Aging is the primary risk factor for the majority of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). There are almost 40 million people aged 65+ in the United States. Statistics predict that if you reach age 65 you can expect to live almost 20 more years. The average age of onset of PD is 60 years. If you are 85 years of age, you have an almost 50% risk of developing AD. The population of persons 85+ is projected to increase from 4.2 million in the year 2000 to 6.6 million in the year 2020. This suggests that these neurodegenerative diseases will reach a prevalence of epidemic proportions.

The current dogma holds that cellular mechanisms that are associated with aging and those that are related to neuron degeneration in PD and AD *are unrelated*. However, more recent evidence suggests that normal aging and the degeneration of specific neuron populations in AD or PD may be linked by the same cellular mechanisms. This remains a topic of debate. For your comprehensive exam, choose either AD or PD and use this disease to address the following questions:

1) Discuss what is known about one primary molecular mechanism that creates the pathology that occurs in one of these age-related neurodegenerative conditions. Discuss age-related changes in brain physiology that may promote, enhance, and/or allow the appearance of the disease specific pathology to be exaggerated in middle age and beyond.

2) For this section, assume that neurodegenerative disease exists along a continuum with natural aging. The implication of this is that if individuals survive long enough, it is inevitable that they will eventually develop AD or PD. Keep in mind that AD and PD are each viewed as genetically heterogeneous and complex disorders caused or influenced by multiple factors (e.g., specific genes, susceptibility alleles, environmental exposures, gene-environment interactions). Thus the development of "cause-directed therapies" is a goal of future research in these fields. Indeed, one model suggests that elements of lifestyle and genetics that promote healthy aging will decrease the incidence of these diseases in the general population. In this regard, discuss the following issues:

A.) how elements of lifestyle, genetics, or an intervention might impact the incidence of AD or PD.

B.) whether current data suggests a *single* target to cure AD or PD or if a multi-pronged approach is necessary.

C.) In the realm of "personalized medicine," how one could tailor a specific therapy or lifestyle for two patients with different "forms"* of AD or PD .

Alzheimer's disease (AD) affects approximately 5.4 million Americans and by 2050 it is projected that 11-16 million Americans will be living with AD [1]. Thus, understanding the molecular mechanisms of AD and how environmental and/or lifestyle choices may increase the incidence of AD is essential to reduce the number of individuals subject to this growing epidemic. In this paper, I will review research on 1) the molecular mechanism of AD, highlighting β-amyloid plaque formation, 2) age-related changes that may promote AD, 3) factors that contribute to the incidence of AD, specifically genetics, 4) whether a single target or multipronged approach is need to cure AD, and 5) the use of personalized medicine for treating different forms of AD.

Molecular mechanisms of AD: β-amyloid

Alzheimer's disease is characterized two major structural changes in the brain, the formation of neurofibrillary tangles via the tau protein and the formation of senile, or β-amyloid, plaques [1]. Much attention has been given to the accumulation of β-amyloid plaques with one popular hypothesis in the field being the "amyloid cascade hypothesis" (see Fig 1) [2-4]. This hypothesis states that the production and accumulation of the β-amyloid protein (Aβ) in brain contributes to a cascade of pathological events, such as vascular damage, oxidative stress, the production of neurofibrillary tangles, reduced synaptic transmission, and ultimately neuronal death, all of which contribute to dementia in AD patients [2, 3]. However, some researchers have questioned the amyloid hypothesis

