# Project Notes:

**Project Title: Targeting Tau Protein Using Ginger-Derived Nanovesicles**

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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 |
|---|---|---|---|
| Can handwriting diagnose/predict Alzheimer's disease? | Article 3 | Figure 6 and most of the article | September 22nd |
| How can stem cells be engineered? | Article 6, Article 2 | Background information, Implications | October 2nd , Sept 18th |
| How is Alzheimer's Disease caused? | Article 4, Article 5 | They both talk about Amyloid beta causing Alzheimer's Disease when it builds up abnormally | September 28-29th |
| What are exosomes? | Article 6 | Explains they are vesicles in the background information | October 1st |
| What is Amyloid precursor protein and how can it be targeted to inhibit Aß protein? | Article 4 | Results show Aß can be suppressed with PuF and SP1 | September 29th |
| How are tau tangles formed, and can they be inhibited? | Article 6, Article 7 | | October 5-6th |
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# Literature Search Parameters:

These searches were performed between (Start Date of reading) and XX/XX/2019.
List of keywords and databases used during this project.

| Database/search engine | Keywords | Summary of search |
|---|---|---|
| WPI library | Alzheimer's Disease, Exosomes | Search performed between September 15th and September 17th. The results included Article 3 and 4. |
| Google scholar | Amyloid ß, Tau Protein | Search performed between September 22nd and 29th. Results included article 5 and 4. |
| Google scholar | Tau Protein, Exosomes, mesenchymal stem cells | Search performed between September 28th and October 3rd . Results include articles 5 and 6. |
| Google Scholar | Tau protein tangles | Search performed October 5th. Results include article 7 and 8. |

# Tags:

| Tag Name |
|---|
| #biology #Cortisol #endocrinology #sodium_retension #Stem_cells #alzheimers #AD #Ecoli #fluorescence #Alzheimers_Disease #AD_detection #handwriting #motor_skills #ML #Tau #Neurodegeneration #Amyloid-Beta #Amyloid_precursor_protein #Amyloid_beta #PRE #PuF_protein #PuF_regulation #Mesenchymal_stem_cells #Drug_delivery #Biomarkers |

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| #MSCs #Biomarkers #MSC-EV #EVs #Tau_proteins #hyperphosphorylation #treatment #Stem_cells #heterochromatin #MSR_transcript_levels #Protein_folidng #c_elegans #GDNVs #Ginver #nanovesicles #plant_derived_nanovesicles #GDVNs #inflammation #Tau #hyperphosphorylation #AD #inflammation #amyloid_beta #Tau_structure #tau #FlyPI #Florescence_microscope #mCherry |
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# Article #1 Notes: Cortisol and Hypertension

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Cortisol and Hypertension |
| **Source citation (APA Format)** | Kelly, J. J., Mangos, G., Williamson, P. M., & Whitworth, J. A. (1998). Cortisol and hypertension. *Clinical and Experimental Pharmacology & Physiology*, *25*(S1). https://doi.org/10.1111/j.1440-1681.1998.tb02301.x |
| **Original URL** | https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1681.1998.tb02301.x |
| **Source type** | Journal Article |
| **Keywords** | Cortisol, Hypertension, Nitric Oxide, Blood pressure, Hormone regulation |
| **#Tags** | #biology #Cortisol #endocrinology #sodium_retension |
| **Summary of key points + notes (include methodology)** | The text studies the relationship between cortisol and hypertension; mainly on how cortisol can increase blood pressure, leading to hypertension. The study shows that cortisol increases BP in a dose dependent manner, with effects generally seen at doses between 80-200 mg/day. The cortisol-induced hypertension is associated with sodium retention and plasma volume expansion. The study also suggests that cortisol-induced hypertension is not mediated by increased nervous system activity, as commonly believed. Instead, the suppression of the nitric oxide system may play a crucial role in this process. Sheep were infused with adrenocorticotropic hormone (ACTH) or cortisol at different dosages and rates to observe the effects on BP and this was monitored overtime. The same was also done for humans over a period of 5 days. Sodium retention was assessed by measuring body weight changes, urine sodium excretion, and plasma volume. |
| **Research Question/Problem/ Need** | How are cortisol levels related to hypertension and what are the effects of cortisol induced hypertension? |
| **Important Figures** | • Cortisol doses of 80-200 mg/day are linked to hypertension<br>• No change is apparent at 40 mg/day of Cortisol (physiological replacement dose)<br>• BP increase occurs within 24 hours.<br>• Figure 2: shows BP, body weight when administering cortisol |
| **VOCAB: (w/definition)** | • 11ßHSD enzyme: An enzyme that converts cortisone to active cortisol or from cortisol to cortisone. |

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| | • L-arginine: The main amino acid used to build proteins.<br>• Cortisol: Regulates the body's stress response and helps control use of fats, proteins, and carbohydrates by suppressing the digestive system.<br>• Spironolactone: Helps regulate high blood pressure and can reduce sodium absorption.<br>• ACTH: Hormone that regulates cortisol. |
| **Cited references to follow up on** | 34. Oberfield SE, Levine LS, Carey RM, Greig F, Ulick S, New MI. Metabolic and blood pressure responses to hydrocortisone in the syndrome of apparent mineralocorticoid excess. J. Clin. Endocrinol. Metab. 1983; 56: 332-9.<br>49. Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CRW. Glucocorticoid exposure in utero: New model for adult hypertension. Lancet 1993; 341: 33941.<br>51. Watt GCM, Harrap SB, Foy CJW et al. Abnormalities of glucocorticoid metabolism and the renin-angiotensin system: A four-comers approach to the identification of genetic determinants of blood pressure. J. Hypertens. 1992; 10: 473-82. |
| **Follow up Questions** | • What are the specific mechanisms by which cortisol suppresses the nitric oxide system in humans, and how does this suppression contribute to hypertension?<br>• What can be done to break down cortisol (and prevent sodium retention) in individuals with defective 11ßHSD enzymes?<br>• Can interventions that target the nitric oxide system, such as L-arginine supplementation, effectively mitigate cortisol-induced hypertension in humans? |

# Article #2 Notes: Fluorescent protein lifetimes report densities and phases of nuclear condensates during embryonic stem-cell differentiation

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Fluorescent protein lifetimes report densities and phases of nuclear condensates during embryonic stem-cell differentiation |
| **Source citation (APA Format)** | Joron, K., Viegas, J. O., Haas-Neill, L., Bier, S., Drori, P., Dvir, S., Lim, P. S. L., Rauscher, S., Meshorer, E., & Lerner, E. (2023). Fluorescent protein lifetimes report densities and phases of nuclear condensates during embryonic stem-cell differentiation. *Nature Communications, 14*(1), 1–18. https://doi.org/10.1038/s41467-023-40647-6 |
| **Original URL** | https://www.nature.com/articles/s41467-023-40647-6 |
| **Source type** | Journal Article |
| **Keywords** | Fluorescence, embryonic stem cells, HP1α, FLIM, FCS, Fluorescence Anisotropy, Trp Fluorescence Spectra, E. coli, |
| **#Tags** | #biology #Stem_cells #alzheimers #AD #Ecoli #fluorescence |
| **Summary of key points + notes (include methodology)** | Fluorescent protein lifetimes can report on local densities within bio-condensates. In mouse embryonic stem cells, HP1α condensates exhibit heterogeneous densities before differentiation, suggesting a non-liquid phase. Differentiation induces a shift towards a more homogeneous distribution of local densities, indicating a liquid-like phase. Fluorescent proteins were expressed in E. coli, purified through chromatography, and their behavior was investigated using fluorescence lifetime imaging microscopy (FLIM) and fluorescence correlation spectroscopy (FCS) to measure fluorescence lifetimes and diffusion properties in live cells. Furthermore, fluorescence anisotropy was employed to analyze rotational dynamics, while Trp fluorescence spectra were used to observe structural changes. Additionally, molecular dynamics (MD) simulations were conducted to model protein dynamics in diverse environments. |
| **Research Question/Problem/ Need** | Understanding how these fluorescent proteins work can help me learn more about what happens inside cells, including how proteins interact and how they might form aggregates or clumps, which is important for studying diseases like Alzheimer's. |

