding, neither of which have a specific answer to why they are taking place. ([63])

## Conclusion

Amyloid Precursor Protein is very helpful to the body as its use as a neuron pathway exemplifier, however, the interaction between APP and many of its substrates can be detrimental to the creation of Alzheimer's. These proteins and their by-products are key in understanding Alzheimer's as well as treating Alzheimer's. The restriction of these enzymes is still being studied and many of them are soon to enter clinical trials. There has been a multitude of attempts to alter the expression of these proteins and their by-products, in an attempt to restrict the formation of oligomer formation within the brain. Most of these attempts have resulted in unintended consequences in regards to protein production. As illustrated in this report, there is currently a multitude of new research taking place in an attempt to restrict these proteins without having many of the consequences associated with protein restriction.

## References

(1) A Novel Function of Monomeric Amyloid β-Protein Serving as an Antioxidant Molecule against Metal-Induced Oxidative Damage | Journal of Neuroscience https://www.jneurosci.org/content/22/12/4833 (accessed 2021 -11 -14).

(2) Bergström, P.; Agholme, L.; Nazir, F. H.; Satir, T. M.; Toombs, J.; Wellington, H.; Strandberg, J.; Bontell, T. O.; Kvartsberg, H.; Holmström, M.; Boreström, C.; Simonsson, S.; Kunath, T.; Lindahl, A.; Blennow, K.; Hanse, E.; Portelius, E.; Wray, S.; Zetterberg, H. Amyloid Precursor Protein Expression and Processing Are Differentially Regulated during Cortical Neuron Differentiation. *Sci. Rep.* **2016**, *6* (1), 29200. https://doi.org/10.1038/srep29200.

(3) The metalloproteinase ADAM10: A useful therapeutic target? - ScienceDirect https://www.sciencedirect.com/science/article/pii/S016748891730157X (accessed 2021 -11 -14).

(4) Rabbito, A.; Dulewicz, M.; Kulczyńska-Przybik, A.; Mroczko, B. Biochemical Markers in Alzheimer's Disease. *Int. J. Mol. Sci.* **2020**, *21* (6), 1989. https://doi.org/10.3390/ijms21061989.

(5) Pharmaceuticals | Free Full-Text | Alpha-Secretase ADAM10 Regulation: Insights into Alzheimer's Disease Treatment https://www.mdpi.com/1424-8247/11/1/12 (accessed 2021 -11 -14).

(6) Baruch-Suchodolsky, R.; Fischer, B. Aβ40, Either Soluble or Aggregated, Is a Remarkably Potent Antioxidant in Cell-Free Oxidative Systems. *Biochemistry* **2009**, *48* (20), 4354–4370. https://doi.org/10.1021/bi802361k.

(7) Hillen, H. The Beta Amyloid Dysfunction (BAD) Hypothesis for Alzheimer's Disease. *Front. Neurosci.* **2019**, *13*, 1154. https://doi.org/10.3389/fnins.2019.01154.

(8) Proteolytic processing of Alzheimer's β-amyloid precursor protein https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3254787/ (accessed 2021 -11 -14).

(9) Function of β-amyloid in cholesterol transport: a lead to neurotoxicity - Yao - 2002 - The FASEB Journal - Wiley Online Library https://faseb.onlinelibrary.wiley.com/doi/10.1096/fj.02-0285fje (accessed 2021 -11 -14).

(10) What Happens to the Brain in Alzheimer's Disease? http://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease (accessed 2021 -11 -27).

(11) De Strooper, B.; Vassar, R.; Golde, T. The Secretases: Enzymes with Therapeutic Potential in Alzheimer Disease. *Nat. Rev. Neurol.* **2010**, *6* (2), 99–107. https://doi.org/10.1038/nrneurol.2009.218.

(12) What's hAPPening at synapses? The role of amyloid β-protein precursor and β-amyloid in neurological disorders | Molecular Psychiatry https://www.nature.com/articles/mp2012122?error=cookies_not_supported&code=b4890bba-cc%2083-4457-bd38-23de6ef8a18b (accessed 2021 -11 -14).

(13) Zhao, L. N.; Long, H.; Mu, Y.; Chew, L. Y. The Toxicity of Amyloid β Oligomers. *Int. J. Mol. Sci.* **2012**, *13* (6), 7303–7327. https://doi.org/10.3390/ijms13067303.

