Project Notes:

Project Title: Investigating the Effects of Amyloid Plaques on Oxidative Stress throughout the Life Cycle of C. elegans

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Note Well: There are NO SHORT-cuts to reading journal articles and taking notes from them. Comprehension is paramount. You will most likely need to read it several times, so set aside enough time in your schedule.

Contents:

Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
How are current blood tests are preformed	*Universal amplification-free molecular diagnostics by billion-fold hierarchical nanofluidic concentration* and articles mentioning ELISA	doi.org/10.1073/pnas.1904513116	9/21/24
What is SNAP-25	*Correlation of Presynaptic and Postsynaptic Proteins with Pathology in Alzheimer's Disease*	doi.org/10.3390/ijms25063130	9/29/24
How to induce Amyloid plaques in C. elegans	*Methodological considerations for heat shock of the nematode Caenorhabditis elegans*	doi.org/10.1016/j.ymeth.2014.04.015	11/02/24

Literature Search Parameters:

These searches were performed between 07/03/2024 and XX/XX/2024.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search

Nature	Neurons, cancer	I found the article *Neuronal substance P drives metastasis through an extracellular RNA-TLR7 axis*
Nature	Zoonotic diseases, viral transmission, pathogenesis	I found the article *Zoonotic Potential of a Pangolin Coronavirus*
Proceedings of the National Academy of Sciences	Alzheimer's, blood biomarkers	I found the article *Large-scale informatic analysis to algorithmically identify blood biomarkers of neurological damage*
Nature	Alzheimer's diagnosis, biomarkers, genetics	I found the article New insights into the genetic etiology of Alzheimer's disease and related dementias
Proceedings of the National Academy of Sciences	Alzheimer's, neurodegeneration, biomarkers	I found the article *Antigen-specific age-related memory CD8 T cells induce and track Alzheimer's-like neurodegeneration*
PNAS	Biomarkers, diagnostics	I found the article *Universal amplification-free molecular diagnostics by billion-fold hierarchical nanofluidic concentration*
Nature Scientific Reports	Alzheimer's, cell types	I found the article *Spatial cell type composition in normal and Alzheimers human brains is revealed using integrated mouse and human single ce*ll RNA sequencing
Google Scholar	SNAP-25, Alzheimer's	I found the article *Dysfunction of the SNARE complex in neurological and psychiatric disorders.*
Google Scholar	SNARE, Alzheimer's	I found the article *Synaptic biomarkers in the cerebrospinal*

		fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia.
Google Patents	Alzheimer's, treatment	I found the patent *Use of apoe4 motif-mediated genes for diagnosis and treatment of alzheimer's disease.*
Google Patents	Alzheimer's, treatment	I found the patent *Compositions and methods for the treatment of Alzheimer's disease and other neurogenerative disease.*
Nature	Alzheimer's, treatment	I found the article *Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies.*
Google Scholar	Oxidative stress, Alzheimer's	I found the article *Is Mitochondria DNA Variation a Biomarker for AD.*
Google Scholar	Heat stress, C. elegans	I found the article Methodological considerations for heat shock of the nematode Caenorhabditis elegans.
Google Scholar	FlyPi	I found the article *The € 100 lab: A 3D-printable open-source platform for fluorescence microscopy, optogenetics, and accurate temperature control during behaviour of zebrafish, Drosophila, and Caenorhabditis elegans.*

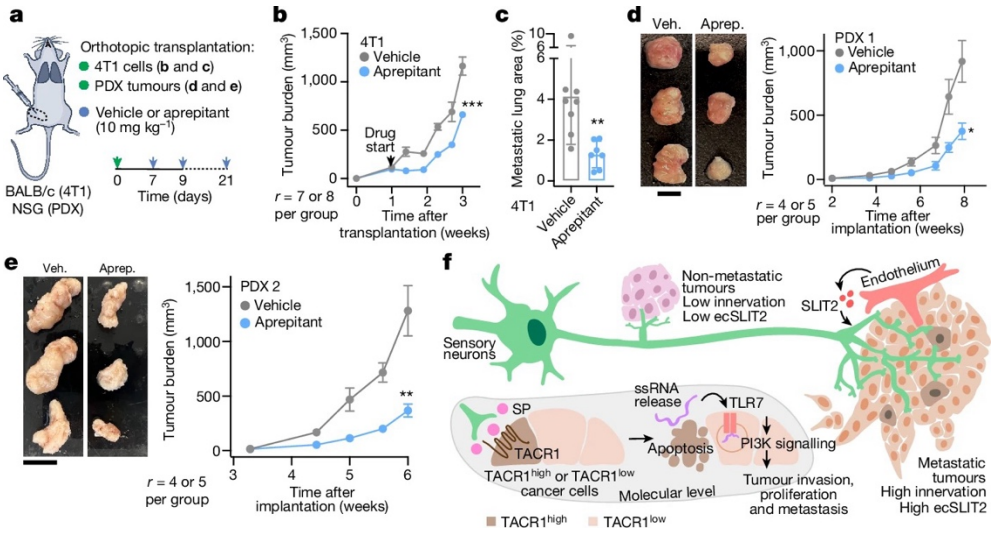
Google Scholar	C. elegans, Alzheimer's	I found the article *Modeling Alzheimer's Disease in Caenorhabditis elegans.*
Google Scholar	Alzheimer's, Amyloid beta, oxidative stress	I found the article *Oxidative Stress and Beta Amyloid in Alzheimer's Disease. Which Comes First: The Chicken or the Egg?*
Google Scholar	Amyloid beta over time	I found the article *Temporal Dynamics of β-Amyloid Accumulation in Aging and Alzheimer Disease*
ScienceDirect	GFP, C. elegans, Fluorescence	I found the article *Fluorescent Protein Methods: Strategies and Applications*
Google Scholar	Oxidative stress and Amyloid beta	I found the article *Oxidative Stress and Beta Amyloid in Alzheimer's Disease. Which Comes First: The Chicken or the Egg?*
Google Scholar	Oxidative stress, aging, Alzheimer's	I found the article *Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin*
Google Scholar	Oxidative stress, age, Alzheimer's	I found the article *Oxidative Stress in Age-Related Neurodegenerative Diseases: An Overview of Recent Tools and Findings*

Tags:

Tag Name	
#methods	#introduction

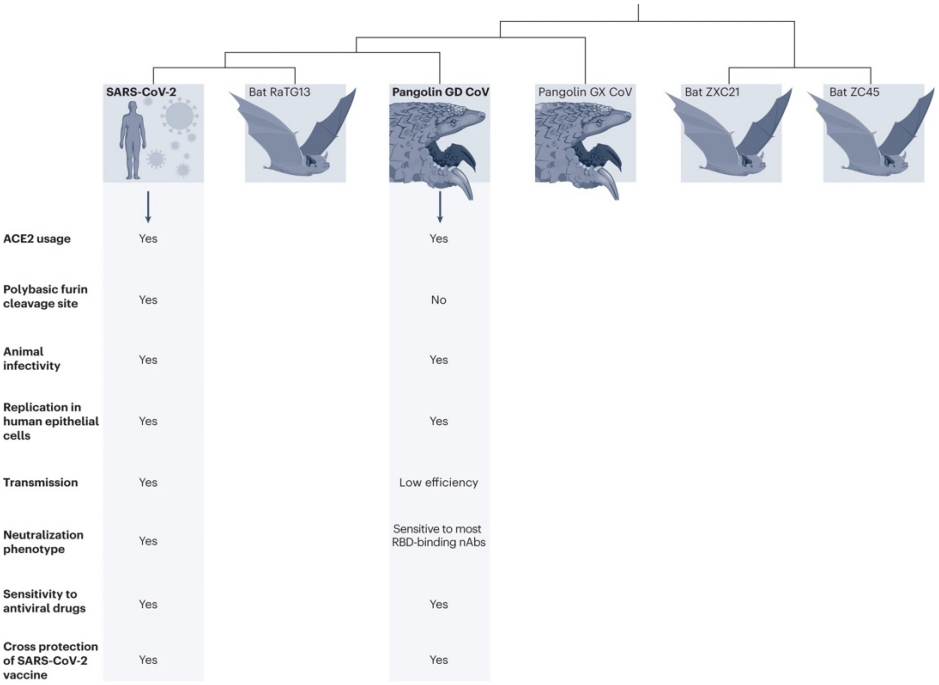
Article #1 Notes: *Neuronal substance P drives metastasis through an extracellular RNA-TLR7 axis*

Source Title	Nature
Source citation (APA Format)	Padmanaban, V., Keller, I., Seltzer, E. S., Ostendorf, B. N., Kerner, Z., & Tavazoie, S. F. (2024). Neuronal substance P drives metastasis through an extracellular RNA–TLR7 axis. *Nature*, *633*(8028), 207–215. doi.org/10.1038/s41586-024-07767-5
Original URL	www.nature.com/articles/s41586-024-07767-5#Abs1
Source type	Journal article
Keywords	Metastasis, Cancer, Breast cancer, Sensory nerves, Aprepitant, Neuronal substance P
#Tags	#introduction
Summary of key points + notes (include methodology)	Tumor innervation has been linked to worse cancer patient outcomes due to a higher likelihood of metastasis. In breast cancer, interactions with sensory nerves appear to be a significant factor in the potential for metastasis of the cancer. The mechanisms of these interactions and the axis that helps tumors grow and spread is starting to be utilized in research for how to stop metastasis. In this axis, the endothelium of these metastatic tumors release SLIT2, an axon-guidance molecule. SLIT2 from the endothelium increases sensory innervation. Then, interactions with the cancerous cells causes spontaneous calcium activity, which triggers the release of neuropeptide substance P (SP). The SP released from the sensory nerves acts on tumoral tachykinin receptors (TACR1). The SP triggers apoptosis and the release of single stranded RNAs (ssRNAs), but only in cells with high levels of TACR1s. The remaining cells, which have low levels of TACR1s, receive the ssRNAs with another type of receptor called a Toll-like receptor 7 (TLR7), causing non-canonically active PIK signaling. PI3K signaling causes tumor invasion, growth, and metastasis. Thankfully, a common anti-nausea medication for chemotherapy patients, named aprepitant, has been shown stop the functional interactions between breast cancer cells and sensory nerves, therefore regulating metastasis
Research Question/Problem/ Need	How does the presence of sensory nerves in breast cancer tumors affect metastasis?

Important Figures	 This figure has data for the effectiveness of Aprepitant for stopping metastasis and has a good visual overview of the whole pathway.
VOCAB: (w/definition)	Neurotrophic factors- a family of proteins that help neurons grow, function, and survive, in mammals, they are controlled by a family of receptors called tropomyosin-related kinases (Trks). Endothelium- a layer of endothelial cells that line the blood and lymphatic vessels, allowing the blood and tissue to interact
Cited references to follow up on	Balood, M., Ahmadi, M., Eichwald, T., Ahmadi, A., Majdoubi, A., Roversi, K., … Talbot, S. (2022). Nociceptor neurons affect cancer immunosurveillance. *Nature*, *611*(7935), 405–412. doi.org/10.1038/s41586-022-05374-w
Follow up Questions	How does the Aprepitant affect this pathway molecularly? Are there other methods to halt this pathway? Could there be a way to stop the innervation of these cells in the first place?

Article #2 Notes: *Zoonotic Potential of a Pangolin Coronavirus*

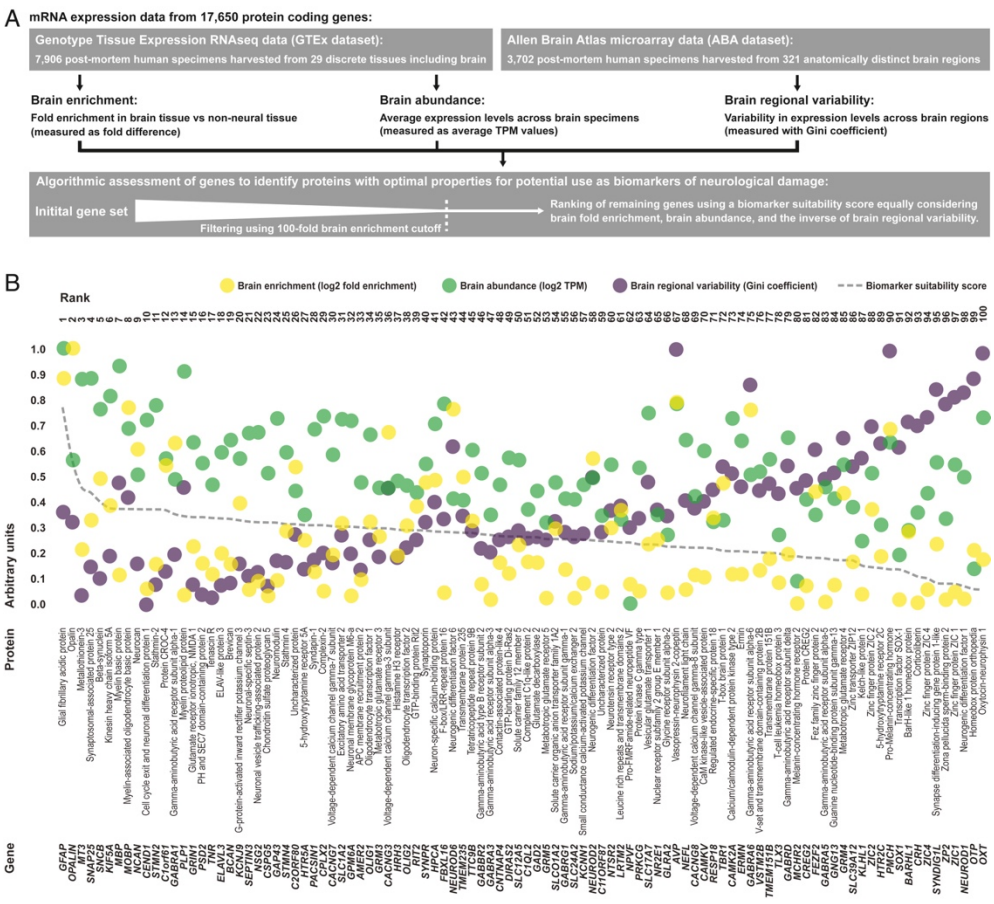
Source Title	Nature Microbiology
Source citation (APA Format)	Shin, W.-J., Kang, S., & Jung, J. U. (2023). Zoonotic potential of a Pangolin coronavirus. *Nature Microbiology*, *8*(10), 1760–1761. https://doi.org/10.1038/s41564-023-01478-9
Original URL	https://www.nature.com/articles/s41564-023-01478-9
Source type	Scientific journal article
Keywords	Viral pathogenesis, viral transmission, zoonoses
#Tags	#introduction
Summary of key points + notes (include methodology)	Pangolin-related Coronavirus, specifically PgCoV GD, are a potential source of the COVID-19 pandemic, although the actual direct intermediate species is unknown. A major difference between SARS-CoV-2 and PgCoV GD is the lack of the polybasic furin cleavage site, found in SARS-CoV-2, in PgCoV GD, but otherwise COVID-19 appears to act like a more easily transmittable PgCoV GD. While SARS-CoV-2 has a higher competitive fitness, PgCoV GD still shows potential for transmission to humans and other naïve animals.
Research Question/Problem/ Need	Could Pangolin Coronavirus spread to humans, and if so, what similarities between Humans and Pangolins would allow it to?

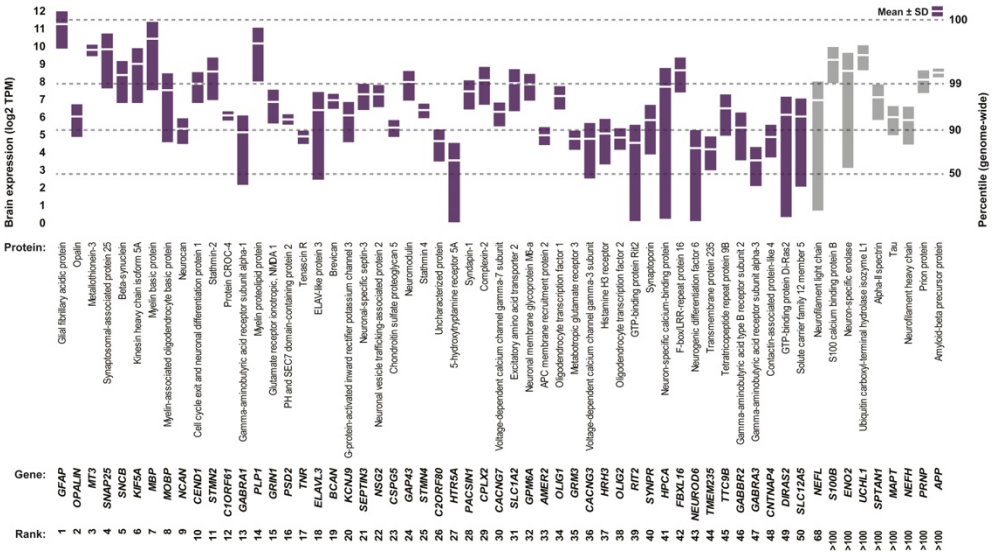
Important Figures	 This figure compares important aspects of transmission, structure, and treatment of SARS-CoV-2 and Pangolin GD CoV.
VOCAB: (w/definition)	Monoclonal antibodies (also known as moAbs or mAbs)- proteins synthesized in a lab that are intended to act like antibodies. Aluminum-containing adjuvant (alum adjuvant)- goes into some vaccines to help increase the effectiveness of the vaccine.
Cited references to follow up on	Hou, Y. J., Chiba, S., Leist, S. R., Meganck, R. M., Martinez, D. R., Schäfer, A., Catanzaro, N. J., Vishwaraj Sontake, West, A., Edwards, C. E., Yount, B., Lee, R. E., Gallant, S. C., Zost, S. J., Powers, J., Adams, L., Kong, E. F., Mattocks, M., Tata, A., & Randell, S. H. (2023). Host range, transmissibility and antigenicity of a pangolin coronavirus. *Nature Microbiology*, *8*(10), 1820–1833. https://doi.org/10.1038/s41564-023-01476-x Peacock, T. P., Goldhill, D. H., Zhou, J., Baillon, L., Frise, R., Swann, O. C., Kugathasan, R., Penn, R., Brown, J. C., Sanchez-David, R. Y., Braga, L., Williamson, M. K., Hassard, J. A., Staller, E., Hanley, B., Osborn, M., Giacca, M., Davidson, A. D., Matthews, D. A., & Barclay, W. S. (2021). The furin cleavage site in the SARS-COV-2 spike protein is required for transmission in ferrets. *Nature Microbiology*, *6*(7), 899–909. https://doi.org/10.1038/s41564-021-00908-w
Follow up Questions	How important is the polybasic furin cleavage site in the transmission of SARS-CoV-2? What other factors influence the viral transmission? Is there a way to predict if a virus could transmit between species without testing it in tissues?