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| **Important Figures** | • FLIM: Showed how the proteins' fluorescence lifetimes varied, to understand their interactions.<br>• FCS: Revealed how the proteins moved and their concentrations inside cells.<br>• Fluorescence Anisotropy: Showed changes in the proteins' movement, indicating interactions or changes in their structure.<br>• Trp Fluorescence Spectra: Indicated structural changes in the proteins.<br>• MD Simulations: Provided a detailed view of how the proteins behave and interact at a molecular level.<br>• Scanned wavelengths in the range 305–400 nm and focusing on excitation at λ = 295 nm.<br>• FVO of ~30%: The crowding threshold above which fluorescent lifetimes begin to reduce significantly. Means the onset of phase separation and higher crowdedness.<br>• Fluorescence Lifetime of mCherry: Standard value around 1.4–1.6 nanoseconds (ns). Lifetime reduction below 1.44 ns indicates increased molecular crowding. |
| **VOCAB: (w/definition)** | • Fractional Volume Occupancy (FVO): The fraction of space inside a cell that is occupied by molecules, rather than being empty.<br>• Phase Separation (PS): A process in which a mixture of molecules separates into different phases, forming distinct compartments without a surrounding membrane.<br>• Fluorescence Lifetime Imaging Microscopy (FLIM): A technique that measures the time a molecule remains in its excited state before emitting a photon (fluorescence) to provide information about molecular interactions and environment.<br>• FRET: Used to measure distance between 2 fluorescent molecules to study molecular interactions.<br>• mCherry: Red fluorescent protein that can be used as a biomarker. |
| **Cited references to follow up on** | • Record, M. T., Courtenay, E. S., Cayley, S. & Guttman, H. J. Biophysical compensation mechanisms buffering E. coli protein–nucleic acid interactions against changing environments. *Trends Biochem. Sci.* **23**, 190–194 (1998).<br>• Novo, C. L. et al. Satellite repeat transcripts modulate heterochromatin condensates and safeguard chromosome stability in mouse embryonic stem cells. *Nat. Commun.* **13**, 3525 (2022). |

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| **Follow up Questions** | • How does local crowding affect amyloid-ß aggregation?<br>• How sensitive is mCherry fluorescence to detecting physicochemical changes at the molecular level that correlate with the formation of toxic Aß? Could mCherry-based sensors be adapted to indicate when the local environment promotes these toxic forms?<br>• Can mCherry be used to also study Tau proteins?<br>• How does cellular metabolism influence the local environment in Alzheimer's-affected cells, and can mCherry detect this?<br>• |

# Article #3 Notes: Diagnosing Alzheimer's disease from on-line handwriting: A novel dataset and performance benchmarking.

Article notes should be on separate sheets

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| **Source Title** | Diagnosing Alzheimer's disease from on-line handwriting: A novel dataset and performance benchmarking. |
| **Source citation (APA Format)** | Cilia, N. D., De Gregorio, G., De Stefano, C., Fontanella, F., Marcelli, A., & Parziale, A. (2022). Diagnosing Alzheimer's disease from on-line handwriting: A novel dataset and performance benchmarking. *Engineering Applications of Artificial Intelligence*, *111*(104822), 104822. https://doi.org/10.1016/j.engappai.2022.104822 |
| **Original URL** | https://www.sciencedirect.com/science/article/pii/S0952197622000902 |
| **Source type** | Journal Article |
| **Keywords** | Alzheimer's Disease, Handwriting, Classes, Datasets, Feature sets, Classifiers, |
| **#Tags** | #Alzheimers_Disease #AD_detection #handwriting #motor_skills #ML |
| **Summary of key points + notes (include methodology)** | This study introduces the DARWIN dataset, which analyzes handwriting to aid early Alzheimer's disease (AD) diagnosis. The dataset includes handwriting samples from 174 participants, both AD patients and healthy controls, and is designed to capture distinctive handwriting features linked to AD. Using 25 different tasks, the researchers extracted 18 features per task and evaluated various machine learning models, achieving accuracy rates between 78.57% and 88.29%. Combining multiple handwriting tasks and classifiers improved diagnostic performance, suggesting that handwriting analysis can offer a cost-effective, non-invasive tool for early AD detection. The study emphasizes the potential of this approach to improve patient outcomes and reduce healthcare costs. The methodology employed in this study aimed to rigorously evaluate the performance of various classifiers in distinguishing between Alzheimer's disease (AD) patients and healthy individuals based on handwriting tasks. The experimental protocol included multiple phases, beginning with a baseline evaluation using the full feature set derived from all 25 tasks. Each classifier was optimized through a 5-fold cross-validated grid search to select the best hyperparameters. To ensure robustness and reduce bias, the dataset was randomly shuffled and split into training and test sets across 20 runs, allowing for comprehensive model evaluation. The Friedman and Nemenyi post-hoc tests were |

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| | applied to statistically assess differences in classifier performance, which helped in identifying significant differences across models. This thorough approach ensured that the results were not skewed by chance, or the randomness of training-test set splits.<br><br>In the task-specific analysis, classifiers were evaluated on individual tasks, revealing that while some classifiers excelled on specific tasks, no single model performed best across all tasks. This further supported the hypothesis that different handwriting tasks elicit unique aspects of motor control, providing a more holistic characterization of AD when combined. The study leveraged both majority-vote based metaclassifier systems and feature-merging techniques to combine task outputs, demonstrating that integrating information from multiple tasks significantly improved classification performance. However, it was noted that combining task-specific classifier outputs generally led to better results than merging feature sets, underscoring the importance of capturing task-specific nuances for accurate diagnosis. |
| **Research Question/Problem/ Need** | Whether a combination of handwriting tasks and machine learning classifiers can effectively discriminate between Alzheimer's disease patients and healthy individuals based on features extracted from their handwriting movements. |
| **Important Figures** | Table 2: Explains the demographic for the study. The standard deviations are also given.<br>Figure 7: Shows how long each task by the AI model requires to complete it as well as the accuracy of each task.<br>Figure 6: Shows a visual of how the results of the tasks can be combined to generate training sets and testing datasets. Each task has a personalized classifier for each task specific vector. The same type of classifier was used to build all 25 task-specific classifiers, and their outputs were aggregated using a majority vote rule to reach the final decision. |
| **VOCAB: (w/definition)** | • The DARWIN dataset contains handwriting samples from people with AD and people without AD.<br>• Temporal Features: Measured the time taken to complete tasks and sub-components of those tasks. For example, Total Time (TT) recorded the total time to finish a task, while Air Time (AT) tracked the time the pen was not in contact with the paper during in-air movements.<br>• Measured Kinematic Features: These features quantified the movement of the pen. This included metrics like Mean Speed on-paper (MSP), Mean Acceleration on-paper (MAP), and Mean Jerk on-paper (MJP), which measured the smoothness and control of movements on the paper. Similar features were calculated for in-air movements.<br>• Multi-classifier Systems: Instead of relying on a single classification model, they explored combining the outputs of multiple models to |

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| | enhance accuracy. They experimented with different combinations, such as combining the outputs of models trained on different handwriting tasks or combining the best-performing models for specific tasks. |
| **Cited references to follow up on** | Pereira, C.R., Weber, S.A.T., Hook, C., Rosa, G.H., Papa, J.P., 2016b. Deep learningaided parkinson's disease diagnosis from handwritten dynamics. In: Proceedings of the SIBGRAPI 2016 - Conference on Graphics, Patterns and Images, pp. 340–346.<br>Pereira et al., 2015<br>Pereira C.R., Pereira D.R., Da Silva F.A., Hook C., Weber S.A.T., Pereira L.A.M., Papa J.P.<br>A step towards the automated diagnosis of parkinson's disease: Analyzing handwriting movements<br>2015 IEEE 28th International Symposium on Computer-Based Medical Systems (2015), pp. 171-176<br>Pereira, C.R., Weber, S.A.T., Hook, C., Rosa, G.H., Papa, J.P., 2016b. Deep learningaided parkinson's disease diagnosis from handwritten dynamics. In: Proceedings of the SIBGRAPI 2016 - Conference on Graphics, Patterns and Images, pp. 340–346. |
| **Follow up Questions** | • This research focused on a single point in time. What would change if the tests were done over a longer period of time (progression of handwriting declining?)?<br>• Could more features, like micro-tremors or pen tilt be recorded to provide more accurate results?<br>• How could this apply to other neurodegenerative disorders |

# Article #4 Notes: PuF, an antimetastatic and developmental signaling protein, interacts with the Alzheimer's amyloid-β precursor protein via a tissue-specific proximal regulatory element (PRE)