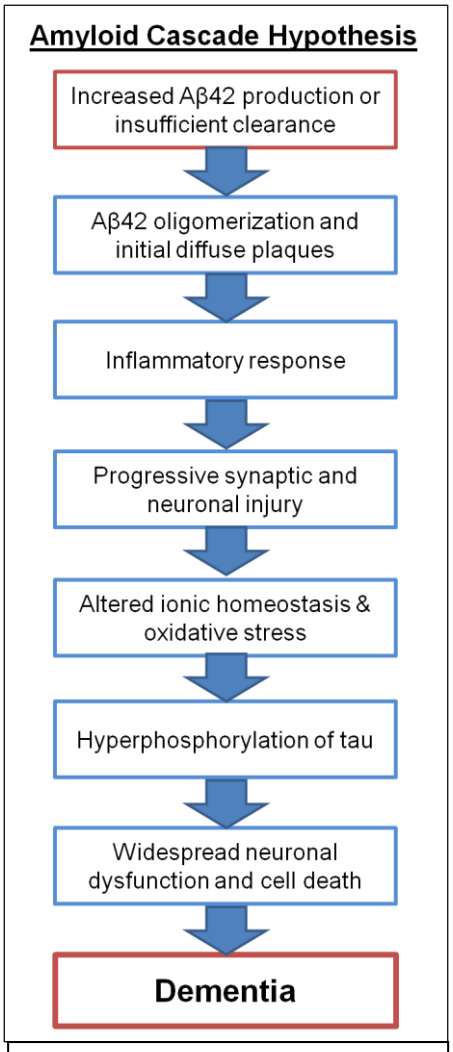

Fig 1. Proposed amyloid cascade hypothesis of AD [2, 4, 10].

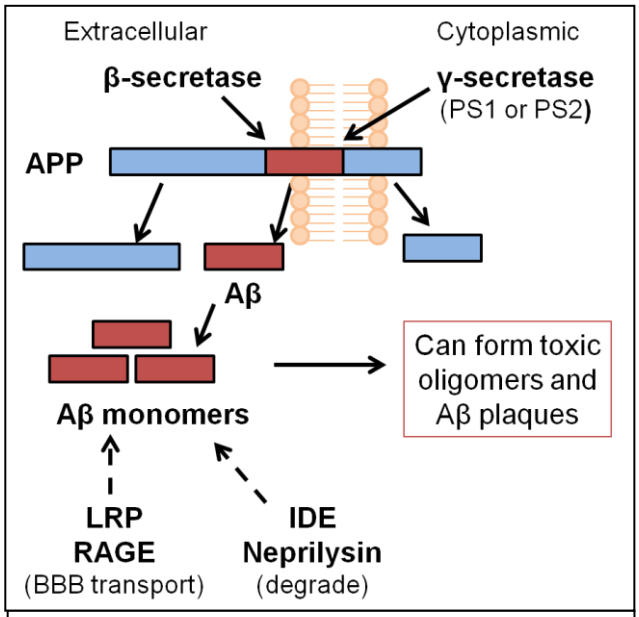

Fig 2. APP metabolism [8, 10, 30, 47].

as placing too much emphasis on Aβ, since many other factors, such as inflammation or vascular damage, may contribute to early AD pathology [5]. Although, Aβ may not be the sole causative factor in the development of AD, the molecular mechanisms contributing to β-amyloid plaques will be highlighted here

β-amyloid plaques are formed from the Aβ protein, a 4-kDa protein derived from protelyic cleavage of the amyloid precursor protein (APP)[6-8] (see Fig 2). APP is a receptor-like protein spanning the cell membrane [9]. Two cell membrane proteases known as β-secretase and γ-secretase remove Aβ from APP [4, 8, 10, 11]; β-secretase first removes the extracellular portion of APP, while the intracellular portion of APP is removed via the presenilin (PS1 or PS2) component of the γ-secretase molecule. This leads to the release of Aβ. Aβ can be carried across the blood brain barrier (BBB) into the blood supply via low-density lipoprotein receptor-related protein (LRP) and receptor for advanced glycation end products, (RAGE) carries Aβ back into the brain; Aβ can also be degraded within the brain by neprilysin or insulin-degrading enzyme (IDE) [12]. Abnormal clearance or production of Aβ in the brain is a major contributor to β-amyloid plaque formation in AD patients [8].