Article #3 Notes: *Large-scale informatic analysis to algorithmically identify blood biomarkers of neurological damage*

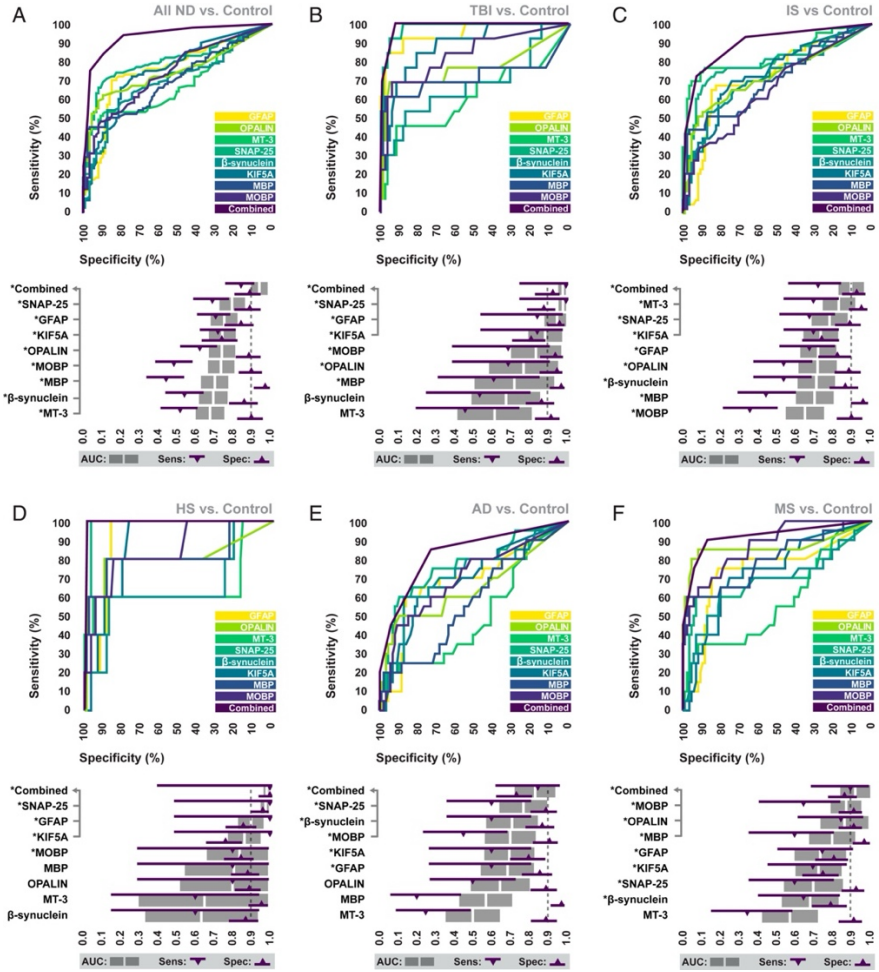
Source Title	Proceedings of the National Academy of Sciences
Source citation (APA Format)	O'Connell, G. C., Alder, M. L., Smothers, C. G., & Chang, J. H. (2020). Large-scale informatic analysis to algorithmically identify blood biomarkers of neurological damage. *Proceedings of the National Academy of Sciences*, *117*(34), 20764–20775. https://doi.org/10.1073/pnas.2007719117
Original URL	https://www.pnas.org/doi/full/10.1073/pnas.2007719117
Source type	Research article
Keywords	Blood biomarkers, Alzheimer's
#Tags	#introduction

Summary of key points + notes (include methodology)	The current methods of diagnosing neurological damage are not very accurate. In order to create more accurate tests of neurological damage, the researchers determined three criteria for accurate biomarkers. The criteria were high enrichment in the brain, high abundance in brain tissue, and expressed equally everywhere in the brain. These criteria were tested through algorithmic analysis, single cell sequencing, and blood tests from people with neurological damage. They found hundreds of potential biomarkers and excluded some previously common biomarkers because they didn't meet the requirements. These new biomarkers can be used to develop more accurate tests for a variety of neurological damages and potentially improve the quality of care for patients with neurological damage.
	
	Notes:
	• Current diagnoses of neurological injuries are not very accurate
	• Disruption of neural cells triggers release of brain-specific proteins out of the cells
	• **Criteria for good biomarkers**
	  ○ Highly enriched in brain/disease relative to other tissues/diseases
	  ○ Highly abundant in brain tissue/expression of disease
	  ○ Ubiquitous expression in all brain regions
	• Previous neurological biomarkers didn't always meet these criteria,

	so they might not be very accurate • Used mRNA expression data to algorithmically evaluate tens of thousands of protein coding genes and give each a biomarker suitability score based on the criteria for good biomarkers • Took top ranked genes of the algorithmic analysis and used single cell sequencing data to see which populations expressed these genes • Filtered data to contain only genes found in both data sets • Took blood from patients with various neurological damage (including AD) and tested for these biomarkers using ELISA • Amyloid beta, Tau, and many other common biomarkers were found to be less specific to the brain and therefore not as good of biomarkers as previously thought • Identified many new biomarkers that had been previously unknown
Research Question/Problem/ Need	Are there specific biomarkers to identify and differentiate types of neurological damage?
Important Figures	 This graph shows the process for determining the optimal biomarkers of neurological damage, and the results of the first two rounds of elimination of biomarkers.



This graph shows the levels of proteins produced from the genes that were assessed, further eliminating biomarkers that were not enriched enough for easy detection.

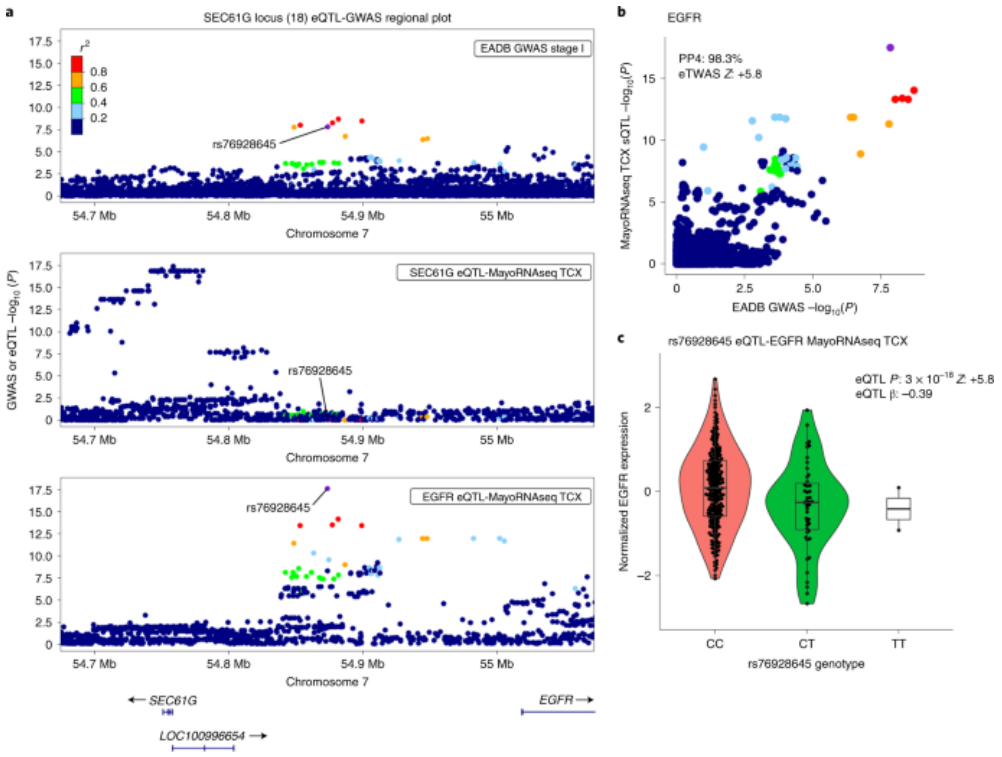


This image shows the sensitivity and specificity of specific genes for

	prediction certain types of neurological damage.
VOCAB: (w/definition)	Astrocytes: a subtype of glial cell that makes up most cells in the Central Nervous system. t-distributed stochastic neighbor embedding: a statistical method for visualizing high dimensional data by putting each data point onto a lower dimensional map. Pathophysiology: the functional changes that come with a particular disease. **Enzyme-linked immunosorbent assay (ELISA)**: a method for detecting and quantifying specific proteins in a complex mixture/sample.
Cited references to follow up on	Ray, S., Britschgi, M., Herbert, C., Takeda-Uchimura, Y., Boxer, A., Blennow, K., Friedman, L. F., Galasko, D. R., Jutel, M., Karydas, A., Kaye, J. A., Leszek, J., Miller, B. L., Minthon, L., Quinn, J. F., Rabinovici, G. D., Robinson, W. H., Sabbagh, M. N., So, Y. T., … Wyss-Coray, T. (2007). Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nature Medicine*, *13*(11), 1359–1362. https://doi.org/10.1038/nm1653
Follow up Questions	Could the same method be used to predict the suitability of specific proteins for diagnosing damages to specific regions of the brain? Are there better biomarkers that could be used instead of Tau and Amyloid beta to better predict and diagnose Alzheimer's disease? What does the lack of specificity of Amyloid beta and Tau mean for the diagnosis of Alzheimer's? What other biomarkers could be used instead of Amyloid beta and Tau? Are Amyloid beta and Tau still useful in helping to detect Alzheimer's because of their specificity to the disease?

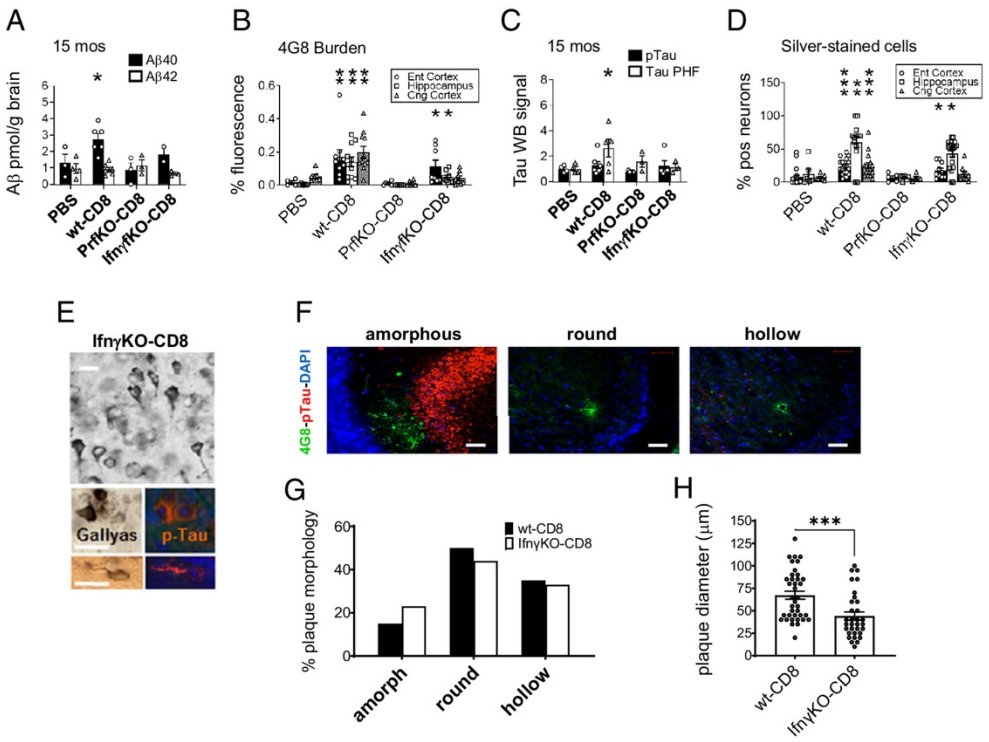
Article # 4 Notes*: New insights into the genetic etiology of Alzheimer's disease and related dementias*

Source Title	Nature genetics
Source citation (APA Format)	Bellenguez, C., Küçükali, F., Jansen, I. E., Kleineidam, L., Moreno-Grau, S., Amin, N., … & Yaqub, A. (2022). New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics*, *54*(4). https://doi.org/10.1038/s41588-022-01024-z
Original URL	https://www.nature.com/articles/s41588-022-01024-z
Source type	Journal article
Keywords	Alzheimers disease, genetics, amyloid beta, tau proteins, pathway analyses, gene prioritization
#Tags	#methods #introduction
Summary of key points + notes (include methodology)	The purpose of this study was to find more genetic markers for Alzheimer's disease and better understand the genetic components of the disease. This study was important because it found more genetic markers for Alzheimer's, which could potentially help improve the current methods of diagnosis and prognosis for this disease. To find these alleles and prove that they were relevant to the development of Alzheimer's, the researchers assessed the frequency of alleles in data from biobanks of people with diagnosed Alzheimer's, proxy Alzheimer's, and without Alzheimer's. Variants not related to APOE, a strong risk factor for Alzheimer's, were assessed to determine if their pathways were relevant to the progression of Alzheimer's. Thirty-one of these genes were still relevant after the pathway analyses and were seen as very important after gene prioritization. This means that the thirty-one of the seventy-five variant alleles that were common among the Alzheimer's and proxy-Alzheimer's patients that proved to be relevant in the pathways of this dementia must be markers of the disease because they are unique and important to Alzheimer's specifically. This answers the question because it proves the existence of new Alzheimer's risk loci and determines which are most important. This could help develop a better test for Alzheimer's and lead us towards preventing and treating Alzheimer's.
Research Question/Problem/ Need	Are there more specific genetic markers for the prediction of Alzheimer's disease?

Important Figures	
VOCAB: (w/definition)	Etiology: cause/causes of a disease/condition
Cited references to follow up on	de Rojas, I., Moreno-Grau, S., Tesi, N., Grenier-Boley, B., Andrade, V., Jansen, I. E., … Ruiz, A. (2021). Common variants in alzheimer's disease and risk stratification by polygenic risk scores. *Nature Communications*, *12*(1). https://doi.org/10.1038/s41467-021-22491-8
Follow up Questions	Are there more genetic components of Alzheimer's? Could these genes be used to easily diagnose Alzheimer's in a cost-effective and non-invasive way? Would a combination of these Alzheimer's alleles be able to predict, with reasonable certainty, the presence of Alzheimer's?

Article #5 Notes: *Antigen-specific age-related memory CD8 T cells induce and track Alzheimer's-like neurodegeneration*

Source Title	Proceedings of the National Academy of Sciences
Source citation (APA Format)	Panwar, A., Rentsendorj, A., Jhun, M., Cohen, R. M., Cordner, R., Gull, N., Pechnick, R. N., Duvall, G., Mardiros, A., Golchian, D., Schubloom, H., Jin, L.-W., Van Dam, D., Vermeiren, Y., De Reu, H., De Deyn, P. P., Raskatov, J. A., Black, K. L., Irvin, D. K., … Wheeler, C. J. (2024). Antigen-specific age-related memory CD8 T cells induce and track alzheimer's-like neurodegeneration. *Proceedings of the National Academy of Sciences*, *121*(29). https://doi.org/10.1073/pnas.2401420121
Original URL	https://www.pnas.org/doi/10.1073/pnas.2401420121
Source type	Research Article
Keywords	Alzheimer's disease, neurodegeneration
#Tags	#introduction #methods
Summary of key points + notes (include methodology)	This study aimed to determine if antigen-specific age-related memory CD8 T cells are upstream causes of Alzheimer's, and therefore good biomarkers. To test this, they used homeostatically induced T cell mice to model the effect of aging CD8 T cells. It was found that these aging T cells induced AD-like neurodegeneration, which Amyloid Beta and Tau could never manage by themselves. Two proteins called Perforin and Interferon gamma play roles in how the T cells cause neurodegeneration. Perforin appeared to have a greater impact on the beginning stages of Alzheimer's, while interferon gamma appeared to affect the later stages of AD. In the absence of Perforin, Alzheimer's-like neurodegeneration did not develop. Age-related CD8 T cells were found to be associated with the current most specific established AD biomarkers. These cells may be a useful, upstream factor of Amyloid and Tau neurodegeneration. Notes: • Amyloid beta and tau are not best choices of biomarker for AD • Mouse model translated well to humans • Findings currently supported in humans, but require more testing • Perforin is essential to the function of CD8 T cells in inducing Alzheimer's • Interferon Gamma would be a good biomarker for the progression of neurodegeneration

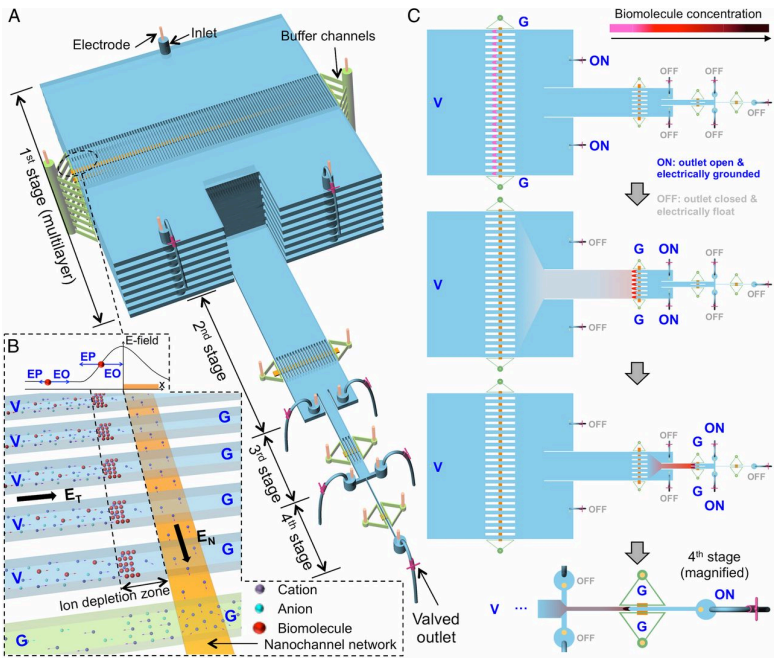
	• Antigen-specific age-related memory CD8 T cells cause amyloid plaques and neurofibrillary tangles
Research Question/Problem/ Need	Do antigen-specific age-related memory CD8 T cells influence the pathogenesis and progression of Alzheimer's?
Important Figures	 This chart shows the Amyloid and Tau pathology of the control, wild type, IFNG knockout, and Perforin knockout, showing that CD8 T cells cause AD-like neurodegeneration that is affected by both the levels of Perforin and IFNG
VOCAB: (w/definition)	Epitope: the spot where the antibody attaches itself to the antigen Homeostatically: relating to the process of homeostasis
Cited references to follow up on	Musiek, E. S., & Bennett, D. A. (2021). Aducanumab and the "post-amyloid" ERA of Alzheimer research? *Neuron*, *109*(19), 3045–3047. https://doi.org/10.1016/j.neuron.2021.09.007 Gate, D., Saligrama, N., Leventhal, O., Yang, A. C., Unger, M. S., Middeldorp, J., Chen, K., Lehallier, B., Channappa, D., De Los Santos, M. B., McBride, A., Pluvinage, J., Elahi, F., Tam, G. K.-Y., Kim, Y., Greicius, M., Wagner, A. D., Aigner, L., Galasko, D. R., … Wyss-Coray, T. (2020). Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. *Nature*, *577*(7790), 399–404. https://doi.org/10.1038/s41586-019-1895-7

Follow up Questions	Is there a substance that could block the effect of Perforins? What are the characteristics of antigen-specific age-related memory CD8 T cells? And how do these specific characteristics affect the pathogenesis and progression of Alzheimer’s?