Article notes should be on separate sheets

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| **Source Title** | PuF, an antimetastatic and developmental signaling protein, interacts with the Alzheimer's amyloid-β precursor protein via a tissue-specific proximal regulatory element (PRE) |
| **Source citation (APA Format)** | Lahiri, D. K., Maloney, B., Rogers, J. T., & Ge, Y.-W. (2013). PuF, an antimetastatic and developmental signaling protein, interacts with the Alzheimer's amyloid-β precursor protein via a tissue-specific proximal regulatory element (PRE). *BMC Genomics*, *14*(1), 68. https://doi.org/10.1186/1471-2164-14-68 |
| **Original URL** | https://bmcgenomics.biomedcentral.com/counter/pdf/10.1186/1471-2164-14-68.pdf |
| **Source type** | Database |
| **Keywords** | Amyloid precursor protein, Alzheimer's disease, Cancer, Gene regulation, Gene transcription, Iron, Latency, nm23 nucleoside diphosphate kinase, Oncogenesis, PuF, SP1, Specificity protein 1, Transcription factor |
| **#Tags** | #AD #Amyloid_precursor_protein #Amyloid_beta #PRE #PuF_protein #PuF_regulation |
| **Summary of key points + notes (include methodology)** | They studied the role of the 30-nucleotide sequence called Proximal Regulatory Element (PRE) in the promoter region of the Amyloid Precursor Protein (APP) gene in regulating APP's gene expression and its implications on AD. They established that PRE interacts with transcription factors like AP2, PuF, SP1, and USF2 to regulate APP expression. Mutations of PRE that impact (most notably) PuF or SP1 binding sites altered the reporter gene expression and APP regulation. This is mostly relevant to placental mammals because binding sites in these mammals are conserved. Environmental factors were proposed as leading factors of DNA damage, that disrupts the balance of PuF and SP1. They hypothesize this imbalance might increase APP expression and contribute to AD risk. If this hypothesis is true, their previous LEARn model (developed for neurobiological disorders or cancer development) might apply to AD. |

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| | The authors discovered that the PRE in the APP gene interacts with transcription factors, including PuF, which is generally associated with inhibiting harmful cell proliferation, and SP1, in a cell-type-specific manner. This interaction modulates APP gene expression. The researchers observed that mutations in the PRE, specifically those disrupting the predicted PuF/SP1 binding site, significantly affected reporter gene expression. This finding suggests that disruptions to these regulatory mechanisms, potentially due to environmental factors or epigenetic modifications, could lead to dysregulated APP expression, potentially contributing to AD. They used methods such as:<br>• Electrophoretic Mobility Shift Assays (EMSA): This technique was central to the study, allowing them to visualize and analyze the interaction between the PRE and proteins found in extracts from different cell types and tissues. Variations of EMSA, including competition EMSA and antibody-super shift EMSA, were used to confirm the specificity of transcription factor binding and to identify the specific transcription factors interacting with the PRE.<br>• Southwestern Blotting: This technique was used to estimate the molecular weights of proteins interacting with the PRE, providing further evidence for the involvement of specific transcription factors.<br>• Site-Directed Mutagenesis: Used to create specific mutations in the PRE sequence to pinpoint the functional importance of the specific nucleotides.<br>• Reporter Gene Assays: By linking the PRE and its variants to a reporter gene (CAT), the researchers could measure the impact of PRE mutations on APP promoter activity and gene expression levels.<br>• Bioinformatic Analysis: Used to compare PRE sequence across species to assess the evolutionary conservation and used to predict potential transcription factor binding sites in the PRE. |
| **Research Question/Problem/ Need** | What is the role of the proximal regulatory element (PRE) in the regulation of the amyloid-ß precursor protein (APP) gene, and could this regulation be implicated for Alzheimer's disease? |
| **Important Figures** | Figure 1: Shows the results of EMSA and reveals the DNA-protein interactions between PRE and nuclear extracts. This showed that proteins had bound to PRE (with different patterns, and stimuli). This showed that this binding is cell-type-specific and can be influenced externally.<br>Table 1: Lists the predicted transcription factor (TF) binding sites within the APP gene's PRE, along with their corresponding TFs and their molecular weights. It offers a comprehensive view of the potential TFs that could interact with the PRE and thus regulate APP gene expression.<br>Figure 5: Shows consequences of the mutating PRE on APP gene expression using |

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| | Reporter Gene Assays. It is a visual expression of the relative CAT expression in cells with either wildtype PRE or one of the 7 mutated sequences. The figure shows that certain mutations (specifically M1, M5, or M6) significantly reduce CAT expression compared to wildtype, linking PRE mutations to changes in APP promoter activities. |
| **VOCAB: (w/definition)** | PRE (Proximal Regulatory Element): A short DNA sequence located close to a gene's transcription start site that plays a role in regulating the gene's expression.<br>Amyloid-ß peptide: The protein fragment that accumulates in the brain which results in memory loss in people with AD.<br>Site-Directed Mutagenesis: A molecular biology technique used to make specific, intentional changes to the DNA sequence of a gene.<br>APP: Protein from which Aß forms through enzymatic cleavage.<br>Single Nucleotide Polymorphism: A variation in a single nucleotide at a specific position in the DNA sequence that can occur within a population.<br>Transcription Factor: A protein that binds to specific DNA sequences, influencing the rate at which a gene is transcribed into RNA and thereby regulating gene expression.<br>Hypoxia: A condition in which cells or tissues are deprived of adequate oxygen supply.<br>Cytokines: Small signaling proteins that mediate communication between cells (for immune responses). |
| **Cited references to follow up on** | 59. Guyant-Marechal L, Rovelet-Lecrux A, Goumidi L, Cousin E, Hannequin D, Raux G, Penet C, Ricard S, Mace S, Amouyel P, et al: Variations in the APP gene promoter region and risk of Alzheimer disease. Neurology 2007, 68(9):684–687.<br>64. Younkin SG, Eckman CB, Ertekin-Taner N, Kawarabayashi T, Yager D, Baker M, Perez-Tur J, Houlden H, Hutton M, Younkin LH, et al: Genetic elevation of plasma amyloid beta protein in typical late onset Alzheimer's disease. Soc Neurosci Abstr 1998, 24:107<br>18. Lahiri DK, Ge Y-W, Maloney B: Characterization of the APP proximal promoter and 50<br>-untranslated regions: identification of cell-type specific domains and implications in APP gene expression and Alzheimer's disease. FASEB J 2005, 19(6):653–655.<br>34. Lukiw WJ, Rogaev EI, Wong L, Vaula G, McLachlan DR, St George Hyslop P: Protein-DNA interactions in the promoter region of the amyloid precursor protein (APP) gene in human neocortex. Brain Res Mol Brain Res 1994, 22(1–4):121–131. |
| **Follow up Questions** | • Could drugs or gene therapies be developed to modulate PuF or SP1 activity to restore normal APP expression?<br>• Can targeted modifications to the PRE sequence, such as strengthening the PuF binding site or weakening the SP1 bindng site, be used to modulate APP gene expression and reduce Aß production |

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| | in cellular or animal models of AD?<br>• Do other mammalian species with conserved PRE sequences exhibit age-related Aß accumulation or AD-like pathology, and if so, is the PRE implicated in these processes?<br>• What is the specific role of the PRE in regulating APP gene expression in different brain cell types, such as neurons, astrocytes, and microglia?<br>• How does the interaction of PuF and SP1 at the PRE change under conditions of oxidative stress, and how do these changes affect APP gene expression? |