The formation of β-amyloid plaques occurs via the accumulation of Aβ in the brain. Originally, Aβ production was viewed as an abnormal event, but it was then discovered that Aβ is metabolized by cells normally [13, 14] and can be present within the brain, cerebrospinal fluid (CSF), and blood under normal conditions [15]. Additionally, AD and healthy age-matched

controls both show levels of Aβ in the CSF with individual variation [14], further suggesting that Aβ itself is not leading the pathological production of β-amyloid plaques, but a certain form of Aβ is considered to be involved in this process. Aβ consists of two forms, a short form (such as $A\beta_{40}$, 40 amino acids in length) and a long form (such as $A\beta_{42}$, 42 amino acids in length)[10, 11, 16]. The $A\beta_{42}$ form is considered to be the culprit of the β-amyloid plaque pathology, since $A\beta_{42}$ aggregates quickly compared to $A\beta_{40}$ [17] and the majority of plaques in AD patients consist of $A\beta_{42}$ [18]. Overproduction or an increased $A\beta_{42}$/ $A\beta_{40}$ production ratio contributes to β-amyloid plaque formation [10]. Additionally, it is believed that the formation of $A\beta_{42}$ oligomers contribute to the cytotoxic and synaptic dysfunctions in AD, since $A\beta_{42}$ oligomers induce high oxidative stress and apoptotic events [19] and Aβ oligomers block long-term potentiation (LTP) in rats *in vivo* [20]. Thus, the molecular mechanism of β-amyloid plaque pathology in AD patients is via $A\beta_{42}$ formation and accumulation.

AD and age-related changes in the brain

Alzheimer's disease is not considered a normal part of aging, but many age-related changes that occur in the brain may enhance the detrimental effects of AD, such as mitochondrial dysfunction and oxidative stress. Within the cell, mitochondria serve to store intracellular calcium and produce energy in the form of adenosine triphosphate (ATP); production of ATP occurs via the electron transport chain [21]. During ATP production, electrons may escape from the electron transport chain and reduce oxygen within the cell causing the formation of reactive oxygen species (ROS) [21]. ROS can then damage cellular structures, a process known as oxidative stress. Oxidative stress can affect many cellular components and cause structural changes in nucleic acids, proteins (leading to protein aggregations), and lipid membranes [22].

Both mitochondrial damage and oxidative stress have been associated with aging. Mutations in mitochondrial DNA (mtDNA) increase with age [23, 24], such that higher levels of mtDNA deletions are found with advanced age [25]. Interestingly, the whole brain is not subject to high levels of mtDNA deletions in the aging process, as very few occur in the cerebellum, while more mutations occur in the putamen and cortical areas [25]. Increased damage to mitochondria can lead to mitochondrial dysfunction, increased ROS production causing oxidative stress, reduced ATP levels, and further damage mitochondria and other cellular components [26]. Additionally, oxidative stress can induced programmed cell death pathways [23] . Thus, it is likely that these damaging effects of mitochondrial damage and oxidative stress are enhancing the deleterious effects of protein aggregation and neurodegeneration in AD.

Oxidative stress is believed to be enhanced during AD. In fact, neurons in the frontal cortex of AD patients have an increased expression of 8-OHG (a marker of oxidative damage) compared to age-matched controls [27]. However, individuals without AD still express 8-OHG in some neurons, further suggesting that oxidative damage is a normal part of aging [27]. Furthermore, cellular ROS levels are increased in AD versus normal human fibroblast cells and levels of a protein important in mitochondrial division (dynamin-related protein, DLP1) are also decreased in AD cells [28]. Based on these data, it is tempting to speculate that increased oxidative stress during aging is playing a role in the pathology of AD and it may be doing so by damaging cellular structures and potentially increasing aggregations of proteins. This is not to say that normal changes in oxidative stress during aging cause AD, but rather that such conditions enhance the pathology associated with AD. In fact, Aβ does interact with mitochondria in human AD tissue and this interaction is believed to induce mitochondrial

dysfunction and oxidative stress [29, 30], so it is likely oxidative stress as a result of normal aging is enhancing the oxidative stress induced by Aβ during AD.