Article #6 Notes: *Universal amplification-free molecular diagnostics by billion-fold hierarchical nanofluidic concentration*

Source Title	PNAS
Source citation (APA Format)	Ouyang, W., & Han, J. (2019). Universal amplification-free molecular diagnostics by billion-fold hierarchical nanofluidic concentration. *Proceedings of the National Academy of Sciences*, *116*(33), 16240–16249. https://doi.org/10.1073/pnas.1904513116
Original URL	https://www.pnas.org/doi/full/10.1073/pnas.1904513116
Source type	Research article
Keywords	Biomarkers, diagnostics
#Tags	#introduction #methods

Summary of key points + notes (include methodology)	There was a lack of methods to measure biomarkers with lower abundances, and many techniques for measuring biomarkers were time consuming and complicated. This study was to find more simple, accurate method of measuring biomarkers with lower abundances in the blood. A hierarchical nanofluidic molecular enrichment system (HOLMES) was created to detect these low-abundance biomolecules reliably, efficiently, and accurately. They used vertically stacked parallel microchannels with perpendicular nanochannels to get the biomolecules trapped, so that they would become concentrated. Selective enrichment allows this technique to eliminate the interfering biomolecules. This technique could help detect biomarkers and widen the scope of biomarkers that can be used.
	
	Notes:
	• hierarchical nanofluidic molecular enrichment system (HOLMES)
	  ○ massively paralleled and hierarchically cascaded nanofluidic concentrators
	  ○ billion-fold enrichment (nucleic acids & proteins) in 30 min
	  ○ detects attomolar nucleic acids in 35 min
	• many biomarkers have subfemtomolar concentrations, current methods couldn't detect this low of a concentration
	• detects below concentrations detectible by ELISA faster than ELISA
	• lots of restrictions on previous techniques that made them impractical for

	clinical diagnosis • universally functional in clinical settings • HOLMES is simple and cost effective • Vertically stacked massively parallel microchannels, the number of which gets less throughout • In each stage, perpendicular nanochannels bridge them and buffer side channels at the bottom • Nanochannels made of cation-selective membrane enriches positively charged biomolecules • Eventually, biomolecules get trapped, and concentrations of the biomolecules grow, process continues through each stage • Reconcentration steps lower detection limits • Tested using ssDNA and BSA, shows success on both nucleic acids and proteins • More accurate than qPCR due to lack of amplification • Selective enrichment of targets and depletion of interfering biomolecules • fluorescently labeled complementary peptide nucleic acid (PNA) probe and neutral DNA • separates background proteins and DNA • used a high-mobility capture antibody (Ab) with fluorescently labeled ssDNAs • generic and versatile tool for diagnostic applications
Research Question/Problem/ Need	Is there a rapid, reliant, and universal way to detect low-abundance biomolecules without amplification?
Important Figures	 This diagram shows how the HOLMES functions.

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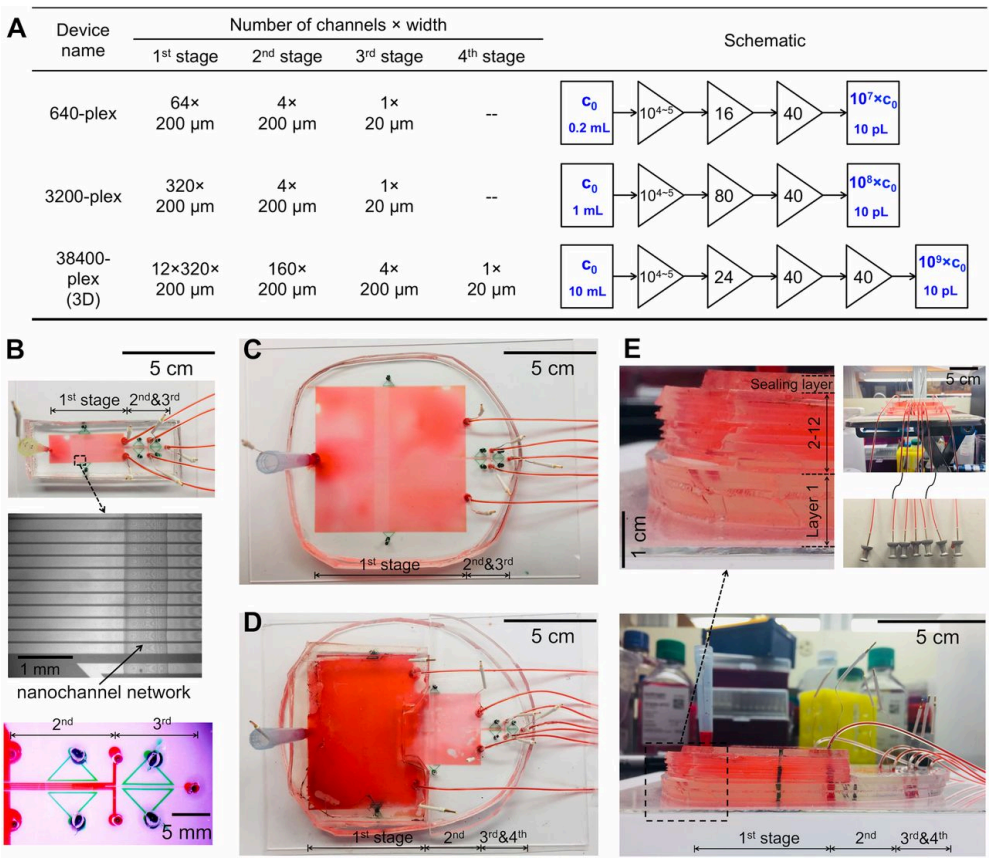

This diagram shows the different sizes of device and pictures of the actual HOLMES.
</td>
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<tr>
<td>VOCAB: (w/definition)</td>
<td>Attomolar: concentration of 10^{-18} mole per liter
Tangential: along a tangent
fluid drag force: the resistance force of a fluid</td>
</tr>
<tr>
<td>Cited references to follow up on</td>
<td>Yang, S., & Rothman, R. E. (2004). PCR-based diagnostics for infectious diseases: Uses, limitations, and future applications in acute-care settings. The Lancet Infectious Diseases, 4(6), 337–348. https://doi.org/10.1016/s1473-3099(04)01044-8</td>
</tr>
<tr>
<td>Follow up Questions</td>
<td>What are the concentrations of biomarkers for Alzheimer's? Are they detectable through this test? Could this test be made faster or more specific?</td>
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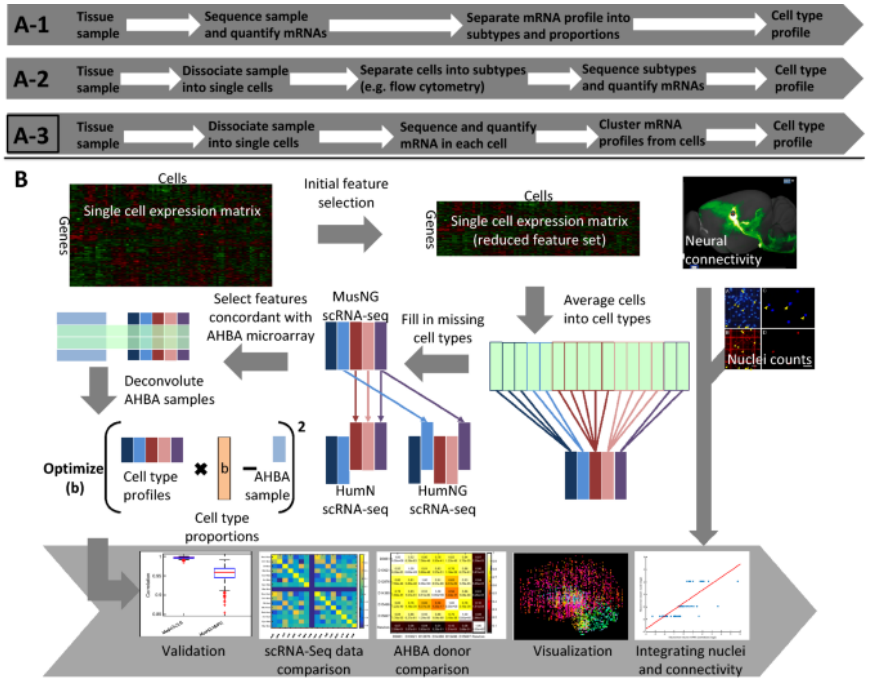
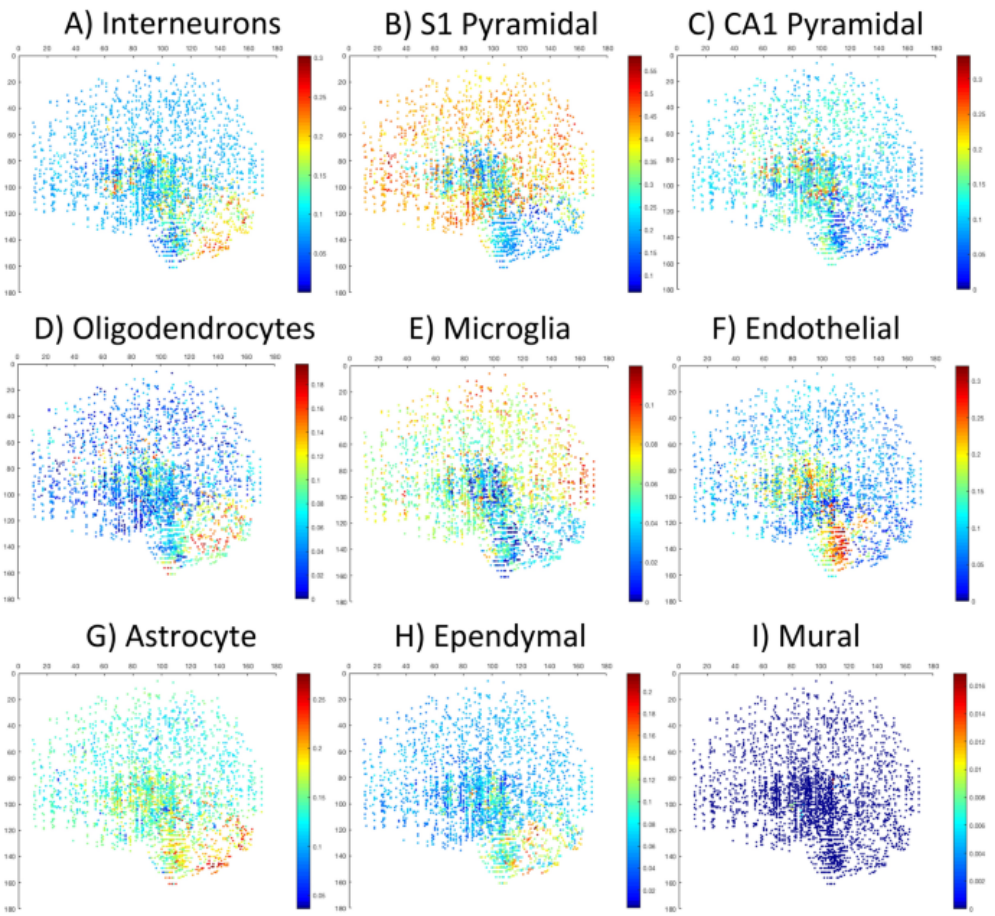
Article #7 Notes: *Spatial cell type composition in normal and Alzheimers human brains is revealed using integrated mouse and human single cell RNA sequencing*

Source Title	Nature scientific reports
Source citation (APA Format)	Johnson, T. S., Xiang, S., Helm, B. R., Abrams, Z. B., Neidecker, P., Machiraju, R., Zhang, Y., Huang, K., & Zhang, J. (2020). Spatial Cell type composition in normal and Alzheimers human brains is revealed using integrated mouse and human single cell RNA sequencing. *Nature Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-74917-w .
Original URL	https://www.nature.com/articles/s41598-020-74917-w
Source type	Journal article
Keywords	Alzheimer's, cells
#Tags	#introduction #methods
Summary of key points + notes (include methodology)	Due to a lack of human brains, these researchers wanted to find a way to make accurate models of the cell types in different regions of the brain using a model organism. They took samples from mice brains and used single cell RNA sequencing (scRNA-seq) to separate cell types in each region of the brain based on cell type-specific gene expression. There were significant differences between mice and human brains, but overall, the mice samples were very accurate to previously known information on the cell types of each brain region. This accuracy was even translated to predicting Alzheimer's with differences in cell type ratios of Interneurons, S1 Pyramidal cells, CA1 Pyramidal cells, and Microglial cells. Notes: • lack of human brains for research • structural, anatomic, and cellular differences in brain cells affects brain development, health, and degeneration • spatially explicit functionality • used single cell RNA sequencing (scRNA-seq) to classify and characterize brain cell type-specific gene expression • using mice, decent differences between mouse and human brain, but cell function and anatomical structure are conserved • integrative transcriptomic feature selection

	• 9 major neuronal cell types/subtypes: interneuron, S1 Pyramidal, CA1 pyramidal, oligodendrocytes, microglia, astrocytes, endothelial, ependymal, and mural • The mouse model translated well to humans in both normal and Alzheimer's brain cell type measurements • Spatial location using nuclei doesn't work, but neural connectivity could be useful in determining cell type distribution due to long axons of some neuronal cells. • Used cell size correlation to increase accuracy • General cell type RNA expression profiles are consistent across mouse and human samples • AD causes microglial cells to proliferate and Interneurons, S1 Pyramidal cells, and CA1 Pyramidal cells to die • Used the Braak stage scores (BBS), Amyloid plaque scale (Plaque means), and Clinical dementia rating scale (CDR) to measure the clinical traits of Alzheimer's for comparison to find the correlations • Interneurons, S1 Pyramidal cells, and CA1 Pyramidal cells are negatively correlated with AD clinical traits • Microglia are positively correlated with AD clinical traits
Research Question/Problem/ Need	How are the various types of neurons distributed throughout the brain?
Important Figures	 This diagram helps visually explain their methods.



These graphs show the proportions of each cell type throughout the sagittal view of the brain from the MusNG samples.

VOCAB: (w/definition)

Interneurons: types of neurons that are typically found in specific integrative areas of the CNS, and do not extend between areas of the brain

Pyramidal neurons: neurons that have a pyramid-shaped cell body

S1 Pyramidal neurons: pyramidal neurons in the primary somatosensory cortex (S1) region of the parietal lobe that process the sensory input to this area

CA1 pyramidal neurons: pyramidal neurons in the Cornu Ammonis region of the hippocampus that help process sensory and motor input to aid in the consolidation of memories

Glial cells: cells that keep nerve cells in place and help them function, such as oligodendrocytes, astrocytes, microglia, and ependymal cells

Oligodendrocytes: cells that produce myelin to protect the axons of neurons

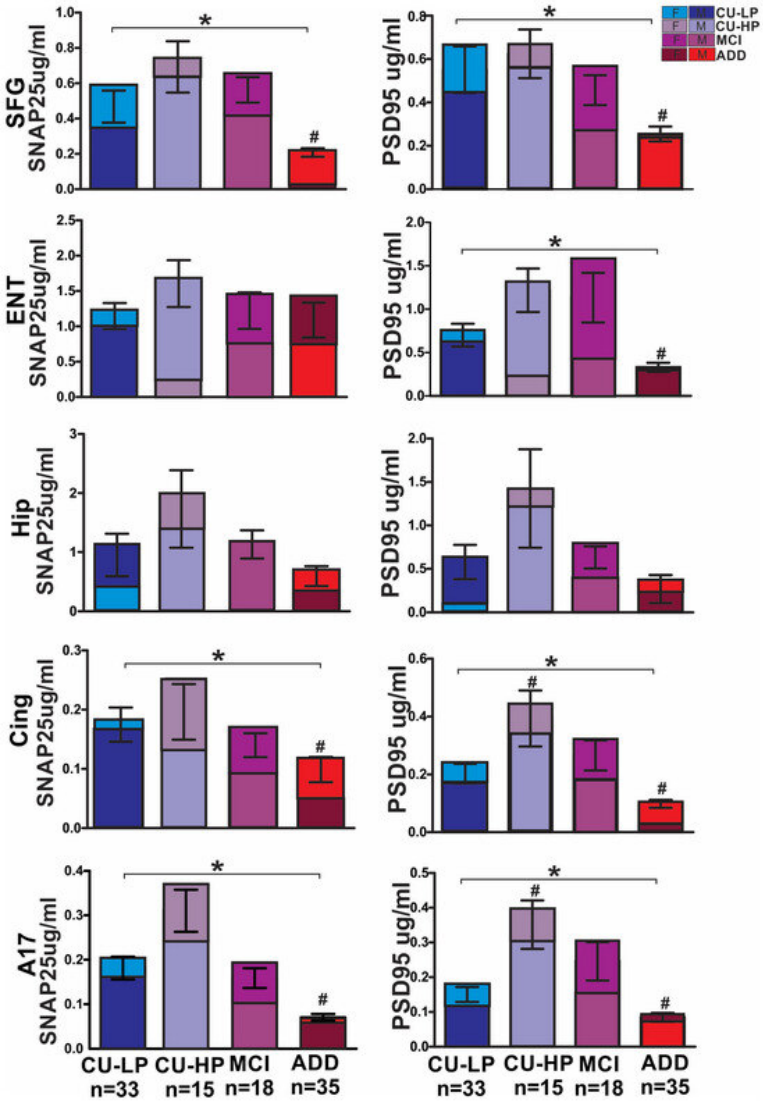
Microglia: They are the most common immune cells of the CNS. They respond to pathogens or injury by changing and going to destroy the pathogen or remove the damaged cells.