# Article #5 Notes: Tau protein and neurodegeneration

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Tau protein and neurodegeneration |
| **Source citation (APA Format)** | Goedert, M. (2004). Tau protein and neurodegeneration. *Seminars in Cell & Developmental Biology*, *15*(1), 45–49. https://doi.org/10.1016/j.semcdb.2003.12.015 |
| **Original URL** | https://www.sciencedirect.com/science/article/pii/S1084952103001204 |
| **Source type** | Journal article |
| **Keywords** | Alternative mRNA splicing; Amyloid; Frontotemporal dementia; Microtubule assembly; Neurodegeneration; Tau protein |
| **#Tags** | #Tau #Neurodegeneration #AD #Amyloid-Beta |
| **Summary of key points + notes (include methodology)** | • Tau proteins are found in neurons and provide structure to the microtubes in the axon.<br>• They can form abnormal clumps when misfolded and can cause conditions such as Tauopathies or AD.<br>In tauopathies, tau protein becomes misfolded and aggregates into abnormal clumps inside neurons. This process is often accompanied by hyperphosphorylation, where the tau protein is excessively modified with phosphate groups, further contributing to its aggregation. There are six different isoforms of tau in the adult human brain, generated by alternative splicing of the Tau gene. These isoforms differ slightly in their structure, impacting their function and propensity to aggregate. They highlight research on familial forms of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). FTDP-17 is a hereditary neurodegenerative disorder characterized by dementia and movement problems, with prominent tau pathology in the brain. They also identified 2 results caused by mutations in the Tau gene:<br>1. Impaired microtubule binding: Some mutations decrease tau's ability to bind to and stabilize microtubules. This can lead to microtubule breakdown, disrupting essential cellular functions and potentially contributing to neuronal dysfunction. |

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| | 2. Increased aggregation: Other mutations make tau protein more prone to aggregating into filaments. These aggregates can form the toxic tangles characteristic of tauopathies, disrupting neuronal function and leading to cell death.<br>The research also found that Exon 10 of the Tau gene is associated with neurodegenerative diseases. Mutations near the Exon 10 can disrupt the ratio of 3 repeat and 4 repeat isoforms, which has a ratio of around 1:1 in normal adult human brains.<br><br>Methodologies discussed:<br>• Electron microscopy of negatively stained isolated filaments provided images of tau filaments from diseased human brains. This technique allowed them to visualize the structure of tau filaments, showing variation in filament width and spacing between crossovers.<br>• Selected area electron diffraction, X-ray diffraction from macroscopic fibers, and Fourier transform infrared spectroscopy were utilized to study the structure of tau filaments. These methods determined that filaments assembled from either three repeat, or four repeat Tau showed cross-ß structure, a defining feature of amyloid fibers.<br>• Transgenic mouse lines were created that express mutant human tau protein. These models were used to study the effects of tau dysfunction on neurodegeneration. They observed abundant tau filaments and neurodegeneration in mice expressing four-repeat tau with either the P301L or the P301S mutation. |
| **Research Question/Problem/ Need** | Given Exon 10 mutations impact the Tau Protein function and Tauopathies, could mutations affecting Tau filaments be linked to neurodegenerative disease. |
| **Important Figures** | Figure 1: Shows a visual of abnormal tau protein filaments.<br>Figure 2a: Shows schematic of the 6 tau isoforms in the human brain and some mutations in them. |
| **VOCAB: (w/definition)** | • Tauopathies: General term used to describe a group of neurodegenerative diseases caused by the abnormal accumulation of the tau protein in the brain.<br>• Isoforms: Slightly different versions of the same protein, like the six isoforms of the tau protein in the human brain, each with variations in their amino acid sequence |

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| | due to alternative splicing.<br>• Exon: Sequence that carries genetic information for protein synthesis; exon 10 in the Tau gene is significant because of its role in alternative splicing and the resulting tau isoforms.<br>• Microtubules: Long cylindrical structures inside a neuron made of tubulin that maintain cell shape, aid intercellular signals/communication, or cell division. An example of this is the Tau protein when it is not deformed.<br>• Phosphorylation: A process in which phosphor group is added to a protein to influence protein activity, structure, or interactions with other proteins or cells. The tau protein is hyperphosphorylated in tauopathies.<br>• Transgenic: When DNA from a foreign source has been introduced into an organism's genome. This can include mice or C. Elegans that can express mutant human tau protein behavior or structure. |
| **Cited references to follow up on** | [9] Wischik CM, Novak M, Thogersen HC, Edwards PC, Runswick MJ, Jakes R, et al. Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci USA 1988;85:4506–10<br>[17] Goedert M, Jakes R, Crowther RA. Effects of frontotemporal dementia FTDP-17 mutations on heparin-induced assembly of tau filaments. FEBS Lett 1999;450:306–11.<br>[30] Kraemer BC, Zhang B, Leverenz JB, Thomas JH, Trojanowski JQ, Schellenberg GD. Neurodegeneration and defective neurotransmission in a Caenorhabditis elegans model of tauopathy. Proc Natl Acad Sci USA 2003;100:9980–5. |
| **Follow up Questions** | • How do mutations in Tau that affect exon 10 splicing specifically lead to the death of nerve cells?<br>• What are the differences in the structures of tau filaments composed of three-repeat versus four-repeat tau isoforms, and how might these structural differences relate to the extent of their neurological impact?<br>• Could modulating the alternative splicing of Tau exon 10 be a potential therapeutic strategy for tauopathies, and what are the challenges and considerations for developing such therapies? |

# Article #6 Notes: Engineered mesenchymal stem cell-derived extracellular vesicles: A state-of-the-art multifunctional weapon against Alzheimer's disease

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Engineered mesenchymal stem cell-derived extracellular vesicles: A state-of-the-art multifunctional weapon against Alzheimer's disease. |
| **Source citation (APA Format)** | Yin, T., Liu, Y., Ji, W., Zhuang, J., Chen, X., Gong, B., Chu, J., Liang, W., Gao, J., & Yin, Y. (2023). Engineered mesenchymal stem cell-derived extracellular vesicles: A state-of-the-art multifunctional weapon against Alzheimer's disease. *Theranostics*, *13*(4), 1264–1285. https://doi.org/10.7150/thno.81860 |
| **Original URL** | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10008732/ |
| **Source type** | Journal Article |
| **Keywords** | Mesenchymal stem cells; Extracellular vesicles; Alzheimer's disease; Drug delivery; Nanoparticles |
| **#Tags** | #Mesenchymal_stem_cells #AD #Drug_delivery #stem_cells |
| **Summary of key points + notes (include methodology)** | MSC-EVs can treat AD due to their ability to cross the blood-brain barrier (BBB), low immunogenicity, and therapeutic potential inherited from their parent cells, mesenchymal stem cells (MSCs). These cells can be engineered to enhance their therapeutic efficacy against AD using methods like:<br>• Preconditioning: This involves manipulating the parent MSCs' environment before EV isolation. For example, hypoxic preconditioning can increase the levels of hypoxia-inducible factor (HIF-1α), reactive oxygen species (ROS), and anti-inflammatory cytokines, leading to enhanced neuroprotective effects in AD models. Another approach is preconditioning with proinflammatory cytokines like TNF-α and INFγ, which can improve the immunomodulatory capacity of MSC-EVs.<br>• Drug Loading: MSC-EVs can act as carriers for therapeutic cargo, including nucleic acids, proteins, and drugs. For instance, loading MSC-EVs with miR-29b, which is |

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| | downregulated in AD patients, has shown to restore learning function and prevent memory loss in an AD mouse model. Another strategy is overexpressing the Aß-degrading enzyme neprilysin (NEP) in MSCs, leading to increased NEP levels in derived EVs. This approach has been shown to improve memory and cognitive function in AD mice.<br>• Surface Modification: This technique involves modifying the EV surface to enhance targeting specificity. For example, decorating MSC-EVs with the rabies virus glycoprotein (RVG) peptide, which binds to receptors highly expressed in brain cells, enhances EV delivery to the brain, reduces Aß accumulation, and regulates inflammatory responses in AD mice.<br><br>Advantages include:<br>• High biocompatibility and low immunogenicity compared to MSCs or artificial nanoparticles.<br>• High drug delivery efficiency due to their nanoscale size and inherent homing abilities, allowing them to bypass biological barriers and reach target cells in the brain.<br>• Ease of modification using preconditioning, drug loading, and surface modification techniques to enhance their therapeutic efficacy.<br>• Ease of industrialization because human MSCs are easily accessible, highly proliferative, and approved for clinical use.<br>Challenges include:<br>• The very complex and ambiguous composition of MSC-EVs makes it hard to target specific components for therapeutic solutions for AD.<br>• Isolating MSC-EVs with high purity due to the small size and can hinder large scale solutions. |
| **Research Question/Problem/ Need** | What are the advantages and disadvantages of mesenchymal stem cell-derived extracellular vesicles (MSC-EV) therapy for Alzheimer's Disease (AD) as compared to direct MSC therapy? |
| **Important Figures** | Figure 1: Explains the structure of an exosome and where in the cell they can be found and how they enter the cell.<br>Figure 3: Lists different strategies for engineering EVs: “(A) preconditioning of parental cells to enhance the inherent treatment effect; (B) loading of therapeutic cargoes; (C) surface modification; and (D) fabrication of artificial EVs through the top-down disruption of parent cell membranes.” |