Incidence of AD: Genetics

Alzheimer's disease a multidimensional disorder with many factors contributing to its development. One factor that increases the incident of AD in some individuals is genetics. Familial AD, is a very rare, < 5% of all AD cases, and genetically-linked form of AD [16, 31]. Individuals with FAD have "early-onset" AD (< 65 years of age) and some individuals develop AD as early as 30 years of age [16, 31]. FAD is an autosomal dominant disease, so there is a 50% chance that an individual will develop AD if one of his/her parent's has the gene [11]. The genetic basis for this form of AD is gene mutations on a particular chromosomes encoding proteins involved in the production of Aβ (refer to "Molecular mechanisms of AD: β-amyloid). Well-known Gene mutations that cause FAD may occur on chromosome 21, 14, or 1 [16].

The first discovered gene mutation associated with FAD was a point mutation on chromosome 21 encoding the APP gene [32]. Mutations on the APP gene are associated with increased Aβ production or an increased ratio of $A\beta_{42}/A\beta_{40}$ [31, 33]. Another mutation discovered to contribute to the development of FAD was on chromosome 14, which encodes the presenilin 1 (PS1; gene: *PSEN1*) protein. PS1 is part of the γ-secretase molecule associated with cleavage of the APP protein in Aβ production (refer to Fig 2). Mutations of *PSEN1* have been found throughout this gene [34], are associated with an increased ratio of $A\beta_{42}/A\beta_{40}$, and are the most common mutation associated with FAD [31, 34]. The least common gene mutation associated with FAD is on chromosome 1; this gene encodes the presenilin 2 protein (PS2; gene: *PSEN1*), a homolog of PS1. PS2 is also part of the γ-secretase molecule (either PS1 or PS2 is

present). The *PSEN2* mutation creates an increased ratio of $A\beta_{42}/A\beta_{40}$, similar to *PSEN1* [31]. Overall, the three common known gene mutations associated with the development of FAD encode proteins involved in Aβ production and enhance the production of $A\beta_{42}$, a major component of β-amyliod plaques [18]. While mutations in *APP*, *PSEN1*, and *PSEN2* are the three known genetic mutations causing FAD, some individuals with FAD do not have any of these mutations; this has lead to further investigation of potential gene mutations responsible for FAD [31].

Although many genetically-linked mutations are associated with FAD, the more common form of AD, known as sporadic AD (SAD), is not considered to be hereditable, but SAD can be under a genetic influence. SAD accounts for the majority of AD cases and has a "late-onset" (>65 years of age) [16, 31]. The major genetic risk contributing to late-onset AD is associated with the apolipoprotein E gene (*ApoE*) on chromosome 19. ApoE is involved in lipid and cholesterol metabolism [31]. There are 3 different alleles for the *ApoE* gene: ε2, ε3, and ε4. Interestingly, ε4 allele frequency in AD patients is high [35, 36] and is associated with an earlier AD diagnosis [35] suggesting that the ε4 allele poses a higher risk for AD. The ε4 allele of ApoE binds readily to Aβ [37] and is associated with increased amyloid plaque density in SAD brain tissue [38]. Thus, the ε4 allele may aid in the progressive development of β-amyloid plaques in AD pathology. In contrast to the ε4 allele, the ε2 allele is believed to be protective, since the ε2 allele frequency is lower in AD patients [36]. However, there is stronger evidence supporting the increased risk of AD with the ε4 allele versus the decreased risk with the ε2 allele (note, increased risk does not infer causation like is the case for the genetically-linked genes of FAD) [31]. In recent years, many other genes have been discovered that may increase the risk of developing SAD and each one has been linked to Aβ production, aggregation or clearance; these

genes include BIN1, CD33 (involved in immune system response), CLU, CR1, and PICALM [31]. While these genes may increase an individual's risk of developing SAD, many other environmental factors come into play to impact the increase the incidence of AD.

Curing AD: Single target or multipronged approach?

Current data suggest that a multipronged approach is necessary for finding a cure for AD. As discussed in the previous section, AD has a genetic basis for some individuals, but for many individuals the cause of AD is unknown. Many other factors such as vascular dysfunction, inflammation, and oxidative damage are associated with AD [30, 39, 40] and many researchers are suggesting that potential cures/treatments for AD be targeted from multiple angles to take into account these multiple factors [5, 39-42]. Thus, a potential cure for AD would need to be multi-dimensional and potentially personalized for each individual due to the many factors contributing to the diseased state. Since there is currently no cure for AD, most of the efforts are based on methods for early diagnosis and earlier treatment options to slow the progression of the disease.