Astrocytes: common cells in the CNS that preform metabolic, structural, homeostatic, and neuroprotective functions, such as regulating the Blood-brain

	barrier, promoting synapse formation, and clearing excess neurotransmitters Ependymal neurons: Mural cells: types of mural cells called pericytes work with endothelial cells and astrocytes to make up the Blood-brain barrier Deconvolution: the process of mathematically separating data into the components that make it up to clarify it Pearson correlation coefficient (PCC): a common way to measure a correlation between two variables that gives a number between -1 and 1. This measures the strength and direction of the correlation of these variables. If there is not a correlation, the value is 0.
Cited references to follow up on	Rajendran, L., & Paolicelli, R. C. (2018). Microglia-Mediated Synapse Loss in Alzheimer's Disease. *The Journal of Neuroscience*, *38*(12), 2911–2919. https://doi.org/10.1523/jneurosci.1136-17.2017
Follow up Questions	Can cellular heterogeneity contribute to testing for neurological injury to a specific area? How do the differences between mice and human brains affect the progression of diseases? What other model organisms be used to model Alzheimer's effect on brain cells? Do these mice have the same biomarkers of Alzheimer's as in humans? Are there specific biomarkers for the loss of Interneurons, S1 Pyramidal cells, and CA1 Pyramidal cells or the gain of Microglia?

Article #8 Notes: *Correlation of Presynaptic and Postsynaptic Proteins with Pathology in Alzheimer's Disease*

Source Title	International Journal of Molecular Sciences
Source citation (APA Format)	Serrano, G. E., Walker, J., Nelson, C., Glass, M., Arce, R., Intorcia, A., Cline, M. P., Nabaty, N., Acuña, A., Huppert Steed, A., Sue, L. I., Belden, C., Choudhury, P., Reiman, E., Atri, A., & Beach, T. G. (2024). Correlation of presynaptic and postsynaptic proteins with pathology in alzheimer's disease. *International Journal of Molecular Sciences*, *25*(6), 3130. https://doi.org/10.3390/ijms25063130
Original URL	https://www.mdpi.com/1422-0067/25/6/3130
Source type	Research Article
Keywords	Alzheimer's, SNAP-25
#Tags	#introduction
Summary of key points + notes (include methodology)	Synapse dysfunction plays a major role in many neurodegenerative diseases. The proteins synaptosome-associated protein 25 (SNAP-25) and postsynaptic density protein 95 (PSD95) are vital the functioning of synapses, so this study aimed to study the levels of these proteins in patients with Alzheimer's, mild cognitive impairments, and no cognitive impairments to test the correlations of these proteins to AD. They found that the expressions of these proteins was lower in patients with Alzheimer's, meaning that there was a statistically significant correlation between these proteins and AD. Notes: • Studies have estimated that the major brain weight loss in AD is due to synapse and axonal loss, not neuronal loss • Studied presynaptic protein synaptosome-associated protein 25 (SNAP-25) & postsynaptic protein postsynaptic density protein 95 (PSD95) • Used immunochemical assays to estimate expressions of SNAP-25 and PSD95 relative to each other • SNAP-25 and PSD95 expressions were significantly lowered in AD patients • Greater SNAP-25 and PSD95 reductions in the cingulate, frontal and visual cortices of females compared to the same regions in males • Both proteins showed that they affect the cognition and progression

	of patients with Alzheimer's • Can't differentiate synaptic loss vs synaptic protein expression loss • Synaptic loss most likely starts long before clinical symptoms, and may even be a normal aging process
Research Question/Problem/ Need	Are the expressions of presynaptic and postsynaptic proteins, specifically SNAP-25 and PSD95 correlated with the pathology of Alzheimer's disease?
Important Figures	 These graphs show the expression levels of SNAP-25 and PSD95 across the different testing groups, including mildly cognitively impaired, AD patients, and two groups of cognitively unimpaired patients (separated by high and low levels of AD pathology).

SNAP25 protein per brain region

Predictors	Odds Ratio	95% CI	*p<0.05
Equation SFG			* 0.000
Sex	1.833	0.747, 4.498	0.186
Age	0.935	0.877, 0.996	*0.038
MMSE	0.895	0.826, 0.970	*0.007
Equation SFG			*0.001
Sex	2.041	0.864, 4.820	0.104
Age	0.955	0.906, 1.006	0.083
Tangles	1.165	1.054, 1.287	*0.003
Equation SFG			*0.002
Sex	1.995	0.856, 4.653	0.110
Age	0.943	0.895, 0.994	*0.029
Plaques	1.100	1.025, 1.181	*0.008
Equation ENT			*0.046
Sex	2.033	0.882, 4.688	0.096
Age	0.985	0.933, 1.040	0.591
MMSE	0.949	0.894, 1.007	0.081
Equation CING			*0.009
Sex	2.007	0.854, 4.721	0.110
Age	1.002	0.947, 1.059	0.956
MMSE	0.917	0.857, 0.982	*0.013
Equation CING			*0.020
Sex	2.139	0.934, 4.900	0.072
Age	0.992	0.945, 1.041	0.743
Tangles	1.124	1.024, 1.235	*0.014
Equation A17			*0.000
Sex	1.469	0.587, 3.673	0.411
Age	0.926	0.866, 0.989	*0.022
MMSE	0.871	0.795, 0.954	*0.003
Equation A17			*0.000
Sex	1.781	0.732, 4.332	0.203
Age	0.947	0.896, 1.000	0.052
Tangles	1.225	1.099, 1.366	*0.000
Equation A17			*0.000
Sex	1.749	0.727, 4.209	0.212
Age	0.931	0.880, 0.985	*0.013
Plaques	1.144	1.062, 1.233	*0.000

PSD95 protein per brain region

Predictors	Odds Ratio	95% CI	*p<0.05
Equation SFG			* 0.005
Sex	2.018	0.850, 4.790	0.111
Age	0.990	0.936, 1.048	0.740
MMSE	0.913	0.850, 0.981	*0.013
Equation SFG			*0.012
Sex	2.183	0.943, 5.051	0.068
Age	0.998	0.950, 1.048	0.927
Tangles	1.139	1.035, 1.254	*0.008
Equation SFG			*0.020
Sex	2.165	0.940, 4.986	0.070
Age	0.986	0.940, 1.035	0.581
Plaques	1.093	1.020, 1.170	*0.011
Equation ENT			*0.001
Sex	2.674	1.115, 6.410	*0.028
Age	1.003	0.947, 1.061	0.922
MMSE	0.906	0.847, 0.970	*0.005
Equation ENT			*0.016
Sex	2.292	1.279, 6.708	*0.011
Age	0.993	0.946, 1.042	0.766
Tangles	1.093	0.997, 1.198	0.058
Equation ENT			*0.028
Sex	2.887	1.269, 6.570	*0.011
Age	0.985	0.939, 1.033	0.526
Plaques	1.055	0.986, 1.129	0.118
Equation HIP			*0.000
Sex	3.962	1.532, 10.251	*0.005
Age	0.951	0.891, 1.014	0.126
MMSE	0.873	0.794, 0.90	*0.005
Equation HIP			*0.000
Sex	4.084	1.652, 10.098	*0.002
Age	0.970	0.920, 1.022	0.247
Tangles	1.168	1.051, 1.298	*0.004
Equation HIP			*0.002
Sex	3.663	1.543, 8.697	*0.003
Age	0.960	0.913, 1.010	0.118
Plaques	1.067	0.994, 1.146	*0.071
Equation CING			*0.053
Sex	1.160	0.503, 2.678	0.727
Age	0.996	0.943, 1.052	0.892
MMSE	0.927	0.871, 0.988	*0.019
Equation A17			* 0.002
Sex	2.941	1.236, 6.999	*0.015
Age	0.993	0.939, 1.051	0.812
MMSE	0.923	0.865, 0.985	*0.016
Equation A17			*0.005
Sex	3.033	1.306, 7.045	*0.010
Age	0.998	0.950, 1.048	0.929
Tangles	1.124	1.023, 1.235	*0.015
Equation A17			*0.006
Sex	3.042	1.310, 7.064	*0.010
Age	0.987	0.940, 1.036	0.592
Plaques	1.089	1.016, 1.167	*0.016

This chart shows the expressions of both SNAP-25 and PSD95 in the different parts of the brain and their correlations.

VOCAB: (w/definition)

Postsynaptic density protein 95 (PSD95): a postsynaptic protein that has a large role in synaptic plasticity and strength
Stereological: the sampling and counting of a 2D material to obtain an estimate of a quantitative parameter of the sample in 3 dimensions
postmortem interval (PMI): the amount of time that has passed since the death of a person
Thal Phase: a method for characterizing the pattern of amyloid plaque distributions

Cited references to follow up on

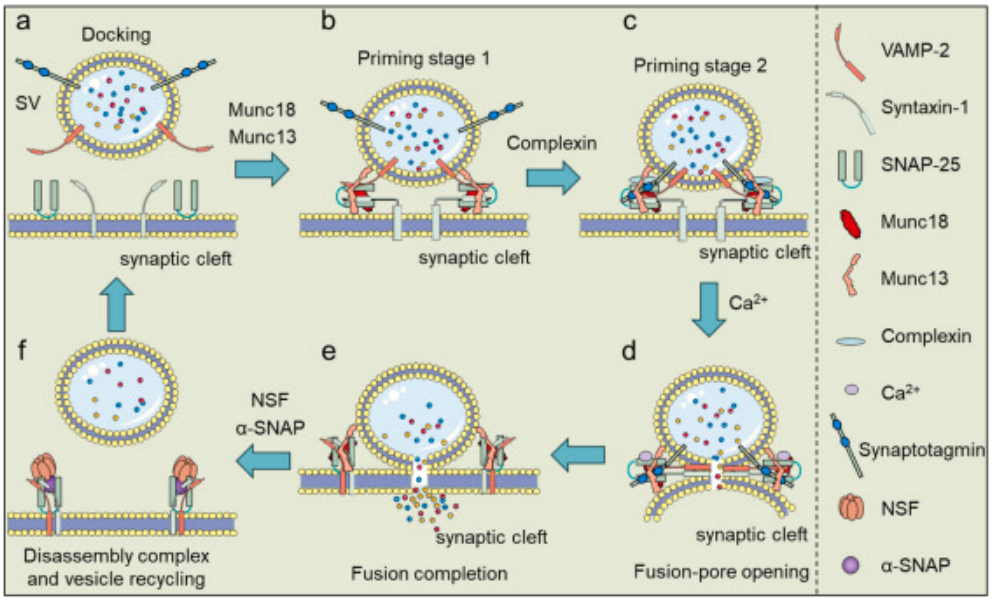
Spires-Jones, Tara L., & Hyman, Bradley T. (2014). The Intersection of Amyloid Beta and Tau at Synapses in Alzheimer's Disease. *Neuron*, *82*(4), 756–771. https://doi.org/10.1016/j.neuron.2014.05.004

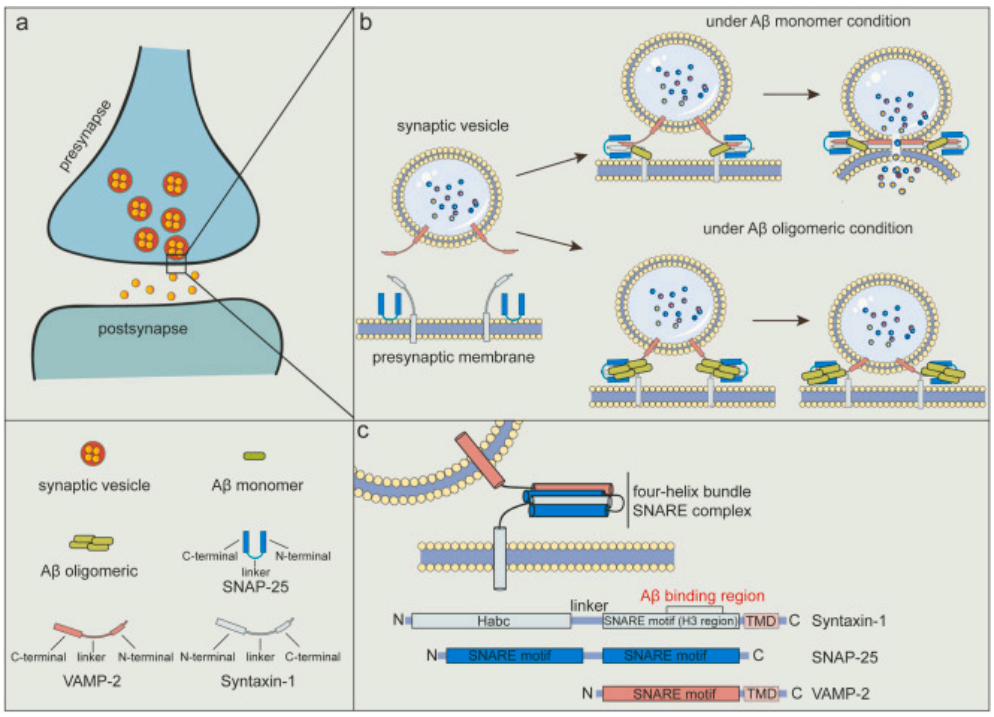
Kivisäkk, P., Carlyle, B. C., Sweeney, T., Quinn, J. P., Ramirez, C. E., Trombetta, B. A., Mendes, M., Brock, M., Rubel, C., Czerkowicz, J., Graham, D., & Arnold, S. E. (2022). Increased levels of the synaptic proteins PSD-95, SNAP-25, and neurogranin in the cerebrospinal fluid of patients with Alzheimer's

	disease. *Alzheimer's Research & Therapy*, *14*(1). https://doi.org/10.1186/s13195-022-01002-x
Follow up Questions	What stops the AD pathology from causing Alzheimer's in some people? What differences in the male and female brains cause the differences in synaptic protein levels as they age? Could these proteins be used as biomarkers for the disease?

Article #9 Notes: *Dysfunction of the SNARE complex in neurological and psychiatric disorders*

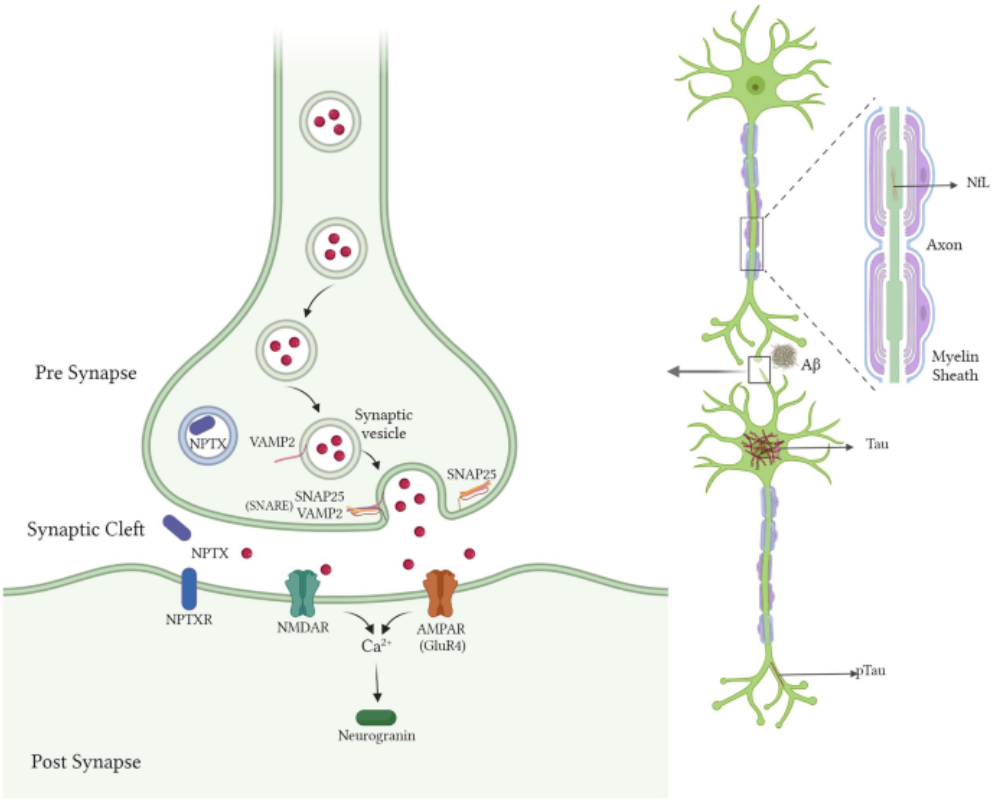
Source Title	Pharmacological Research
Source citation (APA Format)	Chen, F., Chen, H., Chen, Y., Wei, W., Sun, Y., Zhang, L., Cui, L., & Wang, Y. (2021). Dysfunction of the SNARE complex in neurological and psychiatric disorders. *Pharmacological Research*, *165*, 105469. https://doi.org/10.1016/j.phrs.2021.105469
Original URL	https://www.sciencedirect.com/science/article/pii/S1043661821000530
Source type	Review Article
Keywords	SNARE, neurodegenerative diseases, neuropsychiatric diseases
#Tags	#introduction
Summary of key points + notes (include methodology)	Synapses are vital to the communication between neurons in the nervous system. When the SNARE complex, which is vital to the function of synaptic vesicle exocytosis, dysfunctions, it can contribute to many neurodegenerative diseases. SNARE has three main proteins, which are Synaptobrevin2 (AKA vesicle-associated membrane protein-2 (VAMP-2)), Syntaxin-1, and synaptosome-associated protein 25 (SNAP-25). In Alzheimer's, altered expression levels of SNARE proteins and outside factors like Amyloid beta contribute to the decreased functionality of the synapses. Alleles that are risk factors for Alzheimer's, such as ApoE4 often have an effect on the function of the SNARE complex. SNARE dysfunction is a common thread between lots of neurodegenerative diseases, but treatment and detection could be tricky due to the varying expressions across patients. Notes: • The SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex is a presynaptic method of mediating the membrane fusion of exocytotic synaptic vesicles • Presynaptic dysfunction may be an early sign of neurodegeneration • Specific proteins in the SNARE complex are often found to have altered expressions • Major three SNARE proteins are Synaptobrevin2 (AKA vesicle-associated membrane protein-2 (VAMP-2)), Syntaxin-1, and synaptosome-associated protein 25 (SNAP-25) • Syntaxin-1 and SNAP-25 are t-SNAREs found on the membrane, while VAMP-2 is a v-SNARE on the vesicle • SNARE alone can mediate exocytosis of the synaptic vesicles, btu

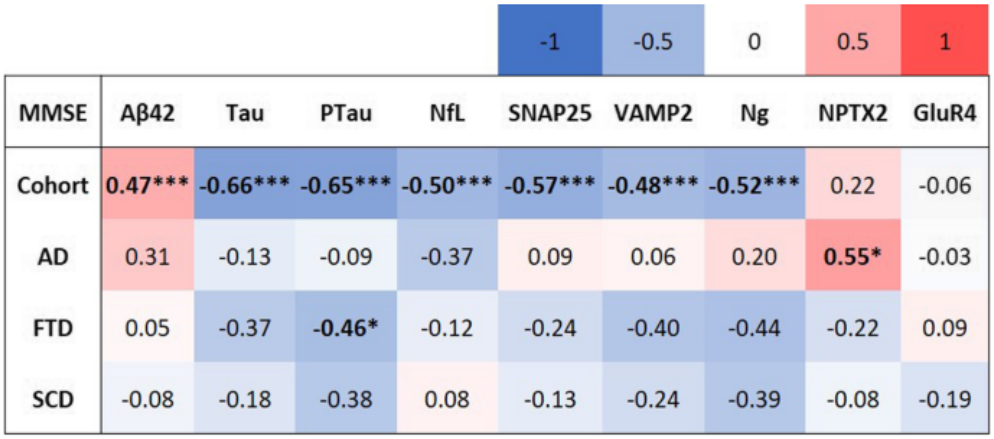
	other proteins, such as Munc18-1 and Munc13-1 are though to help assemble SNARE • Amyloid beta oligomers inhibit SNARE function by binding to the Syntaxin 1 motif, inhibiting fusion step • Amyloid beta monomers don't show the same effect • Amyloid beta oligomers could use steric hinderance to inhibit the "zippering" of the SNARE proteins into the cis-SNARE complex • Amyloid beta has varied effects on synaptic function, based on concentration, exposure time, and what type of Amyloid beta • Abnormalities in SNARE are thought to be related to AD pathology and could be a good biomarker, especially SNAP-25 • ApoE4 is a major genetic risk factor for AD, ApoE3 is neutral and ApoE2 protects against AD • ApoE genes alleles differentially affect the expressions of VAMP-2 and syntaxin-1 proteins • Doesn't account for all factors because they are not all known, and doesn't account for temporal and spatial factors • SNARE dysfunction is a common thread between lots of neurodegenerative diseases • Treatment and detection could be tricky due to the varying expressions across patients
Research Question/Problem/ Need	What is the role of the SNARE complex in the pathologies of neurodegenerative, neuropsychiatric, and neurodevelopmental diseases?
Important Figures	 This diagram shows the normal function of the SNARE complex and its associated proteins in synaptic vesicle exocytosis.