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| **VOCAB: (w/definition)** | Mesenchymal Stem Cell-Derived Extracellular Vesicles (MSC-EVs): These are tiny, membrane-bound sacs released by MSCs. MSCs are multipotent stromal cells that can differentiate into various cell types. Extracellular vesicles (EVs), including exosomes, are a type of cell-to-cell communication. They carry various molecules, such as proteins, RNA, and lipids, that can influence the behavior of recipient cells. In Alzheimer's disease, MSC-EVs are being investigated for their therapeutic potential to deliver drugs, reduce inflammation, and promote nerve regeneration.<br><br>Tau Neurofibrillary Tangles: These are another hallmark of AD, formed by the aggregation of hyperphosphorylated tau protein inside neurons, leading to their dysfunction and death.<br><br>Blood-brain barrier: A semipermeable border that separates blood from the brain and fluid in the nervous system. Basically, protecting the brain during drug delivery.<br><br>Astrocytes: Glial cells in the brain that support neurons and contribute to the blood-brain barrier. Dysfunction of astrocytes is implicated in AD, and MSC-EVs may influence their activity.<br><br>Preconditioning: Treating MSCs with specific stimuli, like hypoxia (low oxygen) or pro-inflammatory cytokines, to enhance the therapeutic properties of the EVs they produce. |
| **Cited references to follow up on** | • Tieu A, Lalu MM, Slobodian M, Gnyra C, Fergusson DA, Montroy J, et al. An Analysis of Mesenchymal Stem Cell-Derived Extracellular Vesicles for Preclinical Use. ACS Nano. 2020; 14: 9728-43.<br>• Bachurski D, Schuldner M, Nguyen PH, Malz A, Reiners KS, Grenzi PC, et al. Extracellular vesicle measurements with nanoparticle tracking analysis - An accuracy and repeatability comparison between NanoSight NS300 and ZetaView. J Extracell Vesicles. 2019; 8: 1596016.<br>• Urrutia DN, Caviedes P, Mardones R, Minguell JJ, Vega-Letter AM, Jofre CM. Comparative study of the neural differentiation capacity of mesenchymal stromal cells from different tissue sources: An approach for their use in neural regeneration therapies. PLoS One. 2019; 14: e0213032. |
| **Follow up Questions** | • Can MSC-EVs be engineered to specifically target different subtypes of neurons or brain regions that are vulnerable |

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| | to AD pathology?<br>• Are there any ethical considerations when using MSCs?<br>• What are the potential risks and benefits of using artificial MSC-EVs for AD therapy, and how do these risks and benefits compare to those of using natural MSC-EVs?<br>• What specific protein and RNA components of MSC-EVs are most important for their therapeutic effects in AD, and how can researchers optimize the production of MSC-EVs to maximize the delivery of these beneficial components? |

# Article #7 Notes: Tau Protein and the Neurofibrillary Pathology of Alzheimer's Disease

Article notes should be on separate sheets

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| **Source Title** | Tau Protein and the Neurofibrillary Pathology of Alzheimer's Disease |
| **Source citation (APA Format)** | Goedert, M. (1996). Tau protein and the neurofibrillary pathology of Alzheimer's disease. *Annals of the New York Academy of Sciences*, *777*(1), 121–131. https://doi.org/10.1111/j.1749-6632.1996.tb34410.x |
| **Original URL** | https://nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1111/j.1749-6632.1996.tb34410.x |
| **Source type** | Journal Article |
| **Keywords** | Tau Protein, Neurofibrillary Pathology, Alzheimer's Disease, Protein Phosphatases, Protein Kinases, Hyperphosphorylation |
| **#Tags** | #Tau_protein #AD #PHFs #neurofibrillary_tangles #tau_tangles |
| **Summary of key points + notes (include methodology)** | Tau is a protein primarily found in neurons, where it helps stabilize microtubules, key structures for maintaining cell shape and transport. There are multiple tau isoforms generated through alternative mRNA splicing, meaning the same gene produces different versions of the protein. In the adult human brain, six isoforms have been identified, which differ based on the presence of specific inserts in their structure. The carboxy-terminal half of tau contains three or four tandem repeats, which serve as binding sites for microtubules, an interaction crucial for proper neuronal function.<br><br>Tau undergoes phosphorylation, a process where phosphate groups are added to proteins, influencing their activity. Fetal tau is more heavily phosphorylated than adult tau, but in Alzheimer's, tau becomes hyperphosphorylated, meaning more sites on the protein are phosphorylated than normal. This disrupts tau's ability to bind to microtubules, leading to their breakdown, impairing cell function, and contributing to neuronal damage. Paired helical filaments (PHFs), found in neurofibrillary tangles (NFTs) inside neurons, consist mainly of hyperphosphorylated tau. These PHFs play a significant role in |

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| | the disease, though whether hyperphosphorylation triggers PHF formation or follows it is still unclear.<br><br>Several protein kinases, including glycogen synthase kinase-3 (GSK3) and cyclin-dependent kinase 5 (cdk5), have been shown to phosphorylate tau in ways similar to the abnormal phosphorylation seen in AD. The specific kinases responsible in living systems are still unidentified. Protein phosphatases, such as PP2A, counteract kinases by removing phosphate groups, helping maintain the balance of phosphorylation. A disruption in this balance might contribute to the hyperphosphorylation of tau.<br><br>Methodologies:<br>• Protein Chemistry: This involves studying the structure, properties, and interactions of proteins, such as isolating and characterizing tau protein from different sources.<br>• Molecular Cloning: This technique is used to create copies of DNA fragments, allowing researchers to study specific genes and their protein products, like the tau gene and its isoforms.<br>• Immunohistochemistry: This technique uses antibodies to detect specific proteins in tissue sections, enabling researchers to visualize the distribution and localization of tau in the brain.<br>• Phosphorylation-Dependent Antibodies: These antibodies are designed to recognize and bind to specific proteins only when they are phosphorylated at particular sites. They are valuable tools for studying the phosphorylation status of proteins like tau.<br><br>The research involves developing an in vivo model of PHF formation using transgenic mice. These mice are genetically modified to express the longest human brain isoform of tau in their nerve cells. The researchers observed that human tau in these mice exhibited a different distribution compared to normal mouse tau, accumulating in the cell body and dendrites rather than being concentrated in axons. Furthermore, they found evidence of tau hyperphosphorylation in these transgenic mice. The hope is that these mice will eventually develop PHFs, which would provide a valuable model for studying the progression of neurofibrillary lesions and testing potential therapeutic interventions for AD. |

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| **Research Question/Problem/ Need** | How does the phosphorylation of tau protein relate to Alzheimer's disease? |
| **Important Figures** | • Figure 1 (Schematic Representation of Six Human Brain Tau Isoforms): This figure is important because it provides a clear visual representation of the six different isoforms of the tau protein found in the adult human brain. These isoforms arise from alternative splicing of a single gene. The figure highlights the key structural variations among these isoforms, specifically noting the presence or absence of three inserts in the amino-terminal half of the protein and the consistent presence of three or four tandem repeats in the carboxy-terminal half. Understanding the structural diversity of tau isoforms is essential for grasping the protein's complexity and potential roles in both healthy and diseased neurons.<br>• Figure 2 (PHFs from Alzheimer's Disease Brain and In Vitro Assembled Filaments): This figure provides visual evidence supporting a critical finding discussed in the paper—that tau protein, in a non-phosphorylated form, can self-assemble into filaments that resemble the PHFs found in the brains of individuals with Alzheimer's disease. The figure shows images of PHFs extracted from the brain of an Alzheimer's patient, alongside images of filaments assembled using a non-phosphorylated fragment of the tau protein. The visual similarity between these two types of filaments underscores the idea that tau, under specific conditions, can form the pathological aggregates characteristic of Alzheimer's disease.<br>• Figure 4 (Known Phosphorylation Sites in Fetal Tau, Adult Tau, and PHF-Tau): Shows the concept of hyperphosphorylation in AD. It depicts the known phosphorylation sites on tau protein in three different states: fetal tau, adult tau, and PHF-bound tau. The main takeaway is the difference in phosphorylation patterns between the different stages. PHF-tau exhibits both hyperphosphorylation—meaning it's phosphorylated at more sites—and abnormal phosphorylation, meaning a larger proportion of tau molecules are phosphorylated at these sites compared to fetal or adult tau. |
| **VOCAB: (w/definition)** | • Neuropil threads: Similar in composition to neurofibrillary tangles, these are found in the distal dendrites of nerve cells and are also indicative of Alzheimer's disease. |