(14) He, G.; Luo, W.; Li, P.; Remmers, C.; Netzer, W.; Hendrick, J.; Bettayeb, K.; Flajolet, M.; Gorelick, F.; Wennogle, L. P.; Greengard, P. Gamma-Secretase Activating Protein, a Therapeutic Target for Alzheimer's Disease. *Nature* **2010**, *467* (7311), 95–98. https://doi.org/10.1038/nature09325.

(15) De Jonghe, C.; Esselens, C.; Kumar-Singh, S.; Craessaerts, K.; Serneels, S.; Checler, F.; Annaert, W.; Van Broeckhoven, C.; De Strooper, B. Pathogenic APP Mutations near the γ-Secretase Cleavage Site Differentially Affect Aβ Secretion and APP C-Terminal Fragment Stability. *Hum. Mol. Genet.* **2001**, *10* (16), 1665–1671. https://doi.org/10.1093/hmg/10.16.1665.

(16) Mattson, M. P. Pathways Towards and Away from Alzheimer's Disease. *Nature* **2004**, *430* (7000), 631–639. https://doi.org/10.1038/nature02621.

(17) TCW, J.; Goate, A. M. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. *Cold Spring Harb. Perspect. Med.* **2017**, *7* (6), a024539. https://doi.org/10.1101/cshperspect.a024539.

(18) The same γ-secretase accounts for the multiple intramembrane cleavages of APP - Zhao - 2007 - Journal of Neurochemistry - Wiley Online Library https://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2006.04302.x (accessed 2021 -11 -14).

(19) Lloyd, G. M.; Trejo-Lopez, J. A.; Xia, Y.; McFarland, K. N.; Lincoln, S. J.; Ertekin-Taner, N.; Giasson, B. I.; Yachnis, A. T.; Prokop, S. Prominent Amyloid Plaque Pathology and Cerebral Amyloid Angiopathy in APP V717I (London) Carrier – Phenotypic Variability in Autosomal Dominant Alzheimer's Disease. *Acta Neuropathol. Commun.* **2020**, *8*, 31. https://doi.org/10.1186/s40478-020-0891-3.

(20) Hoe, H.; Lee, H.; Pak, D. T. S. The Upside of APP at Synapses. *CNS Neurosci. Ther.* **2010**, *18* (1), 47–56. https://doi.org/10.1111/j.1755-5949.2010.00221.x.

(21) Tarasoff-Conway, J. M.; Carare, R. O.; Osorio, R. S.; Glodzik, L.; Butler, T.; Fieremans, E.; Axel, L.; Rusinek, H.; Nicholson, C.; Zlokovic, B. V.; Frangione, B.; Blennow, K.; Ménard, J.; Zetterberg, H.; Wisniewski, T.; de Leon, M. J. Clearance Systems in the Brain—Implications for Alzheimer Disease. *Nat.*

*Rev. Neurol.* **2015**, *11* (8), 457–470. https://doi.org/10.1038/nrneurol.2015.119.

(22) Beta secretase - Proteopedia, life in 3D https://proteopedia.org/wiki/index.php/Beta_secretase (accessed 2021 -11 -14).

(23) Gorfe, A. A.; Caflisch, A. Functional Plasticity in the Substrate Binding Site of Beta-Secretase. *Struct. Lond. Engl. 1993* **2005**, *13* (10), 1487–1498. https://doi.org/10.1016/j.str.2005.06.015.

(24) Beta-secretase: Structure, Function, and Evolution https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921875/#R7 (accessed 2021 -11 -14).

(25) Chow, V. W.; Mattson, M. P.; Wong, P. C.; Gleichmann, M. An Overview of APP Processing Enzymes and Products. *Neuromolecular Med.* **2010**, *12* (1), 1–12. https://doi.org/10.1007/s12017-009-8104-z.

(26) Identification of Distinct γ-Secretase Complexes with Different APH-1 Variants* - Journal of Biological Chemistry https://www.jbc.org/article/S0021-9258(20)72591-3/fulltext (accessed 2021 -11 -14).

(27) Kim, S.-H.; Yin, Y. I.; Li, Y.-M.; Sisodia, S. S. Evidence That Assembly of an Active γ-Secretase Complex Occurs in the Early Compartments of the Secretory Pathway *. *J. Biol. Chem.* **2004**, *279* (47), 48615–48619. https://doi.org/10.1074/jbc.C400396200.