	 This diagram shows the effects of Amyloid beta, in both oligomer and monomer forms on the function of the SNARE complex.
VOCAB: (w/definition)	Steric hindrance: the slowing of a reaction due to the structure of a molecule Case-control association studies: a study that detects a potential association between a genetic marker and a trait, such as a disease
Cited references to follow up on	Clarke, M. T. M., Brinkmalm, A., Foiani, M. S., Woollacott, I. O. C., Heller, C., Heslegrave, A., Keshavan, A., Fox, N. C., Schott, J. M., Warren, J. D., Blennow, K., Zetterberg, H., & Rohrer, J. D. (2019). CSF synaptic protein concentrations are raised in those with atypical Alzheimer's disease but not frontotemporal dementia. *Alzheimer's Research & Therapy*, *11*(1). https://doi.org/10.1186/s13195-019-0564-2 Anindit Chhibber, & Zhao, L. (2017). ERβ and ApoE isoforms interact to regulate BDNF–5-HT2A signaling and synaptic function in the female brain. *Alzheimer's Research & Therapy*, *9*(1). https://doi.org/10.1186/s13195-017-0305-3
Follow up Questions	Could changes in cholesterol levels cause neurodegeneration? How do Amyloid Beta oligomers and monomers have different effects on the functioning of the SNARE complex? How do other components of AD contribute to the functions and effects of SNARE proteins? Could protective mutations, such as ApoE2, counteract the effects of other genetic factors that reduce the function of the SNARE complex?

Article #10 Notes: *Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia*

Source Title	Alzheimer's Research & Therapy
Source citation (APA Format)	Das, S., Goossens, J., Jacobs, D., Dewit, N., Pijenburg, Y., In 't Veld, S., Teunissen, C. E., & Vanmechelen, E. (2023). Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia. *Alzheimer's Research & Therapy*, *15*(1). https://doi.org/10.1186/s13195-023-01212-x
Original URL	https://link.springer.com/article/10.1186/s13195-023-01212-x#Sec1
Source type	Research Article
Keywords	Alzheimer's, Biomarkers, synapses
#Tags	#introduction
Summary of key points + notes (include methodology)	Synaptic proteins are associated with neurodegeneration in many diseases, including dementia. The main synaptic proteins in this study were SNAP-25, VAMP-2, Neurogranin (Ng), neuronal pentraxin-2 (NPTX2), and glutamate receptor-4 (GluR4). They found that SNAP-25 was best for differentiation of Alzheimer's from the other groups, but that it was not specific to the disease. They proved that synaptic proteins in the brain are differentially involved in the pathology of diseases, and would be best for a potential biomarker for AD. Notes: • Synaptic proteins are often associated with Tau and pTau levels in Alzheimer's • Synaptic biomarkers were not correlated with CSF neurofilament light, which means that broad spectrum neurodegeneration is not correlated with synaptic dysfunction • Used ELISA for biomarker detection • Core neuronal biomarkers in CSF, Tau, PTau, and NfL were able to differentiate between all groups (AD, FTD, & SCD) significantly • SNAP-25 was best at differentiating between AD and subjective cognitive decline (SCD) patients, and the only protein that could differentiate between AD and FTD

	• Strength of correlations found in AD and FTD were reduced from the SCD group • Synaptic protein levels are altered in different disease states • SNAP-25, VAMP-2 and Ng were found to have strong correlations to each other • Synaptic proteins in the brain are differentially involved in the pathology of diseases
Research Question/Problem/ Need	How are biomarkers of synaptic dysfunction and neurodegeneration related?
Important Figures	 This diagram shows the locations of each protein described in the study.



This chart shows the correlations of each biomarker with the cognition levels of the patients in each cohort.

Table 3 Diagnostic value of the CSF biomarkers

From: Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia

	Clinical groups					
	AD vs SCD		FTD vs SCD		AD vs FTD	
Core biomarker	AUC	*P*-value	AUC	*P*-value	AUC	*P*-value
Aβ42	1.00 (1.00, 1.00)	< 0.001	0.66 (0.48, 0.84)	0.079	0.92 (0.83, 1.00)	< 0.001
Tau	0.98 (0.99, 1.00)	< 0.001	0.87 (0.74, 0.99)	< 0.001	0.82 (0.69, 0.96)	< 0.001
PTau	1.00 (1.00, 1.00)	< 0.001	0.81 (0.67, 0.94)	0.001	0.83 (0.69, 0.96)	< 0.001
NfL	0.88 (0.76, 0.99)	< 0.001	0.98 (0.95, 1.00)	< 0.001	0.88 (0.75, 1.00)	< 0.001
Synaptic biomarker	AUC	*P*-value	AUC	*P*-value	AUC	*P*-value
SNAP25	0.99 (0.96, 1.00)	< 0.001	0.83 (0.70, 0.96)	< 0.001	0.75 (0.58, 0.89)	0.007
VAMP2	0.82 (0.69, 0.95)	< 0.001	0.77 (0.62, 0.92)	0.003	0.50 (0.31, 0.69)	0.978
Ng	0.87 (0.77, 0.98)	< 0.001	0.79 (0.64, 0.93)	0.002	0.65 (0.48, 0.82)	0.110
NPTX2	0.62 (0.45, 0.79)	0.185	0.70 (0.54, 0.87)	0.028	0.57 (0.39, 0.76)	0.402
GluR4	0.60 (0.42, 0.78)	0.291	0.51 (0.32, 0.69)	0.935	0.60 (0.42, 0.78)	0.267
Selected panel	0.99 (0.96, 1.00)	< 0.001	0.97 (0.93, 1.00)	< 0.001	0.84 (0.70, 0.98)	< 0.001

The data is represented as AUC (95% confidence interval). *AUC* area under the curve

This table shows the AUC for each biomarker, which shows how well it differentiates between the two groups being tested.

VOCAB: (w/definition)

glutamate receptor-4 (GluR4): a subunit of a complex called α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) that is involved in excitatory signal transmission in the post-synaptic neuron
prodromal: the time between the first appearance of symptoms and the full development of the symptoms

Cited references to follow up on

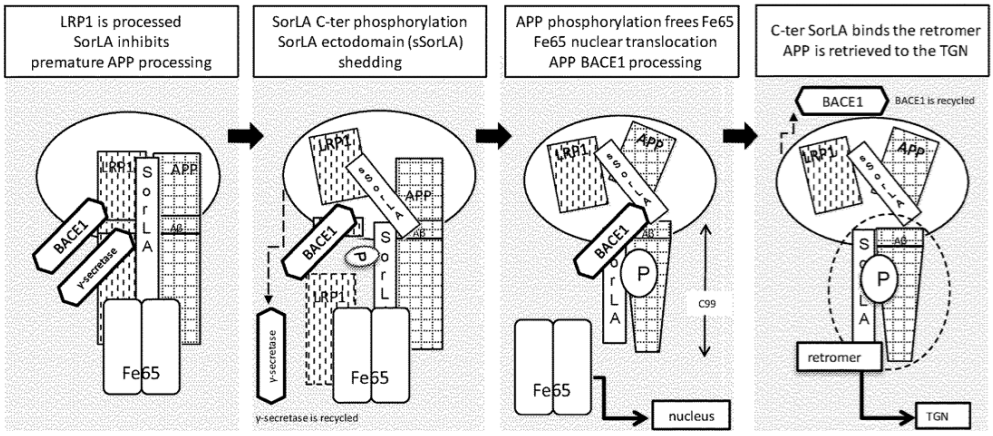
Kivisäkk, P., Carlyle, B., Sweeney, T., Quinn, J., Ramirez, C., Trombetta, B., Mendes, M., Brock, M., Rubel, C., Czerkowicz, J., Graham, D., & Arnold, S. (2022). Increased levels of the synaptic proteins PSD-95, SNAP-25, and neurogranin in the cerebrospinal fluid of patients with Alzheimer's disease. *Alzheimer's Research & Therapy*, *14*(1). https://doi.org/10.1186/s13195-022-01002-x

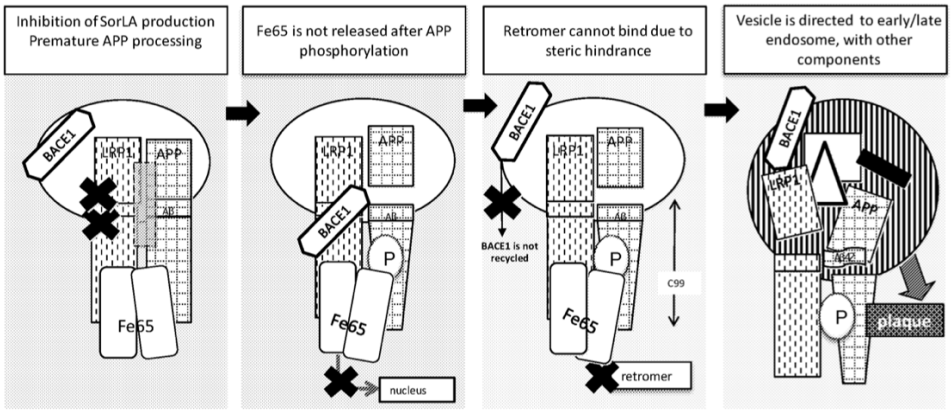
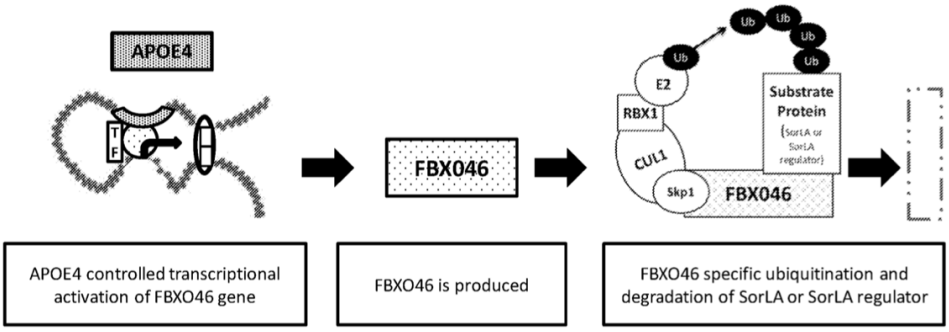
Follow up Questions

How do synapses affect neurodegeneration? Would improving synapse functionality stop neurodegeneration? Are there other synaptic proteins involved in AD that could be better biomarkers?

Patent Entry #1 Notes: Use of apoe4 motif-mediated genes for diagnosis and treatment of alzheimer's disease

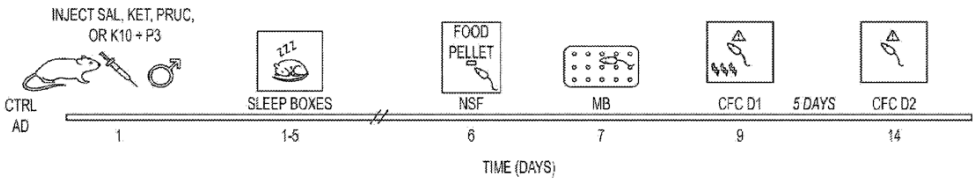
Source Title	Google Patents
Source citation (APA Format)	Urfer-Buchwalder, A. Urfer, R. (2019). *Use of ApoE4 motif-mediated Genes for diagnosis and treatment of Alzheimer's disease* (U.S. Patent No. 20190338363A1). U.S. Patent and Trademark Office. https://patentimages.storage.googleapis.com/b6/9b/1e/87e51cb6171512/US20190338363A1.pdf
Original URL	https://patentimages.storage.googleapis.com/b6/9b/1e/87e51cb6171512/US20190338363A1.pdf
Source type	Patent Application
Keywords	Alzheimer's, ApoE4
#Tags	#methods
Summary of key points + notes (include methodology)	There are no effective methods for diagnosing, preventing, or treating Alzheimer's disease. There were previously many knowledge gaps in the field, which made the development of treatments difficult. In order to help diagnose, treat, and prevent AD, the inventors decided to research APOE4, a known AD associated gene. They found an APOE4 motif-mediated gene called Nuclear respiratory factor 1 (NRF1). This gene is a transcription factor for an Alzheimer's causing gene, FBXO46. They created a method that uses the presence of APOE4 to determine which molecule to give a patient to treat their Alzheimer's. Notes: • Research has focused on amyloid plaques, which are caused by proteolytic cleavages of amyloid precursor protein (APP) and neurofibrillary tangles of hyperphosphorylated microtubule associated protein Tau (MAPT) • Early endosomes are enlarged in sporadic AD • Lack of research on root causes of AD • Apolipoproteins are in volved in transporting cholesterol and triglycerides in the blood, and APOE is mainly produced by astrocytes and transports cholesterol to neurons through APOE receptors • ApoE4 is the motif that modulated the motif-mediated genes that code for Nuclear respiratory factor 1 (NRF1), which is a transcription

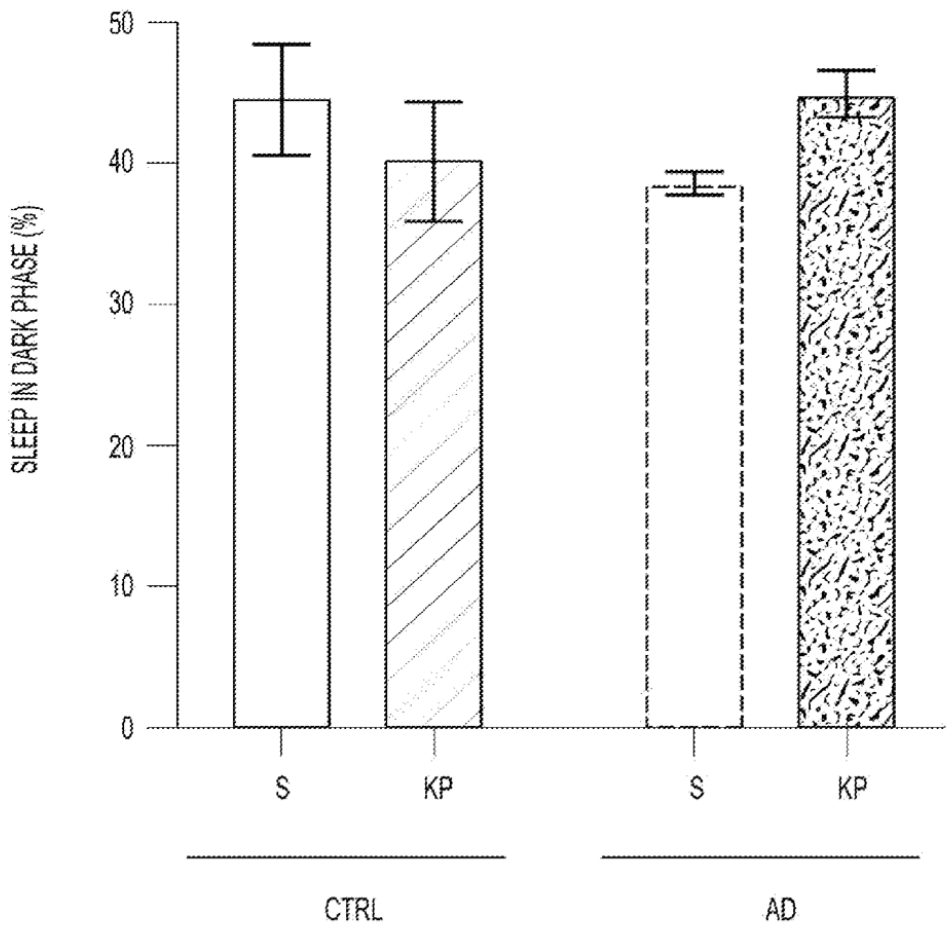
	factor for FBXO46 • FBXO46 is thought to be an AD causing gene, which messes with the function of the physiological amyloidogenic pathway and causes protein sorting dysfunction, cell cycle reentry, and neuronal death • Invention creates method of modulating expressions of ApoE4 motif mediated genes or gene products either by contacting the cell or gene expression product with an inhibitory molecule • In order to use the invention, you must determine the APOE genotype of the individual because it affects the necessary method • Advantages: transformative, targeted, addresses apoe4 motif-mediated dysfunction • AD risk increases with each copy of APOE4 inherited, risk for AD based on APOE is closer to the risks of mendelian diseases than more complex ones • ApoE4 speeds up progression of AD • ½ early onset AD is Familial AD, which is inherited through autosomal dominant mutations in Amyloid Precursor Protein, Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) • SorLA is protective against Alzheimer's • NRF1 has been found to target many neurodegenerative disease genes
Research Question/Problem/ Need	There are not effective methods for diagnosing, preventing, or treating Alzheimer's disease.
Important Figures	 This diagram shows the pathway that they are looking at, when it functions normally.