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| | • Isoforms: These are slightly different versions of the same protein, arising from variations in gene expression or post-translational modifications.<br>• Neuritic plaques: A type of lesion found in Alzheimer's disease, characterized by a central core of amyloid protein surrounded by abnormal neuronal processes called neurites.<br>• Straight filaments (SFs): A minor component of neurofibrillary lesions in Alzheimer's disease, found alongside the more abundant PHFs.<br>• Paired helical filaments (PHFs): These abnormal filaments, primarily composed of hyperphosphorylated tau protein, are the fibrous component of neurofibrillary tangles and neuropil threads in Alzheimer's disease.<br>• Axonal transport: This is the process by which substances are transported along the axon of a neuron, essential for maintaining neuronal function.<br>• Protein kinases: Enzymes that catalyze the addition of a phosphate group (phosphorylation) to proteins, often regulating their activity.<br>• Tandem repeats: These are short, repeating sequences of amino acids within a protein, which can contribute to the protein's structure, isoforms, and function. |
| **Cited references to follow up on** | • GOEDERT, M, M. G. SPILLANTINI, R. JAKES, D. RUTHERFORD & R. A. CROWTHER. 1989. Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of Alzheimer’s disease. Neuron 3: 5 19- 526.<br>• BRAMBLE^, G. T., M. GOEDERT, R. JAKES, S. E. MERRICK, J. Q. TROJANOWSKI & V. M.-Y. LEE. 1993. Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. Neuron 10:1089-1099. |
| **Follow up Questions** | • How does tau protein's phosphorylation state relate to its ability to bind to microtubules?<br>• Can Tau Protein undergo different post-translational modifications?<br>• What other proteins can interact with Tau like this? |

# Article #8 Notes: Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation

Article notes should be on separate sheets

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| **Source Title** | Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation |
| **Source citation (APA Format)** | Ashrafian, H., Zadeh, E. H., & Khan, R. H. (2021). Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation. *International Journal of Biological Macromolecules*, *167*, 382–394. https://doi.org/10.1016/j.ijbiomac.2020.11.192 |
| **Original URL** | https://www.sciencedirect.com/science/article/pii/S0141813020351308 |
| **Source type** | Database (review) |
| **Keywords** | Dementia, Neurofibrillary tangles, Amyloid precursor protein, Amyloid beta plaques |
| **#Tags** | #AD #Amyloid_precursor_protein #tau_tangles #amyloid_beta |
| **Summary of key points + notes (include methodology)** | ### Alzheimer's Disease: Amyloid Beta Plaques and Tau Tangles<br><br>Alzheimer's disease (AD) is a neurodegenerative disorder primarily characterized by the aggregation of amyloid-beta (Aß) plaques outside neuron cells and tau protein tangles inside the cells. The aggregation of these proteins disrupts neuron function, leading to brain atrophy, and is believed to be a key factor in the development of AD. The role of amyloid precursor protein (APP) in the formation of Aß plaques is discussed, highlighting how these plaques can disrupt signaling between neurons, trigger immune responses that lead to inflammation, and deposit on blood vessels, causing angiopathy. Additionally, tau proteins, which normally stabilize microtubules for intracellular transport, become phosphorylated and clump together to form neurofibrillary tangles, further impairing neuronal function.<br><br>Various approaches to inhibit the formation of Aß plaques and tau tangles have been explored, including the use of natural products, peptides, and small molecules. Studies have investigated the potential of natural products, such as those found in green tea, curcumin, and resveratrol, to inhibit amyloid formation and protect against neurotoxicity. Research has also focused on peptides that can break |

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| | down beta sheets and suppress amyloid-beta fibrillation, as well as small molecule inhibitors that target different stages of amyloid formation. In addition to inhibiting Aß plaque formation, strategies for inhibiting tau tangle formation have been discussed, particularly through the targeting of the enzyme GSK-3ß, which plays a role in tau phosphorylation.<br><br>The claims are heavily supported by scientific studies and research, citing numerous investigations into the mechanisms of AD, the roles of Aß plaques and tau tangles, and potential therapeutic approaches. Illustrations, such as diagrams and microscopic images, visually represent the processes involved in AD. The methodology employed includes a comprehensive review of existing literature on AD, with a particular focus on the inhibition of amyloid plaque and tau tangle formation. This review encompasses studies conducted both in vitro and in vivo, highlighting the diverse range of research efforts aimed at understanding and addressing AD. |
| **Research Question/Problem/ Need** | What are the ways to inhibit the formation of amyloid plaques and tau tangles in order to suppress or postpone Alzheimer's disease? |
| **Important Figures** | • Figure 1: It shows the journey of a protein from its creation in the ribosome to its breakdown in the proteasome, emphasizing that misfolding is a natural cellular occurrence. The figure highlights the formation of disordered aggregates or accumulation of unfolded protein and the role of correctly folded proteins.<br><br>• Figure 2A contrasts a healthy neuron with a neuron affected by AD. In a healthy neuron (top), alpha- and gamma-secretase enzymes process amyloid precursor protein (APP), leading to soluble polypeptides.<br>  ○ In an AD-affected neuron (bottom), the interplay of beta-secretase with gamma-secretase results in the production of amyloid-beta (A-beta), an insoluble peptide that aggregates to form detrimental plaques.<br><br>• Figure 2B shows the three major consequences of amyloid-beta plaque buildup:<br>  ○ Disruption of Signaling: Plaques lodge between neurons, obstructing communication pathways crucial for brain function.<br>  ○ Inflammation: Amyloid-beta plaques trigger an immune response, causing inflammation that can damage neighboring neurons. |

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| | • Figure 3: Shows how tau proteins become phosphorylated and detach from the microtubules, clumping together to form neurofibrillary tangles.<br><br>• Figure 9: It focuses on the enzyme synthase kinase 3 (GSK-3ß) and its role in tau phosphorylation, making it a target for AD treatment.<br>  ○ Figure 9A: identifies the two main functional domains of GSK-3ß: the substrate binding domain (where most ligands bind to GSK-3ß) and the kinase domain (responsible for substrate phosphorylation).<br>• Table 3: This table lists peptide inhibitors designed to combat amyloid-beta formation in AD. These peptides primarily function as "beta-sheet breakers." These are protein structures that contribute to the Aß plaques. The table provides the names, sequences, and testing scales (in vitro or in vivo) for various peptides, showcasing the range of approaches being studied<br>• Table 4: Shows small molecule inhibitors as a method for testing Aß aggregation in AD. The table presents the names, structures, proposed mechanisms of action, and testing scales for different small molecules. It shows the diversity of the molecules and their potential when they interfere with Aß fibrillation through different mechanisms. |
| **VOCAB: (w/definition)** | • Angiopathy: Damage or disease to blood vessels. In AD, this is when Aß plaques accumulate on blood vessel walls and cause weakening.<br>• Apoptosis: A regulated process of cell self-destruction. The paper explains that when tau tangles disrupt microtubule function in neurons, it can lead to apoptosis.<br>• Atrophy: Shrinking of tissue, mainly brain tissue due to neuron death.<br>• Chaperones: These are proteins that assist other proteins in folding correctly. Figure 1 highlights their role in helping newly synthesized proteins achieve their proper 3D structures, preventing misfolding that could lead to disease.<br>• Gyri: Gyri are the characteristic ridges or folds on the surface of the brain. The paper mentions that as the brain shrinks (atrophies) in AD, the gyri become narrower. |