(28) Capell, A.; Beher, D.; Prokop, S.; Steiner, H.; Kaether, C.; Shearman, M. S.; Haass, C. γ-Secretase Complex Assembly within the Early Secretory Pathway *. *J. Biol. Chem.* **2005**, *280* (8), 6471–6478. https://doi.org/10.1074/jbc.M409106200.

(29) The Many Substrates of Presenilin/γ-Secretase https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281584/ (accessed 2021 -11 -14).

(30) Amyloid beta: structure, biology and structure-based therapeutic development | Acta Pharmacologica Sinica https://www.nature.com/articles/aps201728 (accessed 2021 -11 -14).

(31) Kroth, H.; Ansaloni, A.; Varisco, Y.; Jan, A.; Sreenivasachary, N.; Rezaei-Ghaleh, N.; Giriens, V.; Lohmann, S.; López-Deber, M. P.; Adolfsson, O.; Pihlgren, M.; Paganetti, P.; Froestl, W.; Nagel-Steger, L.; Willbold, D.; Schrader, T.; Zweckstetter, M.; Pfeifer, A.; Lashuel, H. A.; Muhs, A. Discovery and Structure Activity Relationship of Small Molecule Inhibitors of Toxic β-Amyloid-42 Fibril Formation *. *J. Biol. Chem.* **2012**, *287* (41), 34786–34800. https://doi.org/10.1074/jbc.M112.357665.

(32) Lashuel, H. A.; Hartley, D. M.; Balakhaneh, D.; Aggarwal, A.; Teichberg, S.; Callaway, D. J. E. New Class of Inhibitors of Amyloid-β Fibril Formation: IMPLICATIONS FOR THE MECHANISM OF PATHOGENESIS IN ALZHEIMER'S DISEASE *. *J. Biol. Chem.* **2002**, *277* (45), 42881–42890. https://doi.org/10.1074/jbc.M206593200.

(33) Zhou, S.; Zhou, H.; Walian, P. J.; Jap, B. K. CD147 Is a Regulatory Subunit of the γ-Secretase Complex in Alzheimer's Disease Amyloid β-Peptide Production. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102* (21), 7499–7504. https://doi.org/10.1073/pnas.0502768102.

(34) Ward, M. W.; Concannon, C. G.; Whyte, J.; Walsh, C. M.; Corley, B.; Prehn, J. H. M. The Amyloid Precursor Protein Intracellular Domain(AICD) Disrupts Actin Dynamics and Mitochondrial Bioenergetics. *J. Neurochem.* **2010**, *113* (1), 275–284. https://doi.org/10.1111/j.1471-4159.2010.06615.x.

(35) Presenilin-dependent Intramembrane Proteolysis of CD44 Leads to the Liberation of Its Intracellular Domain and the Secretion of an Aβ-like Peptide* - Journal of Biological Chemistry https://www.jbc.org/article/S0021-9258(19)71566-X/fulltext (accessed 2021 -11 -14).

(36) APP and APLP2 interact with the synaptic release machinery and facilitate transmitter release at hippocampal synapses | eLife https://elifesciences.org/articles/09743 (accessed 2021 -11 -14).

(37) Dulin, F.; Léveillé, F.; Ortega, J. B.; Mornon, J.-P.; Buisson, A.; Callebaut, I.; Colloc'h, N. P3 Peptide, a Truncated Form of Aβ Devoid of Synaptotoxic Effect, Does Not Assemble into Soluble Oligomers. *FEBS Lett.* **2008**, *582* (13), 1865–1870. https://doi.org/10.1016/j.febslet.2008.05.002.

(38) Polis, B.; Srikanth, K. D.; Elliott, E.; Gil-Henn, H.; Samson, A. O. L-Norvaline Reverses Cognitive Decline and Synaptic Loss in a Murine Model of Alzheimer's Disease. *Neurotherapeutics* **2018**, *15* (4), 1036–1054. https://doi.org/10.1007/s13311-018-0669-5.

(39) Affairs, <img src='/content/dam/sm-profiles/profileBGoldmanM jpg img 620 high png/1449287397088 png' alt='Bruce Goldman'> Bruce Goldman Bruce Goldman is a science writer for the medical school's Office of Communication & Public. Scientists reveal how beta-amyloid may cause Alzheimer's http://med.stanford.edu/news/all-news/2013/09/scientists-reveal-how-beta-amyloid-may-cause-alzheimers.html (accessed 2021 -11 -27).