Earlier diagnosis of AD using multiple techniques will play a key role in the effectiveness of potential treatment options. Pathological changes in the brain are believed to occur well before the onset of cognitive decline in AD patients [16, 43]. Thus, detecting these pathologies early is a priority. One method for early diagnosis of AD is through the use of biomarkers. A biomarker is a term used to describe any structural, functional, or biochemical change that can be detected for early diagnosis of AD or to determine if a therapeutic trial is working [16]. A biomarker can be used to both detect a healthy aging state and a diseased state [11, 16, 30, 43]. Currently, there are five well-studied biomarkers divided into two categories: those detecting

amyloid accumulation and those detecting neurodegeneration. Two biomarkers are used to detect changes in amyloid accumulation: one measures CSF $A\beta_{42}$ levels and the other uses positron emission tomography (PET) amyloid plaque imaging [16]. Individuals with AD have lower levels of $A\beta_{42}$ in the CSF compared to controls and these lower $A\beta_{42}$ are associated with increased β-amyloid plaque formation [11]. Another technique to measure plaque formation in the brain is via PET amyloid plaque imaging. This specialized PET scan uses Pittsburg Compound-B (PIB) to image β-amyloid plaques in living humans [44]. In addition to measuring β-amyloid plaques, three biomarkers are used to detect neurodegeneration: CSF tau/phosporylated-tau (p-tau), structural magnetic resonance imaging (sMRI), and fludeoxyglucose (FDG) PET. Measuring CSF tau/p-tau levels is an indicator of the amount of neurofibrillary tangles, since p-tau levels in the CSF positively correlate with neurofibrillary tangles in the cerebral cortical areas [45]. sMRI is a valuable technique to identify changes hippocampal size and cortical thinning [43], while FDG PET measures changes in brain metabolism, such as reduced metabolism in the temporal lobe [16, 43]. Overall, biomarkers are useful for detecting structural and functional changes in the brain associated with AD early in the disease process and to help determine the best treatment options.

In addition to using biomarkers for early diagnosis of AD, the use of earlier treatment options with potential disease modifying drugs is essential. Many disease modifying drugs are undergoing/have undergone clinical trials. The majority of these drugs focus on the formation and production of β-amyloid plaques, while some target p-tau production [46, 47]. The drugs targeted at reducing β-amyloid plaque formation do so by reducing the production of Aβ via inhibiting β- and γ-secretase activity, by preventing the aggregation of Aβ via clearance mechanisms, or by selectively degrading Aβ oligomers [10, 46]. Drugs targeted at p-tau

production do so by inhibiting the phosphorylation of tau [46]. However, many of these drugs have not shown significant improvements thus far, but earlier diagnosis and treatment may increase the likelihood of success [46]. Additionally, other targets such as the reducing inflammatory responses, blood brain barrier breakdown, and oxidative stress may provide useful treatments to the diverse population of AD patients [42].

Personalized medicine and AD

As mentioned continuously throughout this paper, many factors contribute to AD. Therefore, personalized medicine is a key component for treating individuals with different forms of AD. One scenario a practitioner could encounter is a patient with a genetically-linked form of AD and another patient with no genetic basis to their AD. In this case, the practitioner should consider different treatment options for each patient specifically.

In the case of the AD patient with genetic-linkage to AD, the first step would be to confirm with genetic testing the exact genetic mutation that the patient may have. As mentioned in "Incidence of AD: Genetics", FAD can be associated with mutations in genes controlling the production of Aβ; notably, increased production of the toxic form of Aβ ($A\beta_{42}$) [31, 33, 34]. One such mutation is the gene encoding the γ-secretase molecule that cleaves Aβ from APP [19, 31, 33]. Thus, if the hypothetical patient had this mutation, potential drugs that modify the cleavage actions of γ-secretase to increase the production of short forms of Aβ versus the long forms could be a potential treatment option. For example, γ-secretase modifying drugs can reduce $A\beta_{42}$ production and increase $A\beta_{38}$ production [48]. These drugs could benefit some individuals by preventing accumulation of further β-amyloid plaques or toxic oligomers [10, 19]. However, this

diseased modifying drug targeting reduced $A\beta_{42}$ production would need to be administered earlier in the disease process to have maximal effects, so early diagnosis would be key.