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| | • Kinases: Enzymes that modify other molecules, typically proteins, by adding a phosphate group (phosphorylation). In AD, kinases are involved in phosphorylating tau proteins.<br>• Proteasome: A cellular structure responsible for breaking down proteins that are damaged, misfolded, or no longer needed<br>• Sulci: Sulci are the grooves or furrows on the surface of the brain. In AD, brain atrophy leads to widening of the sulci, another indication of brain tissue shrinkage.<br>• Ventricles: Ventricles are fluid-filled cavities in the brain. In AD, as brain tissue shrinks, the ventricles become larger.<br>• Synapse: A synapse is the junction between two neurons, where nerve impulses are transmitted from one neuron to another. The paper emphasizes the importance of proper tau function for maintaining synapse integrity.<br>• Neuritic Plaques: Abnormal structures found in the brains of individuals with AD, consisting of a core of amyloid-beta surrounded by degenerating nerve fibers. |
| **Cited references to follow up on** | [56] N. Chauhan, K. Wang, J. Wegiel, M. Malik, Walnut extract inhibits the fibrillization of amyloid Beta-protein, and also defibrillizes its preformed fibrils, CAR 1 (2004) 183–188, https://doi.org/10.2174/1567205043332144.<br><br>[64] Y. Wu, Z. Wu, P. Butko, Y. Christen, M.P. Lambert, W.L. Klein, C.D. Link, Y. Luo,<br>Amyloid-induced pathological behaviors are suppressed by Ginkgo biloba extract<br>EGb 761 and ginkgolides in transgenic Caenorhabditis elegans, J. Neurosci. 26<br>(2006) 13102–13113, https://doi.org/10.1523/JNEUROSCI.3448-06.2006.<br><br>[10] A. Boutajangout, T. Wisniewski, Tau-based therapeutic approaches for Alzheimer's disease - a mini-review, Gerontology 60 (2014) 381–385, https://doi.org/10.1159/ 000358875.<br><br>[107] J.G. Wood, S.S. Mirra, N.J. Pollock, L.I. Binder, Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau), Proc. Natl. Acad. Sci. 83 (1986) 4040–4043, https://doi.org/10.1073/pnas.83.11.4040 .<br><br>[112] J.Q. Trojanowski, M.L. Schmidt, R.-W. Shin, G.T. Bramblett, D. |

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| | Rao, V.M.-Y. Lee, Altered tau and neurofilament proteins in neuro-degenerative diseases: diagnostic implications for Alzheimer's disease and Lewy body dementias, Brain Pathol. 3 (1993) 45–54, https://doi.org/10.1111/j.1750-3639.1993.tb00725.x. |
| **Follow up Questions** | • What are the long-term effects and safety profiles of these inhibitors? Have any shown promise in clinical trials for long-term use in humans?<br>• Do the inhibitors discussed exhibit high specificity for their targets, or are there concerns about off-target effects that could lead to unintended consequences?<br>• Are there reliable biomarkers for detecting early tau pathology and monitoring the effectiveness of tau-targeted therapies? How can the development of such biomarkers facilitate clinical trials and treatment strategies?<br>• What is the current understanding of the roles of these other enzymes? |

# Article #9 Notes: A T231E Mutant that Mimics Pathologic Phosphorylation of Tau in Alzheimer's disease Causes Activation of the Mitochondrial Unfolded Protein Response in C. elegans touch neurons

Article notes should be on separate sheets

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| **Source Title** | A T231E Mutant that Mimics Pathologic Phosphorylation of Tau in Alzheimer's disease Causes Activation of the Mitochondrial Unfolded Protein Response in C. elegans touch neurons |
| **Source citation (APA Format)** | Guha, S., Fischer, S., Cheng, A., Johnson, G. V. W., & Nehrke, K. (2020). A T231E Mutant that Mimics Pathologic Phosphorylation of Tau in Alzheimer's disease Causes Activation of the Mitochondrial Unfolded Protein Response in C. elegans touch neurons. *microPublication Biology*, *2020*. https://doi.org/10.17912/micropub.biology.000306 |
| **Original URL** | https://pubmed.ncbi.nlm.nih.gov/32939445/ |
| **Source type** | Article |
| **Keywords** | Alzheimer's disease, Tau protein, Phosphorylation, Mitochondrial unfolded protein response, Touch neurons, HSP-60, Cell-autonomous activation |
| **#Tags** | #Tau_protein #C_elegans #protein response #phosphorylation |
| **Summary of key points + notes (include methodology)** | The impact of Alzheimer's disease-associated tau protein modifications on mitochondrial function in *C. elegans* touch neurons was investigated. The focus was on the T231E tau mutation, which mimics phosphorylation at the threonine 231 residue, a modification implicated in Alzheimer's disease pathogenesis. CRISPR-Cas9 gene editing was used to introduce this mutation into the *C. elegans* genome, and its effects on the mitochondrial unfolded protein response (UPRmt), a cellular stress response pathway activated by mitochondrial dysfunction, were examined.<br><br>Fluorescence microscopy was used to monitor the expression of a |

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| | UPRmt reporter gene (Phsp-60::GFP) in *C. elegans* expressing either wild-type tau or the T231E mutant. Fluorescence intensity in touch neurons and intestinal cells was measured at different ages, specifically day 3 and day 10 of adulthood. Statistical analysis was performed using ANOVA and Tukey's post hoc test to assess significant differences between groups.<br><br>Results showed that the T231E mutant, but not wild-type tau, led to a significant increase in Phsp-60::GFP expression specifically in touch neurons of young adult worms (day 3), suggesting cell-autonomous activation of the UPRmt. This effect was transient and not observed in older worms (day 10). The T231E mutation did not induce a UPRmt in intestinal cells, indicating that the observed effect was localized to neurons. These findings imply that the T231E tau mutation, which mimics a disease-relevant phosphorylation event, can cause mild mitochondrial stress and activate the UPRmt in a cell-specific manner. This localized and transient UPRmt activation could potentially interfere with the neuron's ability to respond to subsequent mitochondrial stress, contributing to the neurodegenerative process in Alzheimer's disease. |
| **Research Question/Problem/ Need** | Does the T231E tau mutation, mimicking a phosphorylation event associated with Alzheimer's disease, cause activation of the mitochondrial unfolded protein response (UPRmt) in C. elegans touch neurons? |
| **Important Figures** | Figure 1A: a table listing the C. elegans strains used in the study. All strains carry transgenes encoding translational fusions of the TauT4 protein and the photoconvertible protein Dendra2, driven by the mec-7 promoter, leading to their expression in touch neurons. Specific mutations were introduced into the TauT4 open reading frame (ORF) using CRISPR-Cas9 gene editing. These mutations include T231A (a phospho-ablation mutation at threonine 231), T231E (a phospho-mimetic mutation at threonine 231), and K274/281Q (an acetyl-mimetic mutation at lysines 274 and 281). The setup is essential for assessing the specific effects of tau protein modifications on mitochondrial stress responses in neurons.<br>Figure 1C: shows fluorescence images of touch neurons from day 3 adult worms expressing the T231E mutant Dendra2::TauT4 translational fusion, with dashed circles indicating the location of the PLM cell body, magnified in the inset. The images show the effects of the T231E mutation on tau expression, facilitating comparisons between the wild-type and mutant strains.<br>Figure 1F: quantifies fluorescence signal intensity in the posterior intestinal region for the strains listed in Figure 1A. The data represent the mean ± SD (N=20 animals from two independent replicates). "ns" denotes not significant, as determined by one-way ANOVA followed by Tukey’s multiple comparisons test. This result demonstrates that |

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| | UPRmt activation is cell-autonomous, as it is observed in touch neurons but not in intestinal cells, supporting the localized effect of the T231E mutation on mitochondrial stress. |
| **VOCAB: (w/definition)** | • Acetylation: the attachment of an acetyl group to a molecule, frequently a protein, and like phosphorylation, it plays a regulatory role in cellular processes, including tau protein localization and function<br>• UPRmt (Mitochondrial Unfolded Protein Response): A cellular stress response pathway specifically activated by the accumulation of unfolded or misfolded proteins within mitochondria.<br>• HSP-60: A mitochondrial chaperone protein whose expression is upregulated during UPRmt activation, making it a useful marker for monitoring UPRmt activity.<br>• Touch Neurons: Neurons responsible for detecting mechanical stimuli, and in this study, they serve as the primary cell type for investigating the effects of tau mutations on the UPRmt.<br>• CRISPR-CAS9: Allows for precise modifications to DNA sequences, enabling researchers to create specific mutations, such as the T231E mutation in tau, for studying their effects on cellular processes. |
| **Cited references to follow up on** | Reddy, P.H. 2011. Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. Brain Res. 1415:136-48 PMID: 21872849.<br><br>Haynes, C.M., K. Petrova, C. Benedetti, Y. Yang, and D. Ron. 2007. ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans. Dev Cell. 13(4). PMID: 17925224.<br><br>Bennett, C.F., H. Vander Wende, M. Simko, S. Klum, S. Barfield, H. Choi, V.V. Pineda, and M. Kaeberlein. 2014. Activation of the mitochondrial unfolded protein response does not predict longevity in Caenorhabditis elegans. Nat Commun. 5:3483 PMID: 24662282. |
| **Follow up Questions** | • Are other neuronal subtypes also susceptible to T231E tau-mediated UPRmt activation?<br>• Could manipulating the UPRmt pathway in T231E-expressing neurons protect against tau-mediated neurotoxicity?<br>• Does T231E tau directly interact with mitochondrial |