(40) Wei, W.; Norton, D. D.; Wang, X.; Kusiak, J. W. Abeta 17-42 in Alzheimer's Disease Activates JNK and Caspase-8 Leading to Neuronal Apoptosis. *Brain J. Neurol.* **2002**, *125* (Pt 9), 2036–2043. https://doi.org/10.1093/brain/awf205.

(41) Beta-Amyloid and the Amyloid Hypothesis. 4.

(42) Identification of β-Secretase (BACE1) Substrates Using Quantitative Proteomics https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2793532/ (accessed 2021 -11 -14).

(43) Ghosh, A. K.; Osswald, H. L. BACE1 (β-Secretase) Inhibitors for the Treatment of Alzheimer's Disease. *Chem. Soc. Rev.* **2014**, *43* (19), 6765–6813. https://doi.org/10.1039/c3cs60460h.

(44) Luo, Y.; Bolon, B.; Damore, M. A.; Fitzpatrick, D.; Liu, H.; Zhang, J.; Yan, Q.; Vassar, R.; Citron, M. BACE1 (β-Secretase) Knockout Mice Do Not Acquire Compensatory Gene Expression Changes or Develop Neural Lesions over Time. *Neurobiol. Dis.* **2003**, *14* (1), 81–88. https://doi.org/10.1016/S0969-9961(03)00104-9.

(45) Kimura, A.; Hata, S.; Suzuki, T. Alternative Selection of β-Site APP-Cleaving Enzyme 1 (BACE1) Cleavage Sites in Amyloid β-Protein Precursor (APP) Harboring Protective and Pathogenic Mutations within the Aβ Sequence. *J. Biol. Chem.* **2016**, *291* (46), 24041–24053. https://doi.org/10.1074/jbc.M116.744722.

(46) Beta Secretase - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/medicine-and-dentistry/beta-secretase (accessed 2021 -11 -28).

(47) Jeppsson, F.; Eketjäll, S.; Janson, J.; Karlström, S.; Gustavsson, S.; Olsson, L.-L.; Radesäter, A.-C.; Ploeger, B.; Cebers, G.; Kolmodin, K.; Swahn, B.-M.; von Berg, S.; Bueters, T.; Fälting, J. Discovery of AZD3839, a Potent and Selective BACE1 Inhibitor Clinical Candidate for the Treatment of Alzheimer Disease. *J. Biol. Chem.* **2012**, *287* (49), 41245–41257. https://doi.org/10.1074/jbc.M112.409110.

(48) TNFRSF21 - Tumor necrosis factor receptor superfamily member 21 precursor - Homo sapiens (Human) - TNFRSF21 gene & protein https://www.uniprot.org/uniprot/O75509 (accessed 2021 -11 -14).

(49) Buxbaum, J. D.; Liu, K. N.; Luo, Y.; Slack, J. L.; Stocking, K. L.; Peschon, J. J.; Johnson, R. S.; Castner, B. J.; Cerretti, D. P.; Black, R. A. Evidence That Tumor Necrosis Factor Alpha Converting Enzyme Is Involved in Regulated Alpha-Secretase Cleavage of the Alzheimer Amyloid Protein Precursor. *J. Biol. Chem.* **1998**, *273* (43), 27765–27767. https://doi.org/10.1074/jbc.273.43.27765.

(50) Bai, X.; Yan, C.; Yang, G.; Lu, P.; Ma, D.; Sun, L.; Zhou, R.; Scheres, S. H. W.; Shi, Y. An Atomic Structure of Human γ-Secretase. *Nature* **2015**, *525* (7568), 212–217. https://doi.org/10.1038/nature14892.

(51) Ray, W. J.; Yao, M.; Mumm, J.; Schroeter, E. H.; Saftig, P.; Wolfe, M.; Selkoe, D. J.; Kopan, R.; Goate, A. M. Cell Surface Presenilin-1 Participates in the γ-Secretase-like Proteolysis of Notch *. *J. Biol. Chem.* **1999**, *274* (51), 36801–36807. https://doi.org/10.1074/jbc.274.51.36801.

(52) Lu, P.; Bai, X.; Ma, D.; Xie, T.; Yan, C.; Sun, L.; Yang, G.; Zhao, Y.; Zhou, R.; Scheres, S. H. W.; Shi, Y. Three-Dimensional Structure of Human γ-Secretase. *Nature* **2014**, *512* (7513), 166–170. https://doi.org/10.1038/nature13567.