In the case of an AD patient with no genetic-linkage, the first step would be to determine factors that may have increased that individual's risk of developing AD. Screenings should be done to help narrow down possible factors. For example, many lifestyle/environmental factors may have contributed to an increased incidence of AD, such as a traumatic head injury, vascular disease, and type 2 diabetes [39]. Another aspect to consider is whether the individual has an ApoE allele increasing their risk for AD. Interestingly, some studies suggest that the ApoE ε4 allele may interact with other risk factors such as diabetes or dietary factors to further increase the risk of AD [39, 49]. This situation should be taken into account when monitoring each case, especially since the ApoE ε4 allele can decrease the effectiveness of some drugs used for treatments [46, 48]. However, consider that the hypothetical AD patient has neurovascular disintegrations leading to the blood brain barrier (BBB) breakdown (note that vascular dementia is not the same as AD, but AD patients may have vascular dysfunction associated with the disease) [16, 42]. Treatment options to consider would be those that help stabilize the BBB and enhance clearance of Aβ molecules from the brain [42]. One such therapy is using a multi-target approach such as using a molecule similar to activated protein C (APC); APC inhibits further BBB breakdown and can reduce inflammation in the spinal cord of amyotrophic lateral sclerosis models [42], so using a similar drug for the brain would be ideal in this patient's case. Furthermore, drugs target to enhance Aβ clearance from the brain, such as intravenous immunoglobulins could also be used in this patient to reduce β-amyloid plaque formation [48].

Overall personalized medicine should be used for treating AD, since many factors could cause (such as genetics) or influence the likelihood of developing AD. It is important to consider

these factors when prescribing treatment options or lifestyle changes to individuals, since the root cause of the disease may be different in different cases. Additionally, a multi-target strategy for treating AD is ideal, since many factors contribute to the disease process (oxidative stress, inflammation, vascular damage, etc.).

Conclusion

Age is the major contributor to the development of AD and since people are now living longer lives, more individuals are at risk for developing AD. It is essential to keep in mind that AD is a multi-dimensional disease and that many risk factors promote the incidence of it. New therapies aimed at the different dimensions of this disease and personalizing treatment toward each patient is an ideal goal for the future to ensure that patients get the best treatment to promote a higher quality of life.

1. Association, A.s., *2012 Alzheimer's disease facts and figures.* Alzheimers & Dementia, 2012. **8**(2): p. 131-168.
2. Hardy, J.A. and G.A. Higgins, *Alzheimer's disease - the amyloid cascade hypothesis.* Science, 1992. **256**(5054): p. 184-185.
3. Hardy, J. and D.J. Selkoe, *Medicine - The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics.* Science, 2002. **297**(5580): p. 353-356.
4. Karran, E., M. Mercken, and B. De Strooper, *The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics.* Nature Reviews Drug Discovery, 2011. **10**(9): p. 698-U1600.
5. Marchesi, V.T., *Alzheimer's Disease 2012 The Great Amyloid Gamble.* American Journal of Pathology, 2012. **180**(5): p. 1762-1767.
6. Masters, C.L., et al., *Amyloid plaque core protein in Alzheimer's disease and down syndrome.* Proceedings of the National Academy of Sciences of the United States of America, 1985. **82**(12): p. 4245-4249.
7. Glenner, G.G. and C.W. Wong, *Alzheimer's disease: Initial report of the purification and characterizaton of a novel cerebrovascular amyloid protein.* Biochemical and Biophysical Research Communications, 1984. **120**(3): p. 885-890.