	 This is the pathway, when it causes Amyloid plaques.  This is the genetic expression for the APOE4 pathway.
VOCAB: (w/definition)	Motif: a nucleotide or amino acid pattern in biological sequences Proteolytic: breaks down proteins Endosomes: organelles that carry out endocytoses and regulate movement of proteins and lipids along subcellular compartments, interacting with the secretory and endocytic pathway, specifically the plasma membrane Golgi, trans-Golgi network (TGN), and vacuoles/lysosomes Oligonucleotide: a short single strands of synthetic nucleic acids Moiety: a distinct part of a large molecule CpG island: regions of the genome that contain a high frequency of cytosine and guanine nucleotides that are connected with a phosphodiester bond, which are often found around the promoter regions of genes
Cited references to follow up on	Davies, G., Harris, S. E., Reynolds, C. A., Payton, A., Knight, H. M., Liewald, D. C., Lopez, L. M., Luciano, M., Gow, A. J., Corley, J., Henderson, R., Murray, C., Pattie, A., Fox, H. C., Redmond, P., Lutz, M. W., Chiba-Falek, O., Linnertz, C., Saith, S., & Haggarty, P. (2014). A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. *Molecular Psychiatry*, *19*(1), 76–87. https://doi.org/10.1038/mp.2012.159
Follow up Questions	Do the effects of ApoE4 on Cholesterol affect the progression of Alzheimer's? Could the SorLA protein be used to potentially be used to help prevent AD? What other causes of Alzheimer's could counteract the effect of this treatment?

Patent Entry #2 Notes: *Compositions and methods for the treatment of Alzheimer's disease and other neurogenerative disease*

Source Title	Google Patents
Source citation (APA Format)	Denny, C., Chen, B. Hunsberger, H. (2024). *Compositions and methods for the treatment of alzheimer's disease and other neurogenerative disease* (U.S. Patent No. 20190338363A1). U.S. Patent and Trademark Office. https://patentimages.storage.googleapis.com/49/cf/58/b4f5c6c2b70e48/WO2024044355A2.pdf
Original URL	https://patentimages.storage.googleapis.com/49/cf/58/b4f5c6c2b70e48/WO2024044355A2.pdf
Source type	Patent
Keywords	Alzheimer's, treatment
#Tags	#methods
Summary of key points + notes (include methodology)	There is a lack of treatments for Alzheimer's disease, and even less if the neuropsychiatric symptoms are considered. These inventors used the AMPAR, 5-HT4R, and NMDAR pathways to find a treatment for the cognitive decline and neuropsychiatric symptoms of AD. They used (R, S)-ketamine as an antagonist of NMDAR, and prucalopride as an agonist of 5-HT4R. The testing was performed on mice, and it was found that the combination of (R, S)-ketamine and prucalopride was effective at reducing cognitive decline, improving sleep, and improving the neuropsychiatric condition. This will help treat AD and other neurodegenerative diseases in the future, which will improve the lives of many people with neurodegenerative diseases. Notes: • Combinational treatments may be necessary to treat each cause of AD • Method uses agonist of serotonin 4 receptor (5-HT4R) and agonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR) in combination to treat AD • Works for mammals • The drug improved sleep in the mice, which was affected by AD • Feeding was also improved, but learning wasn't

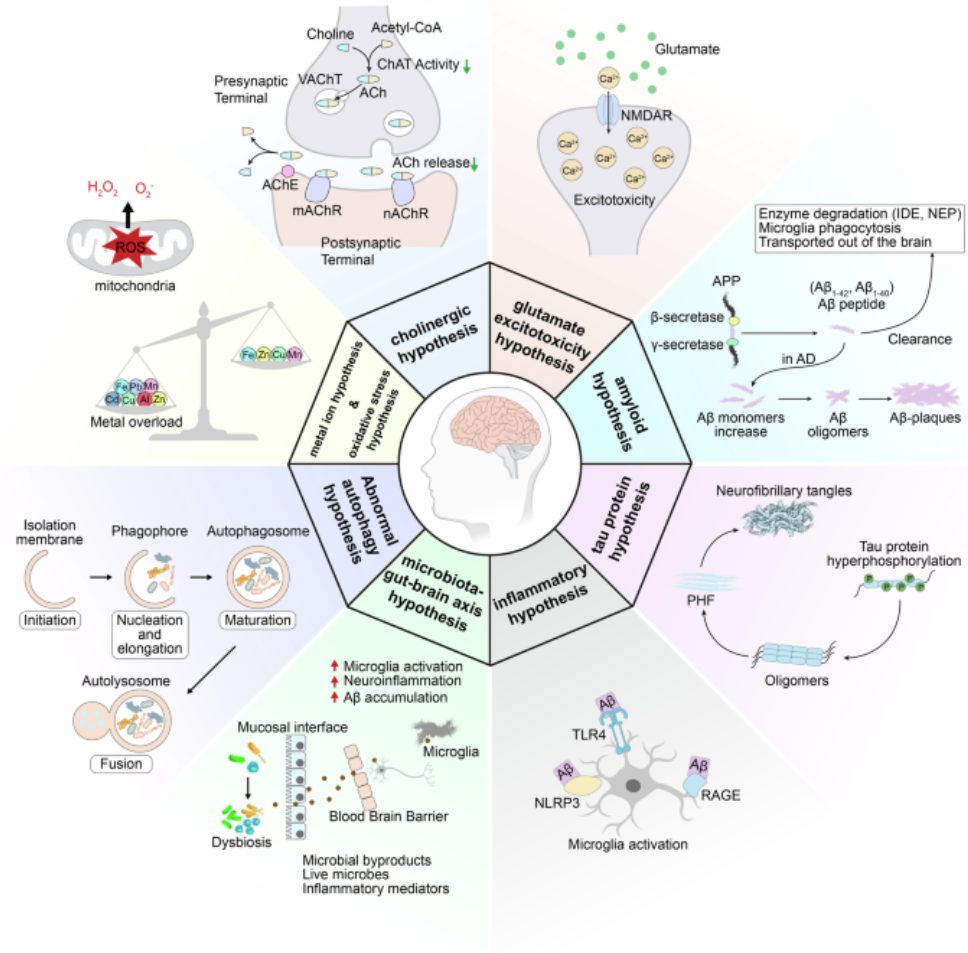
	• Mainly treats neuropsychiatric effects of AD • Tested (R, S)-ketamine and prucalopride, which ended up improving sleep and cognitive decile, as well as decreasing perservative behavior when used in tandem • Ketamine antagonizes the NMDA receptor, predicted that molecularly similar compounds will work the same • serotonin 4 receptor (5-HT4R) is a G protein coupled receptor that eventually causes the cleavage of the Amyloid Precursor Protein • 5-HT4R agonist, NMDAR antagonist, and AMPAR agonists are used
	There are no effective methods for treating Alzheimer's disease, especially the neuropsychiatric symptoms of the disease.
Important Figures	 This timeline shows their process for testing their treatment on mice.

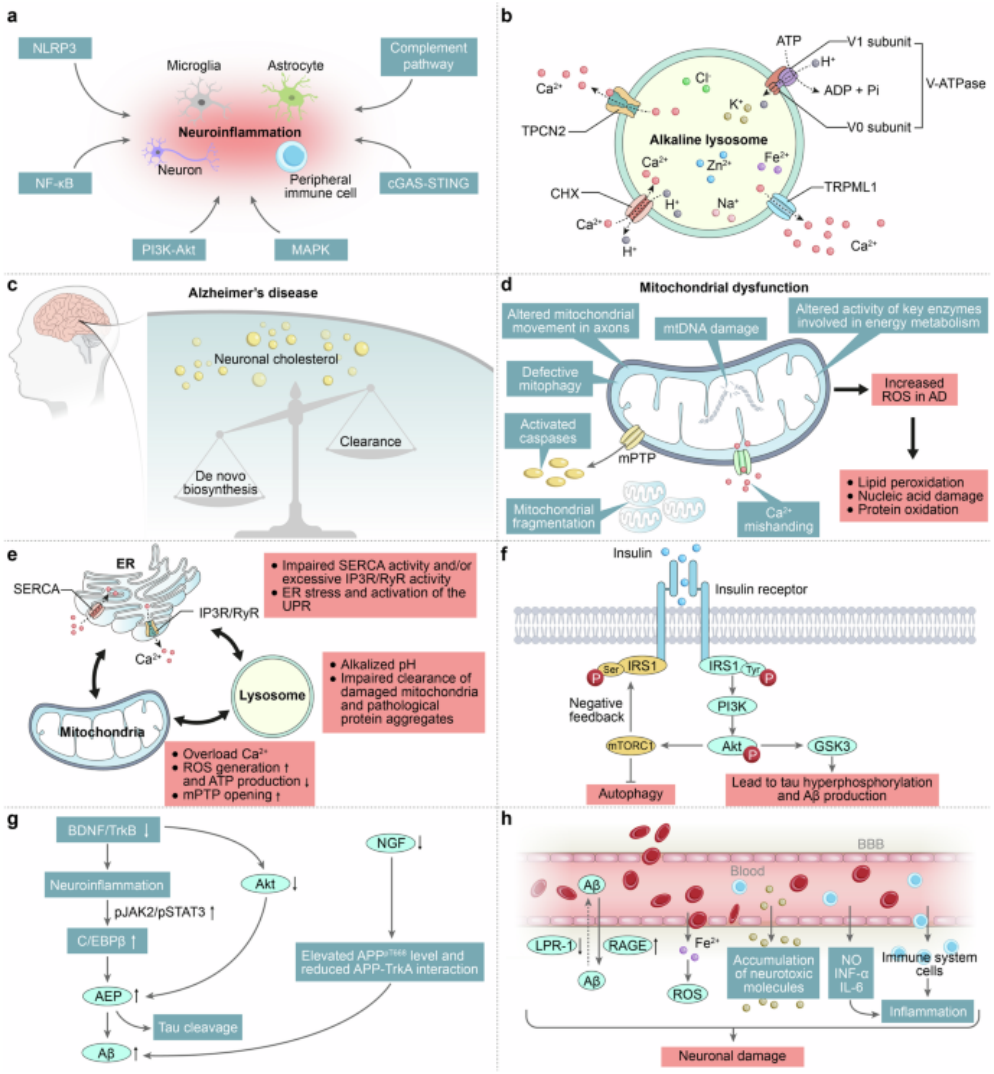
	 This graph shows the effects of Ketamine and prucalopride versus saline on the sleep of AD and control mice.
VOCAB: (w/definition)	Nootropic: drugs that increase mental alertness, concentration, energy levels and wakefulness. They are often used to improve memory and thinking by increasing the release of neurotransmitters. Perservative: repetitive behaviors due to cognitive changes
Cited references to follow up on	None
Follow up Questions	Would this method of regulating the 5-HT4R be able to be combined with the APOE4 mediation technique in Patent 1? Would this combination make them more effective? Do any of these pathways have proteins or RNA that could be good biomarkers for Alzheimer's? Are these treatments less effective for AD because they have a broad range of applications?

Article #11 Notes: *Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies*

Source Title	Nature
Source citation (APA Format)	Zhang, J., Zhang, Y., Wang, J., Xia, Y., Zhang, J., & Chen, L. (2024). Recent advances in alzheimer's disease: Mechanisms, clinical trials and New Drug Development Strategies. *Signal Transduction and Targeted Therapy*, *9*(1). https://doi.org/10.1038/s41392-024-01911-3
Original URL	https://www.nature.com/articles/s41392-024-01911-3
Source type	Review Article
Keywords	Alzheimer's disease, mechanisms, treatments
#Tags	#introduction
Summary of key points + notes (include methodology)	There are many existing methods of treatment and many more under investigation for Alzheimer's, which each treat one of the many overlapping hypotheses for the pathology of the disease. The hypotheses for the pathology of Alzheimer's are the cholinergic, amyloid, tau protein, inflammatory, oxidative stress, metal ion, glutamate excitotoxicity, microbiota-gut-brain axis, and abnormal autophagy hypotheses. Each hypothesis explains a different symptom or method of Alzheimer's and many of them are caused by or affect each other. Notes: • Etiology comes from combination of factors such as aging, genetics, and environment • various hypotheses, such as the cholinergic, amyloid, tau protein, inflammatory, oxidative stress, metal ion, glutamate excitotoxicity, microbiota-gut-brain axis, and abnormal autophagy, which are interconnected • symptoms are amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) in the brains, along with a cascade of pathological processes like neuroinflammation, synaptic dysfunction, mitochondrial and bioenergetic disturbances, and vascular abnormalities • diverse clinical phenotypes • connection between comorbidities and the pathological changes in AD, ongoing research • pathological changes can begin decades before clinical symptoms

	• acetylcholine deficiency, neuroinflammation, oxidative stress, biometal dyshomeostasis, glutamate imbalance, insulin resistance, gut microbiome abnormalities, cholesterol homeostasis disruption, mitochondrial dysfunction, and autophagy abnormalities contribute to AD as well as Amyloid beta and Tau • New/current AD drugs/trials are sodium oligomannate, aducanumab, lecanemab, and donanemab • Cholinergic hypothesis is that the cholinergic neurons are damaged, which causes a decrease in choline acetyltransferase (ChAT), which is what makes the acetylcholine, but it doesn't fully explain AD • Amyloid beta itself is not a viable option for treating AD, but its interactions with Tau could be useful • Imbalance of Phosphatases and kinases lead to hyperphosphorylated Tau • Microglial cells cause neuroinflammation due to increased Amyloid Beta • Microglia help increase tau • Microglia may also excessively attack synapses, worsening AD symptoms • Excessive Reactive Oxygen Species (ROS) accumulate in AD brains, due to many factors, such as metal accumulation, overexpression of related enzymes, and mitochondrial dysfunction. • Oxidative stress bridges gaps in other hypotheses, such as tau, amyloid beta, metals, and the neuroinflammatory cycle • Dyshomeostasis of Fe2+, Cu2+, and Zn2+ are associated with AD • Metal ion chelators, which treat metal ion build ups, are hard to administer through the BBB • Glutamate is the main excitatory neurotransmitter of glutamatergic neurotransmission in CNS, and in AD some of the receptors arr overstimulated, which overcomes the regulatory effects of magnesium, allowing excessive sodium and calcium ions into the brain • Glutamatergic excitotoxicity helps cause mitochondrial dysfunction • Autophagy can affect the function of mitochondria in AD • Mitochondrial dysfunction is found in many AD brains • Amyloid beta helps cause the excessive production of ROS • AD damages mitochondrial DNA • Alterations in expression levels of proteins related to fission/fusion of mitochondria (such as Opa1, Drp1, MFN1/2,fis1, and post-translational modifications of Drp1) can bias the mitochondria towards too much fission, which can lead to damage in mitochondrial energy biology and the more DNA damage in the

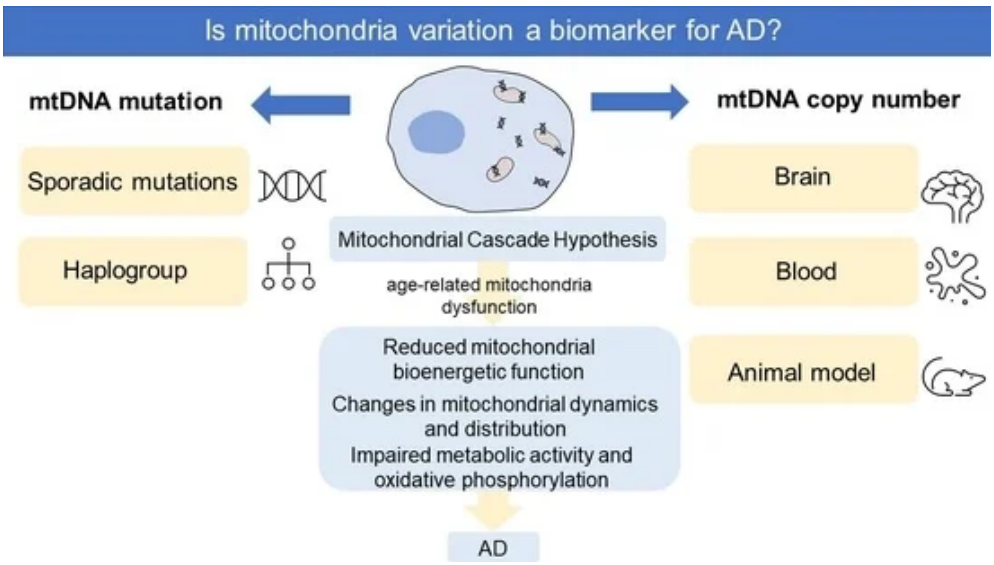
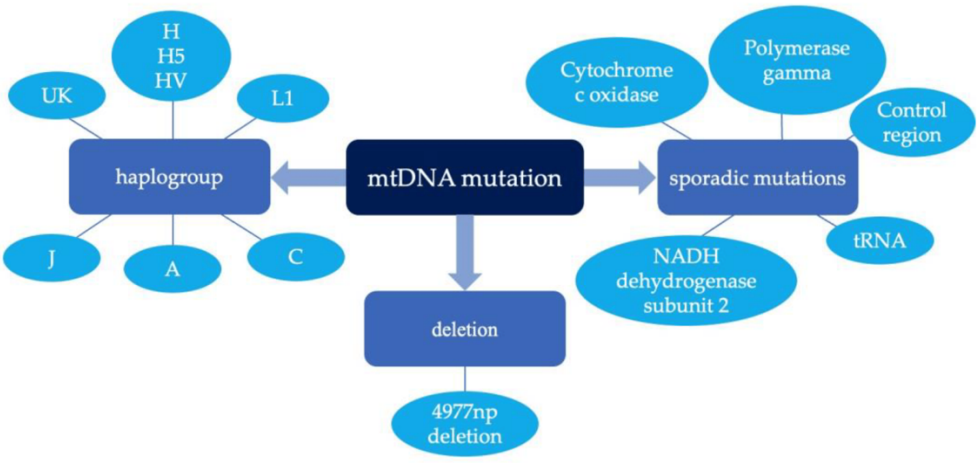
	mitochondria
Research Question/Problem/ Need	What are the current methods of treatment and diagnosis for the various mechanisms of Alzheimer's disease?
Important Figures	 This diagram shows the many hypotheses for understanding AD pathology.