(53) Kaether, C.; Haass, C.; Steiner, H. Assembly, Trafficking and Function of γ-Secretase. *Neurodegener. Dis.* **2006**, *3* (4–5), 275–283. https://doi.org/10.1159/000095267.

(54) Crystal structure of the γ-secretase component nicastrin | PNAS https://www.pnas.org/content/111/37/13349 (accessed 2021 -11 -14).

(55) Sirour, C.; Hidalgo, M.; Bello, V.; Buisson, N.; Darribère, T.; Moreau, N. Dystroglycan Is Involved in Skin Morphogenesis Downstream of the Notch Signaling Pathway. *Mol. Biol. Cell* **2011**, *22* (16), 2957–2969.

https://doi.org/10.1091/mbc.E11-01-0074.

(56) Zlokovic, B. V.; Frangione, B. *Transport-Clearance Hypothesis for Alzheimer's Disease and Potential Therapeutic Implications*; Landes Bioscience, 2013.

(57) Kuhn, A. J.; Raskatov, J. Is the P3 Peptide (Aβ17-40, Aβ17-42) Relevant to the Pathology of Alzheimer's Disease?1. *J. Alzheimers Dis.* **2020**, *74* (1), 43–53. https://doi.org/10.3233/jad-191201.

(58) Watanabe, N.; Tomita, T.; Sato, C.; Kitamura, T.; Morohashi, Y.; Iwatsubo, T. Pen-2 Is Incorporated into the γ-Secretase Complex through Binding to Transmembrane Domain 4 of Presenilin 1 *. *J. Biol. Chem.* **2005**, *280* (51), 41967–41975. https://doi.org/10.1074/jbc.M509066200.

(59) Vestweber, D. VE-Cadherin: The Major Endothelial Adhesion Molecule Controlling Cellular Junctions and Blood Vessel Formation. *Arterioscler. Thromb. Vasc. Biol.* **2008**, *28* (2), 223–232. https://doi.org/10.1161/ATVBAHA.107.158014.

(60) Branca, C.; Sarnico, I.; Ruotolo, R.; Lanzillotta, A.; Viscomi, A. R.; Benarese, M.; Porrini, V.; Lorenzini, L.; Calzà, L.; Imbimbo, B. P.; Ottonello, S.; Pizzi, M. Pharmacological Targeting of the β-Amyloid Precursor Protein Intracellular Domain. *Sci. Rep.* **2014**, *4* (1), 4618. https://doi.org/10.1038/srep04618.

(61) Benseny-Cases, N.; Klementieva, O.; Cotte, M.; Ferrer, I.; Cladera, J. Microspectroscopy (MFTIR) Reveals Co-Localization of Lipid Oxidation and Amyloid Plaques in Human Alzheimer Disease Brains. *Anal. Chem.* **2014**, *86* (24), 12047–12054. https://doi.org/10.1021/ac502667b.

(62) Bogoyevitch, M. A.; Boehm, I.; Oakley, A.; Ketterman, A. J.; Barr, R. K. Targeting the JNK MAPK Cascade for Inhibition: Basic Science and Therapeutic Potential. *Biochim. Biophys. Acta BBA - Proteins Proteomics* **2004**, *1697* (1), 89–101. https://doi.org/10.1016/j.bbapap.2003.11.016.

(63) A new Alzheimer's drug has been approved. But should you take it? - Harvard Health https://www.health.harvard.edu/blog/a-new-alzheimers-drug-has-been-approved-but-should-you-take-it-202106082483 (accessed 2021 -11 -14).

(64) Sobhanifar, S.; Schneider, B.; Löhr, F.; Gottstein, D.; Ikeya, T.; Mlynarczyk, K.; Pulawski, W.; Ghoshdastider, U.; Kolinski, M.; Filipek, S.; Güntert, P.; Bernhard, F.; Dötsch, V. Structural Investigation of the C-Terminal Catalytic Fragment of Presenilin 1. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107* (21), 9644–9649. https://doi.org/10.1073/pnas.1000778107.

(65) Aducanumab Approved for Treatment of Alzheimer's Disease https://alz.org/alzheimers-dementia/treatments/aducanumab (accessed 2021 -11 -30).