8. Crews, L. and E. Masliah, *Molecular mechanisms of neurodegeneration in Alzheimer's disease.* Human Molecular Genetics, 2010. **19**: p. R12-R20.
9. Kang, J., et al., *The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor.* Nature, 1987. **325**(6106): p. 733-736.
10. Haass, C. and D.J. Selkoe, *Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide.* Nature Reviews Molecular Cell Biology, 2007. **8**(2): p. 101-112.
11. Blennow, K., M.J. de Leon, and H. Zetterberg, *Alzheimer's disease.* Lancet, 2006. **368**(9533): p. 387-403.
12. Tanzi, R.E., R.D. Moir, and S.L. Wagner, *Clearance of Alzheimer's A beta peptide: The many roads to perdition.* Neuron, 2004. **43**(5): p. 605-608.
13. Haass, C., et al., *Amyloid beta-peptide is produced by cultured-cells during normal metabolism.* Nature, 1992. **359**(6393): p. 322-325.
14. Shoji, M., et al., *Production of the Alzheimer amyloid-beta protein by normal proteolytic processing.* Science, 1992. **258**(5079): p. 126-129.
15. Seubert, P., et al., *Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids.* Nature, 1992. **359**(6393): p. 325-327.
16. Jack, C.R., *Alzheimer Disease: New Concepts on Its Neurobiology and the Clinical Role Imaging Will Play.* Radiology, 2012. **263**(2): p. 343-360.
17. Jarrett, J.T., E.P. Berger, and P.T. Lansbury, *The carbozy terminus of the beta-amyloid protein is critical for the seeding of amyloid formation: Implications for the pathogenesis of Alzheimer's disease.* Biochemistry, 1993. **32**(18): p. 4693-4697.
18. Iwatsubo, T., et al., *Visualization of A-beta-42(43) and A-beta-40 in senile plaques with end-specific a-beta monoclonals: Evidence that an intially deposited species is a-beta-42(43).* Neuron, 1994. **13**(1): p. 45-53.
19. Tamagno, E., et al., *The various aggregation states of beta-amyloid 1-42 mediate different effects on oxidative stress, neurodegeneration, and BACE-1 expression.* Free Radical Biology and Medicine, 2006. **41**(2): p. 202-212.
20. Walsh, D.M., et al., *Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo.* Nature, 2002. **416**(6880): p. 535-539.
21. Schmitt, K., et al., *Insights into Mitochondrial Dysfunction: Aging, Amyloid-beta, and Tau-A Deleterious Trio.* Antioxidants & Redox Signaling, 2012. **16**(12): p. 1456-1466.
22. Kern, A. and C. Behl, *The unsolved relationship of brain aging and late-onset Alzheimer disease.* Biochimica Et Biophysica Acta-General Subjects, 2009. **1790**(10): p. 1124-1132.
23. Lin, M.T. and M.F. Beal, *Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.* Nature, 2006. **443**(7113): p. 787-795.
24. Lin, M.T., et al., *High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer's disease brain.* Human Molecular Genetics, 2002. **11**(2): p. 133-145.
25. Corraldebrinski, M., et al., *Mitochondrial DNA deletions in human brain: Regional variability and increase with advanced age.* Nature Genetics, 1992. **2**(4): p. 324-329.
26. Finkel, T. and N.J. Holbrook, *Oxidants, oxidative stress and the biology of ageing.* Nature, 2000. **408**(6809): p. 239-247.
27. Manczak, M., et al., *Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease - Implications for early mitochonrial dysfunction and oxidative damage.* Neuromolecular Medicine, 2004. **5**(2): p. 147-162.