	 This diagram shows the signaling pathways linked to AD pathogenesis, such as Neuroinflammatory signaling, Lysosomal dysfunction, Aberrant cholesterol metabolism, Mitochondrial dysfunction, Calcium signaling, Insulin signaling, Dysregulated neurotrophic signaling pathways, and BBB dysfunction.
VOCAB: (w/definition)	Cholinergic system: a pathway in the CNS and PNS that regulates brain function and other bodily functions through the use of neurotransmitter Acetylcholine, which is made in the cholinergic neurons of the brain Endogenous: originating from inside the organism Free radical: an unstable molecule that is made in cell metabolism glutamatergic neurotransmission: they are glutamate pathways, where the glutamate receptors are excited by glutamate, which is linked to many neurotransmission pathways in the neurons and glia of the CNS Microbiota-gut-brain axis: the bidirectional communication between the gut and brain, which includes the metabolic, neural, endocrine, and immune pathways, whether they operate independently or together

Cited references to follow up on	Chen, W., Zhao, H., & Li, Y. (2023). Mitochondrial dynamics in health and disease: Mechanisms and potential targets. *Signal Transduction and Targeted Therapy*, *8*(1). https://doi.org/10.1038/s41392-023-01547-9 Kerr, J., Adriaanse, B., Greig, N. H., Mattson, M., Cader, M., Bohr, V., & Fang, E. (2017). Mitophagy and Alzheimer's disease: cellular and molecular mechanisms. *Trends in Neurosciences*, *40*(3), 151–166. https://doi.org/10.1016/j.tins.2017.01.002
Follow up Questions	Could the blood be filtered to help stop the progression of Alzheimer's? Are there any mitochondrial genes that contribute to the oxidative stress of AD? How does oxidative stress affect the accumulation of Amyloid Beta? Is it possible to simulate the damages to mitochondrial DNA from AD?

Article #12 Notes: *Is Mitochondria DNA Variation a Biomarker for AD?*

Source Title	Genes
Source citation (APA Format)	Gao, R., & Ma, S. (2022). Is Mitochondria DNA Variation a Biomarker for AD? *Genes*, *13*(10), 1789. https://doi.org/10.3390/genes13101789
Original URL	https://www.mdpi.com/2073-4425/13/10/1789
Source type	Review article
Keywords	Mitochondria DNA, Alzheimer's
#Tags	#introduction
Summary of key points + notes (include methodology)	Alzheimer's disease is known to have altered mitochondrial function in the brain. It is unclear ad to whether this is a cause or effect of other mechanisms of the disease, but it is definitely interwoven into the total pathology of Alzheimer's. The mitochondrial DNA is often mutated in Alzheimer's patients and those with mild cognitive impairment. Amyloid beta and tau proteins are also known to decrease the function of mitochondria and increase the oxidative stress and Reactive Oxygen Species production. Overall, it is not known exactly how the variation in mitochondrial DNA correlates with the rest of AD pathology. Notes: • Either upstream pathologies cause mitochondrial dysfunction, or it directly disrupts normal brain function and directly contributes to neurodegeneration • Mitochondrial dysfunction influences Amyloid precursor protein (APP), production, cleavage, and Amyloid beta accumulation, and can lead to other molecular alterations (like oxidative stress) • AD could be the reactions of the brain to mitochondrial dysfunction • In AD, mitochondrial bioenergetic function reduces, including decreased respiratory chain activity, ATP production and enzymes involved in the mitochondrial tricarboxylic acid cycle, while the content of free radicals and reactive oxygen species (ROS) are elevated, as well as the dysfunction of mitochondrial axonal transport • APP, Amyloid Beta, and gamma secretase complex localize near mitochondria • Tau decreases fission proteins, therefore increasing mitochondrial length and also influences mitochondrial membrane potential and

	increases oxidative stress, eventually raising the sensitivity to different molecules, such as Aβ • Mitochondrial DNA (mtDNA) mutates more often than nuclear DNA • Many mutations found in the control regions of the mtDNA • mtDNA levels in the CSF are lowered before other CSF biomarkers, such as p-tau and t-tau • although there is controversial evidence on how mtDNA is related to AD, it is clear that it is related • mtDNA varies based on cell type and brain region
Research Question/Problem/ Need	Are variations in mitochondrial DNA important and specific enough to be good biomarkers of AD?
Important Figures	 This diagram is the graphical abstract. 

	This diagram shows the mutation in mtDNA that are associated with AD.
VOCAB: (w/definition)	Anterograde: occurring in the normal/forward direction of flow Gamma secretase complex: it carries out a sequential cleavage of the substrate to generate Aβ peptides
Cited references to follow up on	Adlimoghaddam, A., Snow, W., … & Albensi, B. (2019). Regional hypometabolism in the 3xTg mouse model of Alzheimer's disease. *Neurobiology of Disease*, *127*, 264–277. https://doi.org/10.1016/j.nbd.2019.03.008 Ashleigh, T., Swerdlow, R., & Beal, M. (2022). The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. *Alzheimer's & Dementia*, *19*(1), 333–342. https://doi.org/10.1002/alz.12683
Follow up Questions	Could the mutation of specific alleles in the mtDNA across multiple neurons trigger AD? Could this be modeled in a model organism, such as C. elegans? What environmental factors influence the mutation of mtDNA?

Article #13 Notes: *Methodological considerations for heat shock of the nematode Caenorhabditis elegans*

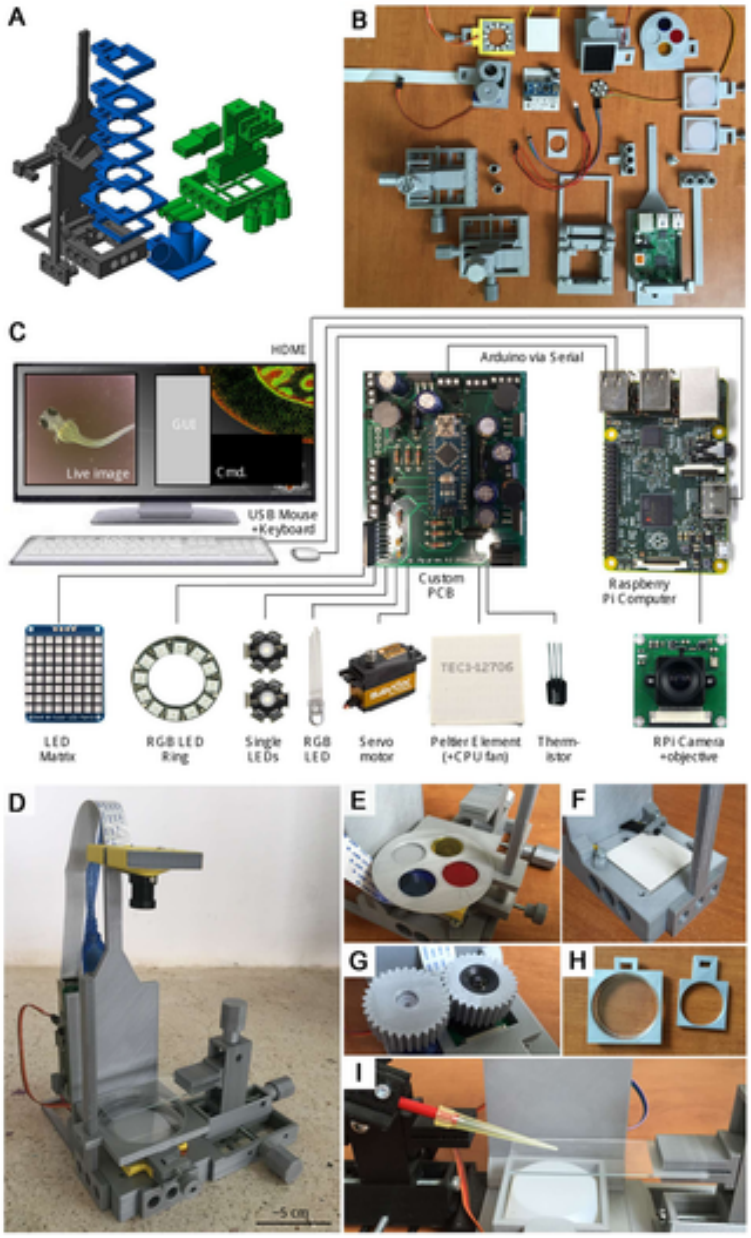
Source Title	Science Direct
Source citation (APA Format)	Zevian, S. C., & Yanowitz, J. L. (2014). Methodological considerations for heat shock of the nematode Caenorhabditis elegans. *Methods*, *68*(3), 450–457. https://doi.org/10.1016/j.ymeth.2014.04.015
Original URL	https://www.sciencedirect.com/science/article/pii/S1046202314001686?via%3Dihub
Source type	Research article
Keywords	Heat shock, Heat stress, Hormesis, C. elegans
#Tags	#methods
Summary of key points + notes (include methodology)	There was a need to standardize the methodology of heat stress experiments in C. elegans. There are three major methods, liquid mediums, preheated plates, and incubators. The incubators are the easiest to keep at temperature and they are most likely to cause other unnecessary stress. There are many other components in the effects of heat stress, which need to be controlled and recorded for the success and reproducibility of the experiment. Notes: • need to standardize the methodology of inducing heat stress, so that the results from different labs are comparable • heat shock proteins (HSPs) are expressed more during heat shock and help to maintain proteostasis • HSPs are very important to stress and aging • The best temperature for C. elegans is 16 degrees Celsius • Duration and time of day of exposure can alter results • Moving the worms causes unwanted extra stress, so try to move them as little as possible, which is why placing the worms in an incubator is the best approach • Make sure you consider the temperature gradient of the incubator • Whenever you open the door, the warm air from the incubator will be replaced with the air from the room, so add a fan when you close the door to increase air flow and increase the surface area of warm objects by adding connected freezer packs to decrease the time

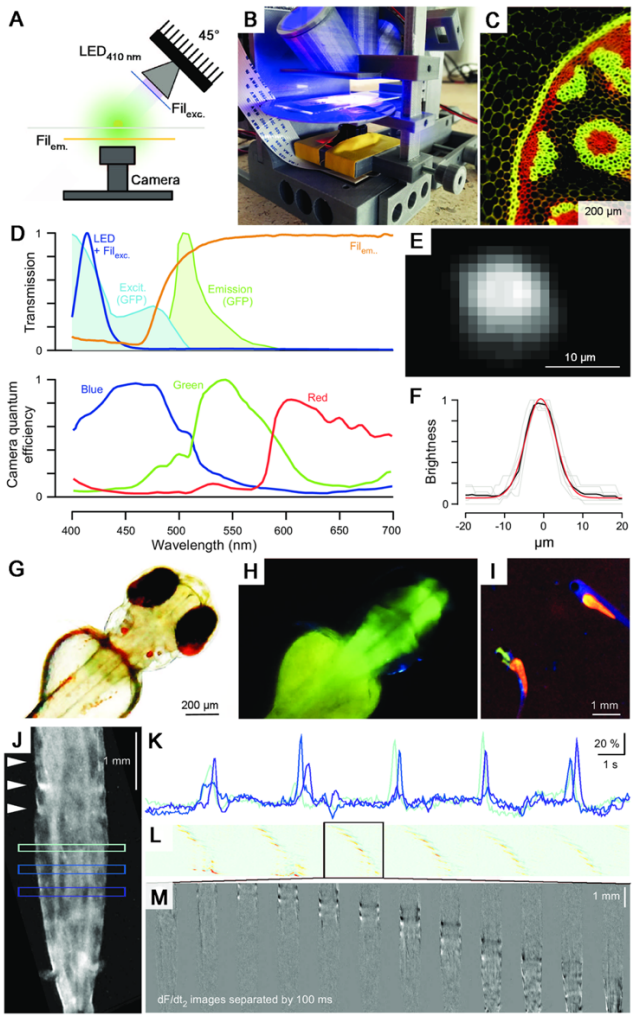
	needed to reheat • Determine time needed to get up to temp before the experiment • Changes in food can affect the results of heat stress, so use standard food for C. elegans • Consider the population density on the plates and keep it standard
Research Question/Problem/ Need	What are the best methods for causing heat stress in C. elegans?
Important Figures	

	The setup of the incubator to minimize time needed to heat it and reheat it after opening the door.
VOCAB: (w/definition)	Rheostats: a resistor that can vary the amount of electric current flowing through a circuit by adjusting its resistance Hormesis: the idea that a moderate amount of stress can help organisms adapt and end up improving their ability to handle more severe challenges later
Cited references to follow up on	None
Follow up Questions	Will heat shock proteins (HSPs) affect the amount of Amyloid beta produced? Are the variants of C. elegans that produce Amyloid plaques when heated going to be affected by the HSPs? Could the age-related deterioration of proteostasis have an effect on amyloid plaques and ROS in the adult C. elegans? Will the developmental delay caused by heat stress affect the results of my experiment?

Article #14 Notes: *The €100 lab: A 3D-printable open-source platform for fluorescence microscopy, optogenetics, and accurate temperature control during behaviour of zebrafish, Drosophila, and Caenorhabditis elegans*

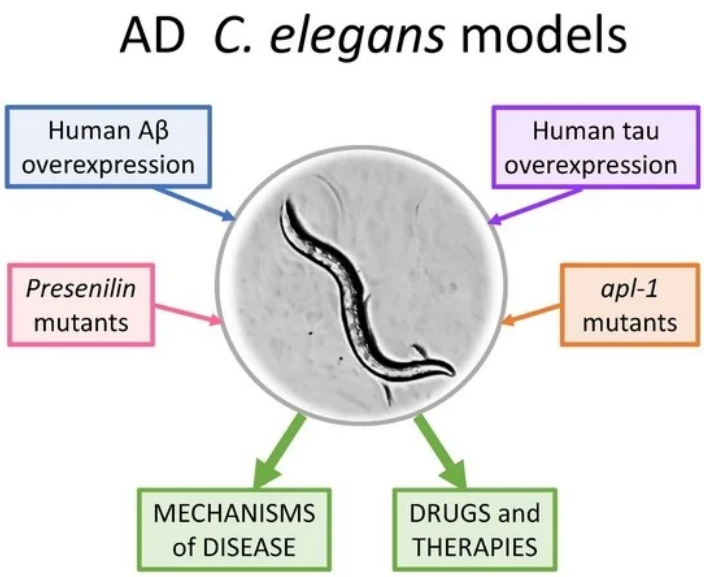
Source Title	PLOS Biology
Source citation (APA Format)	Maia Chagas, A., Prieto-Godino, L. L., Arrenberg, A. B., & Baden, T. (2017). The €100 lab: A 3D-printable open-source platform for fluorescence microscopy, optogenetics, and accurate temperature control during behaviour of zebrafish, Drosophila, and Caenorhabditis elegans. *PLOS Biology*, *15*(7), e2002702. https://doi.org/10.1371/journal.pbio.2002702
Original URL	https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2002702
Source type	Engineering Article
Keywords	Fluorescence microscopy, temperature control, optogenetics, microscope
#Tags	#methods
Summary of key points + notes (include methodology)	The expensiveness of traditional lab equipment limits the research of some labs. These researchers aimed to fix this by creating a microscope with various additional functions for cheap. This device uses a Raspberry Pi and Arduino to operate an adjustable focus camera, LED matrix, and heat module. It can take videos on some specific Raspberry Pis, and pictures on all versions. This microscope has been tested successfully with GFP and C. elegans. Notes: • Uses off the shelf parts, such as an Arduino microcontroller, a Raspberry Pi 3, and some optical and mechanical parts • Basic FlyPi can resolve samples down to about 10 microns, get video at up to 90 Hz, and take time lapse video over several hours • Can add in fluorescence imaging, temperature control, or automated focusing • The open-source GUI can control various aspects of the camera, and allows you to save pictures • Works well for GFP • The design doesn't need all components to function, giving flexibility to the design and allowing the user to only assemble what

	they need • Works well with C. elegans
Research Question/Problem/ Need	The expensiveness of traditional lab equipment limits the research of some labs.
Important Figures	 The parts and assembly of the FlyPi.

	 This figure shows the data for fluorescence detection and examples of fluorescent imaging using the microscope.
VOCAB: (w/definition)	collimate: make light accurately parallel
Cited references to follow up on	none
Follow up Questions	How can I get the specific PCB? How can I make sure the room temperature doesn't affect the temperature of the C. elegans on the temperature control unit? Have further improvements to the FlyPi been made since this paper was published?

Article #15 Notes: *Modeling Alzheimer's Disease in Caenorhabditis elegans*

Source Title	MDPI Biomedicines
Source citation (APA Format)	Alvarez, J., Alvarez-Illera, P., Santo-Domingo, J., Fonteriz, R. I., & Montero, M. (2022). Modeling Alzheimer's Disease in Caenorhabditis elegans. *Biomedicines*, *10*(2), 288. https://doi.org/10.3390/biomedicines10020288
Original URL	https://www.mdpi.com/2227-9059/10/2/288
Source type	Review article
Keywords	C. elegans, Alzheimer's
#Tags	#introduction
Summary of key points + notes (include methodology)	*C. elegans* have been used as model organisms since 1963 as they are great for fluorescence marking and surprisingly have a very homologous genome with humans. C. elegans contain homologous genes with much of the AD genome as well, making them a great model for AD. C. elegans must be engineered to express Amyloid beta though, as they are not naturally able to produce it. Many studies have researched the pathology of both Amyloid beta and oxidative stress in these nematodes. Notes: • *C. elegans* do not naturally express Amyloid beta but they are often given genes that allow them to overexpress amyloid beta as a model for Alzheimer's • Tau proteins normally promote tubulin assembly on microtubules and stabilize their structure • 53% of the human coding genome has recognizable orthologues in *C. elegans*, and many genes related to Alzheimer's also have orthologous genes in the worm • *C. elegans* lacks beta secretase (BACE1), which prevents it from naturally producing Amyloid beta peptides • *C. elegans* don't have APOE • Transparent body of C. elegans allows for easy and simple detection of fluorescence • APP processing is conserved in both organisms • Toxicity of Amyloid peptide determines its toxic effects • Ageing can lead to many damaged or aggregation-prone proteins

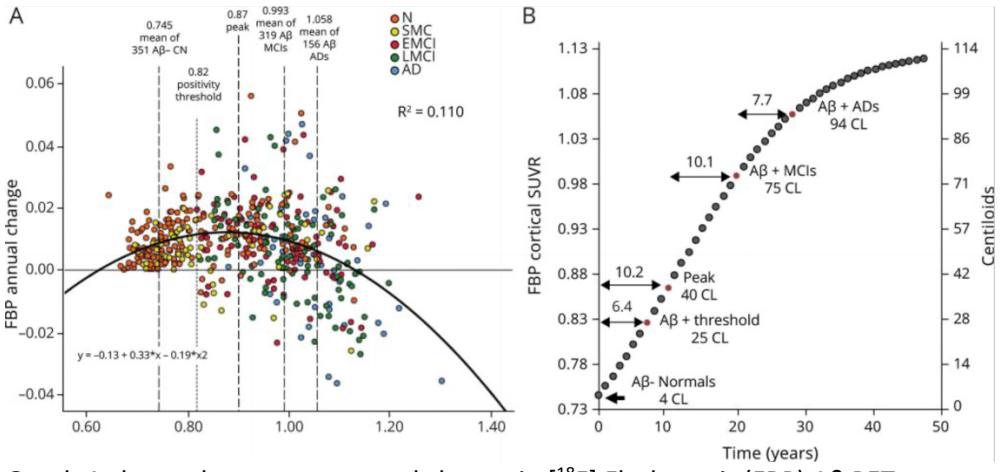
Research Question/Problem/ Need	To bring together the knowledge on the use of C. elegans as a model for AD.
Important Figures	 The graphical abstract.