28. Wang, X.L., et al., *Dynamin-like protein 1 reduction underlies mitochondrial morphology and distribution abnormalities in fibroblasts from sporadic Alzheimer's disease patients.* American Journal of Pathology, 2008. **173**(2): p. 470-482.
29. Lustbader, J.W., et al., *ABAD directly links A beta to mitochondrial toxicity in Alzheimer's disease.* Science, 2004. **304**(5669): p. 448-452.
30. Di Carlo, M., D. Giacomazza, and P.L. San Biagio, *Alzheimer's disease: biological aspects, therapeutic perspectives and diagnostic tools.* J Phys Condens Matter, 2012. **24**(24): p. 244102.
31. Bertram, L., R.E. Tanzi, and B.T. David, *Chapter 3 - The Genetics of Alzheimer's Disease*, in *Progress in Molecular Biology and Translational Science*. 2012, Academic Press. p. 79-100.
32. Goate, A., et al., *Segreation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease.* Nature, 1991. **349**(6311): p. 704-706.
33. Citron, M., et al., *Mutation of the beta-amyloid precursor protein in familial Alzheimers-disease increases beta-protein production.* Nature, 1992. **360**(6405): p. 672-674.
34. Bertram, L. and R.E. Tanzi, *Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses.* Nature Reviews Neuroscience, 2008. **9**(10): p. 768-778.
35. Corder, E.H., et al., *Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late-onset families.* Science, 1993. **261**(5123): p. 921-923.
36. Corder, E.H., et al., *Protective effect of apolipoprotein E type 2 allele for late-onset Alzheimer's disease.* Nature Genetics, 1994. **7**(2): p. 180-184.
37. Strittmatter, W.J., et al., *Binding of human apolipoprotein E to synthetic amyloid-beta peptide: Isoform specific effects and implications for late-onset Alzheimer disease.* Proceedings of the National Academy of Sciences of the United States of America, 1993. **90**(17): p. 8098-8102.
38. Schmechel, D.E., et al., *Increased amyloid beta peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer's disease.* Proceedings of the National Academy of Sciences of the United States of America, 1993. **90**(20): p. 9649-9653.
39. Pope, S.K., V.M. Shue, and C. Beck, *Will a healthy lifestyle help prevent Alzheimer's disease?* Annual Review of Public Health, 2003. **24**: p. 111-132.
40. van Norden, A.G.W., et al., *Dementia: Alzheimer pathology and vascular factors: From mutually exclusive to interaction.* Biochimica Et Biophysica Acta-Molecular Basis of Disease, 2012. **1822**(3): p. 340-349.
41. Foster, T.C., *Biological markers of age-related memory deficits - Treatment of senescent physiology.* Cns Drugs, 2006. **20**(2): p. 153-166.
42. Zlokovic, B.V., *Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders.* Nature Reviews Neuroscience, 2011. **12**(12): p. 723-738.
43. Sperling, R.A., et al., *Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers & Dementia, 2011. **7**(3): p. 280-292.
44. Klunk, W.E., et al., *Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B.* Annals of Neurology, 2004. **55**(3): p. 306-319.
45. Buerger, K., et al., *CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease.* Brain, 2006. **129**: p. 3035-3041.

46. Reitz, C., *Alzheimer's disease and the amyloid cascade hypothesis: a critical review.* International Journal of Alzheimer's Disease, 2012. **2012**: p. 1-11.
47. Gotz, J., A. Ittner, and L.M. Ittner, *Tau-targeted treatment strategies in Alzheimer's disease.* British Journal of Pharmacology, 2012. **165**(5): p. 1246-1259.
48. Salomone, S., et al., *New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs.* British Journal of Clinical Pharmacology, 2012. **73**(4): p. 504-517.
49. Peila, R., B.L. Rodriguez, and L.J. Launer, *Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies - The Honolulu-Asia Aging Study.* Diabetes, 2002. **51**(4): p. 1256-1262.

Student 7:

Overall Analysis: Pass

Clear, lucid writing, very nicely stated, e.g.: “Alzheimer’s disease is not considered a normal part of aging, but many age-related changes that occur in the brain may enhance the detrimental effects of AD, such as mitochondrial dysfunction and oxidative stress.” Good use of a figure (i.e., Fig 1) to illustrate your concept. However, there could have been a better use of primary references. Far more than half of the citations are review articles. While digesting literature through reviews can be a useful preliminary step in synthesizing your general ideas about a fied, only citing other people’s opinions through review articles results in a less scholarly document. Be wary of imprecise use of terms such as “genetics”. This refers to a discipline within biology, it is not “a factor” that affects disease incidence. Perhaps a term “genetic makeup” or “genetic predisposition” are more apt terms. Generally well supported points.

Overall evaluation: Strong in writing style and narrative, less strong in the use of primary references.