Pros
Many human genes possess orthologues in *C. elegans*, among them most (but not all) of the genes involved in Alzheimer's disease
Aβ expression affects similar pathways in worm, mouse and human
Short generation and life cycle, around 3 weeks, and low maintenance and propagation costs
Small nervous system, only 302 neurons, with an invariant neuronal network
Transparent body, allows visualization of fluorescent proteins at all stages of its life
Complete characterization of cell fate lineage and neuronal connectivity
Complete genome sequence and very powerful genetic manipulation tools
Wide availability of mutant strains of most of the genes
Availability of extensive RNAi libraries able to silence most of the genes
Conserved protein interaction networks involved in AD
Numerous methods available for the functional characterization of neurodegeneration, motility disturbances or protein aggregation
Ability to make high throughput chemical screens for drug assay
Cons
Lacks β-secretase and β-amyloid peptide sequence in APP. Unable to generate endogenous Aβ
Lacks *APOE* gene
Lack of many specific mammalian features: circulatory system, myelinated neurons, defined brain structures such as hippocampus or cortex, complex connections of the human brain, adaptative immune system, among others

	The Pros and Cons of C. elegans as a model organism for AD
VOCAB: (w/definition)	Nucleation: the initial process of atoms combining to form a new phase or structure
Cited references to follow up on	none
Follow up Questions	Which of these drugs have been proved to work? Which drugs have failed or are still in testing? What do the most effective drugs target?

Article #16 Notes: *Temporal Dynamics of β-Amyloid Accumulation in Aging and Alzheimer Disease*

Source Title	American Academy of Neurology
Source citation (APA Format)	Jagust, W. J., & Landau, S. M. (2021). Temporal Dynamics of β-Amyloid Accumulation in Aging and Alzheimer Disease. *Neurology*, *96*(9), e1347–e157. doi.org/10.1212/wnl.0000000000011524
Original URL	https://www.neurology.org/doi/10.1212/WNL.0000000000011524
Source type	Research article
Keywords	Amyloid beta, time, aging, Alzheimer's
#Tags	#introduction
Summary of key points + notes (include methodology)	The researchers aimed to determine the time it took amyloid beta to accumulate from the levels of a cognitively normal person to the levels found in AD patents. They took [^{18}F] Florbetapir (FBP) Aβ PET scans of hundreds of participants over the course of 9 years. They found that Amyloid beta accumulation over time produces a sigmoidal graph, which starts with a low slope, which increases until a point where it levels off as it approaches a maximum value. Notes: • Two samples used and monitored over 9 years • Cognitively normal individuals were followed along with those with mild cognitive impairment and AD • Used [^{18}F] Florbetapir (FBP) Aβ PET scan acquired at about two-year intervals • Graphed changes in FBP and used a quadratic line of best fit because it had a better R^2 value. • Used this graph's line of best fit to predict the accumulation of Amyloid beta over time in terms of both FBP SUVR and centiloids • This study used 782 participants and had long follow up times, which makes it more reliable and gives a good insight into the development of the disease • Could mean that the Amyloid hypothesis is correct, at least partially
Research Question/Problem/ Need	How does Amyloid beta accumulate in the brain over time and when does it start?

Important Figures	 Graph A shows the average annual change in [^{18}F] Florbetapir (FBP) Aβ PET scan results for people with early mild cognitive impairment, late mild cognitive impairment, subjective memory complaints, Alzheimer's, and cognitively normal patients, all of whom are suspected to be on the AD pathway. This shows us that each group has a different mean, indicating the role of Amyloid beta in the pathology of Alzheimer's disease, and that it starts to decrease after a certain point in the development of the disease, showing that it must have a larger role in the initial pathology of AD. Graph B is an estimation of events in the accumulation of Amyloid beta over time in patients on the AD pathway, which was created using the quadratic best fit line from graph A. This shows the expected progression of Amyloid beta accumulation over time in humans. As my project will use worms, we will see that the timeline is shorter, but we expect a relatively similar curve to be produced. Abbreviations used in the graphs: CL = Centiloids; CN, N = cognitively normal; EMCI = early mild cognitive impairment; LMCI = late mild cognitive impairment; MCI = mild cognitive impairment; SMC = subjective memory complaints; SUVR = standardized uptake value ratio.
VOCAB: (w/definition)	Centiloids: the unit of the Centiloid (CL) scale, which is a standardized method of measuring Amyloid plaques in the brain as seen on PET scans. This scale use scores of 0 as an Aβ-negative brain and 100 as a brain with moderate AD as benchmarks to help guide the assignment of a score. Standardized uptake value ratio (SUVR): a dimensionless ratio that is used in PET scans to determine if the uptake value in a target area is very different from a reference area. It is calculated with this equation: SUVR = SUV (target region) / SUV (reference region)
Cited references to follow up on	none
Follow up Questions	What were the levels of ROS in these patients during this time? Did oxidative stress increase with the same pattern or was it different? What trends were see throughout this time period for the other hypotheses of AD pathology?

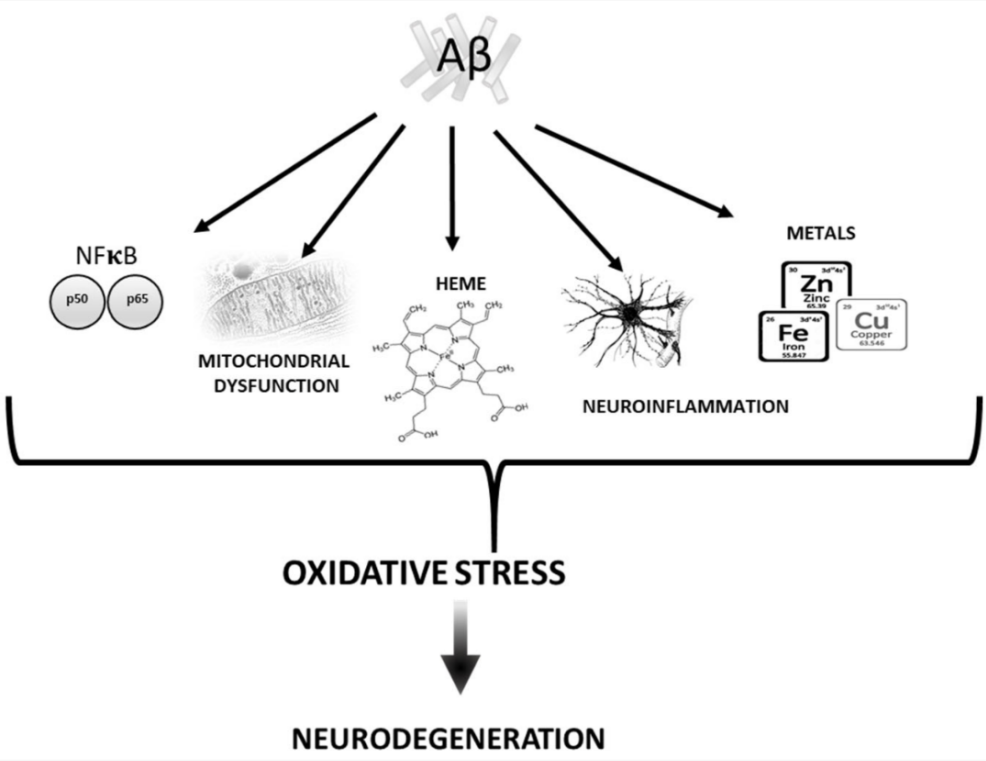
Article #17 Notes: Fluorescent Protein Methods: Strategies and Applications

Source Title	Methods in Cell Biology
Source citation (APA Format)	Hutter, H. (2012). Fluorescent protein methods: strategies and applications. *Methods in Cell Biology*, *107*, 67–92. doi.org/10.1016/B978-0-12-394620-1.00003-5
Original URL	https://www.sciencedirect.com/science/article/abs/pii/B9780123946201000035
Source type	Methods review
Keywords	GFP, C. elegans
#Tags	#methods
Summary of key points + notes (include methodology)	This article reviewed the methods of how to introduce GFP and other fluorescent markers into C. elegans. GFP is the most common fluorescent marker used in C. elegans, and there are many different versions of this protein available. C. elegans are good organisms for the use of fluorescence imaging because they are transparent, which minimizes sample preparation and allows for the study of the worms over time or before and after treatment. Notes: • GFP is a genetically encoded marker is often used because it is so easy to introduce • C. elegans are transparent, making the use of fluorescent markers easier • The number of fluorescent markers has increases significantly, leaving researchers with plenty of choices and allowing them to pick the perfect fluorescent marker for their experiment • C. elegans are imaged alive, which is very useful as they can be imaged multiple times, allowing them to be useful for studies that access changes over time
Research Question/Problem/ Need	What are the current methods and uses of fluorescence in C. elegans?
Important Figures	none
VOCAB: (w/definition)	Autofluorescence- the fluorescence of naturally occurring substances emitted from biological structures.

Cited references to follow up on	none
Follow up Questions	Is roGFP introduced in the same manner as GFP? How is the dye Thioflavin T given to C. elegans? How will the use of these markers affect the molecules and proteins being studied in my experiment?

Article #18 Notes: Oxidative Stress and Beta Amyloid in Alzheimer's Disease. Which Comes First: The Chicken or the Egg?

Source Title	Antioxidants
Source citation (APA Format)	Tamagno, E., Guglielmotto, M., Vasciaveo, V., & Tabaton, M. (2021). Oxidative Stress and Beta Amyloid in Alzheimer's Disease. Which Comes First: The Chicken or the Egg? *Antioxidants*, *10*(9), 1479. https://doi.org/10.3390/antiox10091479
Original URL	https://www.mdpi.com/2076-3921/10/9/1479
Source type	Review article
Keywords	oxidative stress; Beta amyloid; Alzheimer's disease
#Tags	#introduction
Summary of key points + notes (include methodology)	There is conflicting evidence on whether Amyloid plaques or oxidative stress comes first in the pathology of Alzheimer's. This is because both mechanisms cause each other and have a cyclic nature in this disease. Oxidative stress regulates the formation and toxicity of Amyloid plaques, while Amyloid beta changes oxidative phosphorylation to create more ROS. Notes: • Conflicting evidence on whether Amyloid beta comes first or if oxidative stress comes first • Hard to determine because it's a cycle (both mechanisms cause the other) • AD is becoming one of the most expensive and deadly diseases in the world • Pathology of AD has many mechanisms and is not fully understood • Amyloid causes oxidative stress, by changing oxidative phosphorylation, which involves a reduction in the efficiency to transfer electrons, which results in an increase in ROS production (mostly at complex I and complex III) • Oxidative stress regulates the accumulation and toxicity of amyloid beta • A correlation has been found between the induction of OS and the increase in γ-secretase cleavage on APP • Aβ induces OS in vivo and in vitro, and OS increases the production of Aβ

	• Antioxidants are helpful before clinical symptoms occur, but they're useless later in the progression of the disease
Research Question/Problem/ Need	Which mechanism comes first, Amyloid Plaques and Oxidative Stress?
Important Figures	 The Amyloid hypothesis for the pathology of AD.
VOCAB: (w/definition)	Mnemonic- a device, such as a pattern of letters, ideas or associations that is designed to aid with memory
Cited references to follow up on	None
Follow up Questions	Is there research on this relationship in relation to age? How does oxidative stress impact the production of Amyloid plaques in CL2355 C. elegans? Is this cycle changed depending on the age of the patient?

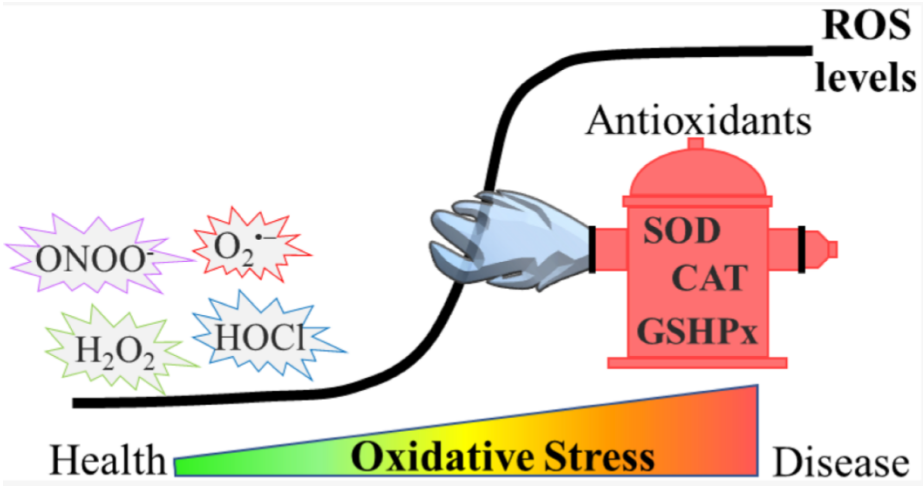
Article #19 Notes: *Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin*

Source Title	International Journal of Molecular Sciences
Source citation (APA Format)	Tchekalarova, J., & Tzoneva, R. (2023). Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin. *International Journal of Molecular Sciences*, *24*(3), 3022. doi.org/10.3390/ijms24033022
Original URL	https://www.mdpi.com/1422-0067/24/3/3022
Source type	Review Article
Keywords	Oxidative stress, aging, Alzheimer's disease, Parkinson's disease, melatonin
#Tags	#introduction
Summary of key points + notes (include methodology)	AD is one of the most age-related diseases, and two major mechanisms of this disease are Amyloid plaque accumulation and oxidative stress. Antioxidants have been shown to be effective in treating, not just oxidative stress, but also Amyloid plaques. This provides further evidence that these two mechanisms are very closely related and might be related to aging as antioxidants are more effective before clinical symptoms appear, which is at a younger age than when clinical symptoms are present. Notes: • AD is one of the most closely related diseases to age • Still a debate over whether oxidative stress or amyloid beta comes first • Astrocytes typically clear out extracellular Amyloid beta and regulate the Blood Brain Barrier, but in conditions of high oxidative stress, the function of astrocytes is impaired, allowing amyloid plaques to build up • Oxidative stress causes more activity of β- and γ-secretase, which split APP into Amyloid beta, which then forms plaques • impairment of cell membranes due to oxidative stress (including the oxidation of neuronal membrane proteins and lipid peroxidation, and oxidation of the low-density lipoprotein receptor-related protein) could cause Amyloid plaques

	• Free radical species (like ROS) in the mitochondria is known to initiate many mechanisms of AD pathology, including Amyloid plaques • Melatonin, an antioxidant, can help to reduce not just oxidative stress, but also Amyloid beta plaques as well, as they are very interrelated mechanisms
Research Question/Problem/ Need	How does the decrease of melatonin that happens as a person ages change the susceptibility of these persons to Alzheimer's and Parkinson's?
Important Figures	None
VOCAB: (w/definition)	Soluble amyloid precursor protein (sAPP): a secreted form of APP that is involved in the regulation of Amyloid beta production and the process of Amyloid Precursor Protein processing sAPPα: a non-amyloidogenic fragment secreted during normal APP processing sAPPβ: byproduct of the amyloidogenic processing of APP
Cited references to follow up on	Ledezma, C., Coria-Lucero, C., María Belén Delsouc, Casais, M., Cecilia Della Vedova, … Ana Cecilia Anzulovich. (2021). Effect of an Intracerebroventricular Injection of Aggregated Beta-amyloid (1–42) on Daily Rhythms of Oxidative Stress Parameters in the Prefrontal Cortex. *Neuroscience*, *458*, 99–107. https://doi.org/10.1016/j.neuroscience.2020.08.016
Follow up Questions	How do other current treatments' effectiveness differ based on the age of the individual? How does age affect the pathologies of AD and Parkinson's? Do their pathologies differ in mechanism or effectiveness with age?

Article #20 Notes: Oxidative Stress in Age-Related Neurodegenerative Diseases: An Overview of Recent Tools and Findings

Source Title	*Antioxidants*
Source citation (APA Format)	Korovesis, D., Rubio-Tomás, T., & Tavernarakis, N. (2023). Oxidative Stress in Age-Related Neurodegenerative Diseases: An Overview of Recent Tools and Findings. *Antioxidants*, *12*(1), 131–131. https://doi.org/10.3390/antiox12010131
Original URL	https://www.mdpi.com/2076-3921/12/1/131
Source type	Review article
Keywords	Aging, age-related pathology, neurodegenerative disease, oxidative stress, protein aggregation, Reactive Oxygen Species (ROS)
#Tags	#introduction
Summary of key points + notes (include methodology)	Oxidative stress has been shown to increase with the age of the patient. Oxidative stress is very important to the pathologies of many age-related neurodegenerative diseases, such as Alzheimer's. Oxidative stress is linked to the accumulation of Amyloid beta, and as oxidative stress increases over time, Amyloid beta must also increase over time. Notes: • ROS molecules: hydrogen peroxide (H_2O_2), superoxide anion radicals ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), singlet oxygen ($^1O_2$), nitrogen dioxide ($NO_2^{\bullet-}$), hypochlorous acid (HOCl) and peroxynitrite ($ONOO^-$) • $O_2^{\bullet-}$, the most common ROS in the mitochondria, is generated by the one-electron reduction in molecular oxygen during oxidative phosphorylation • ROS are produced in other parts of the cell other than mitochondria, such as peroxisomes • To measure ROS, you can use a variety of methods, such as measuring the oxidized biomolecules, measuring Hypohalous Acids (an acid produced in the presence of Oxidative stress), many different variations of fluorescence imaging, protein carbonylation, and protein oxidation
Research Question/Problem/ Need	How does oxidative stress and its effects change with age?

Important Figures	 This is the graphical abstract of the paper.
VOCAB: (w/definition)	electron spin resonance (EPR)- a spectroscopic technique used to study molecules, such as ROS with unpaired electrons
Cited references to follow up on	Murphy, M. P., Bayir, H., Belousov, V., Chang, C. J., Davies, K. J. A., Davies, M. J., … Schumacker, P. T. (2022). Guidelines for measuring reactive oxygen species and oxidative damage in cells and in vivo. *Nature Metabolism*, *4*(6), 651–662. https://doi.org/10.1038/s42255-022-00591-z
Follow up Questions	How does this relationship play a role in the correlation of amyloid plaques and age in individuals developing AD? Which of these methods work best in C. elegans? Do amyloid plaques cause more oxidative stress in the brains of elderly organisms, as opposed to younger organisms?