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| | proteins involved in protein folding or import, leading to UPRmt activation? |

# Article #10 Notes: Colorimetric protein assay techniques

Article notes should be on separate sheets

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| **Source Title** | Colorimetric protein assay techniques |
| **Source citation (APA Format)** | Sapan, C. V., Lundblad, R. L., & Price, N. C. (1999). Colorimetric protein assay techniques. *Biotechnology and Applied Biochemistry*, *29*(2), 99–108. |
| **Original URL** | https://pubmed.ncbi.nlm.nih.gov/10075906/ |
| **Source type** | Journal Article |
| **Keywords** | Colorimetric protein assays, Protein quantification, Biopharmaceuticals, Biuret method, Lowry method, Bradford assay, BCA assay, Protein composition |
| **#Tags** | #Protein_concentration #Protein_identification #biopharmaceuticals |
| **Summary of key points + notes (include methodology)** | The biuret, Lowry, CB, and BCA methods are used to measure protein concentration. The accuracy of the Lowry, CB, and BCA methods can be affected by protein composition. For biopharmaceutical characterization, a standard protein similar to the sample should be used. If this is impossible, other methods like the biuret assay, micro-Kjeldahl technique, or quantitative amino acid analysis can be used.<br><br>The biuret method is less sensitive than the other methods, but it is not affected by protein composition. The Lowry method is more sensitive, but it is affected by specific amino acids. The CB dye-binding assay is easy and sensitive, but it is affected by protein composition. The BCA assay is sensitive and easy to use, but it is affected by protein composition.<br><br>Several substances can interfere with these methods. For example, Tris buffer, ammonium ions, and glycerol can interfere with the biuret method. Nitrogen-containing buffers can interfere with the Lowry method. Protein glycosylation can interfere with the CB dye-binding assay. Many substances can interfere with the BCA assay.<br><br>It is important to validate the assay to ensure accurate protein quantification. This includes verifying the sample protein concentration, validating each sample type for potential interfering substances, and selecting a standard protein that represents the |

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| | sample. GLP and cGMP guidelines should be followed to ensure reliable results in biopharmaceutical production. |
| **Research Question/Problem/ Need** | Examining the accuracy and reliability of commonly used colorimetric protein assays and what advantages each one has. |
| **Important Figures** | Had no figures |
| **VOCAB: (w/definition)** | • Colorimetric/Chromogenic: Refers to methods that detect proteins based on color change, crucial for quantifying protein concentration.<br>• Biuret Reaction: A chemical reaction forming a purplish-violet complex between cupric ions and peptide bonds, fundamental to the Biuret method for protein quantification.<br>• Bicinchoninic Acid (BCA) Assay: A technique that detects cuprous ions formed by protein interactions, widely used for determining protein concentration due to its sensitivity.<br>• Dye-Binding: Interaction between proteins and dyes like Coomassie Blue, forming a colored complex that aids in determining protein amounts, such as in the Bradford assay.<br>• Metachromatic Response: A change in a dye's absorption spectrum upon protein binding, as seen in assays like the Coomassie Blue method.<br>• Folin Phenol Reagent: Used in the Lowry method to enhance the color change for increased sensitivity by reacting with specific amino acids (tyrosine and tryptophan).<br>• Assay Validation: The process of ensuring that a protein assay meets predefined standards for accuracy, sensitivity, and precision to guarantee reliable results. |
| **Cited references to follow up on** | Diezel, W., Kopperschlager, G. and Hoffman, E. (1972) Anal. Biochem. 48, 617–620<br>Albu, M. (1996) Sci. Comput. Automation, May, 29–32 |
| **Follow up Questions** | • How can the potential impact of protein modifications, such as phosphorylation, on colorimetric protein assays be assessed and mitigated?<br>• How do colorimetric protein assays compare to other protein quantification methods, such as those based on fluorescence or UV absorbance?<br>• How does the choice of standard impact the accuracy of a |

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| | colorimetric protein assay, and what factors should be considered when selecting a standard? |

# Patent #1 Notes: Cardiosphere-Derived Cells and Their Extracellular Vesicles for Treatment and Prevention of Cancer

Article notes should be on separate sheets

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| **Source Title** | Cardiosphere-Derived Cells and Their Extracellular Vesicles for Treatment and Prevention of Cancer |
| **Source citation (APA Format)** | (Marban & Grigorian, 2023)<br>Marban, E., & Grigorian, L. (2023). Cardiosphere-derived cells and their extracellular vesicles for treatment and prevention of cancer (Patent No. 3661526:B1). In *European Patent* (3661526:B1). |
| **Original URL** | https://patents.google.com/patent/EP3661526B1/en |
| **Source type** | Patent |
| **Keywords** | Extracellular Vesicles (EVs), Membrane-Tethered TGF-beta, Biomarkers, MSCs, Drug Delivery |
| **#Tags** | #Biomarkers #MSCs #MSC-EV #EVs #Mesenchymal_stem_cells |
| **Summary of key points + notes (include methodology)** | The patent introduces transforming growth factor-beta (TGF-ß) as a key regulator of biological functions like cell proliferation, survival, and differentiation. While soluble TGF-ß has been studied in inflammatory diseases, its use as a reliable indicator of patient response is limited. The patent highlights the discovery of TGF-ß tethered to the membrane of extracellular vesicles (EVs), particularly those derived from mesenchymal stromal cells (MSCs). These EVs, referred to as "MSC-derived membrane-tethered TGF-ß EVs," show significant immunomodulatory potential.<br><br>Some methodologies discussed were:<br>• Isolating MSC membrane-tethered TGF-ß EVs: They could do this by culturing MSCs and then isolating the EVs from the culture medium by one or more of affinity column chromatography, immune affinity capture, tangential flow filtration, precipitation, differential ultracentrifugation, density gradient centrifugation, or size exclusion chromatography.<br>• Modifying TGF-ß tethering to EVs: By pre-conditioning |

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| | MSCs with hypoxia or immune mediators like interferon-gamma (IFNY), tumor necrosis factor (TNF), lipopolysaccharide (LPS), and interleukin 17 (IL-17).<br>• Loading EVs with agents: Can load these therapeutic agents (like polynucleotides, polypeptides, and small molecules, for targeted delivery) into the EVs.<br><br>They found that these EVs can exhibit immunomodulatory effects, and can suppress the proliferation of T cells, showing they can regulate immune responses. Diseases caused by immune dysregulations, like autoimmune disorders, inflammatory diseases, and transplant rejection, where the immune response is heightened, can be use cases for these EVs as they could be administered to suppress the overactive immune system and provide therapeutic benefits. This patent mostly concentrated on cancer, where they found that these EVs can be suppressed, and the body's natural defenses can take over.<br><br>Finally, the levels of TGF-ß tethered to EVs can be used as a biomarker for disease diagnosis. The patent also proposes using these EVs as a targeted drug delivery system. By loading them with therapeutic agents like polynucleotides, polypeptides, or small molecules, these EVs could potentially deliver the treatment directly to cells and tissues expressing TGF-ß receptors, improving treatment efficiency and reducing other effects. |
| **Research Question/Problem/ Need** | Are there any other -- more bioactive and larger sample sizes -- indicators of disease activity other than soluble TGF-ß? |
| **Important Figures** | • Figure 2: This figure shows the results of flow cytometry analysis, which was used to confirm the presence of TGF-ß on the surface of EVs. This figure is important because it provides direct evidence for the central concept of the patent—that TGF-ß is tethered to the membrane of EVs, and this membrane-bound form has distinct biological effects.<br>• Figure 6A: This figure demonstrates the dose-dependent suppression of CD4+ T cell division by MSC-derived EVs. This figure is crucial as it highlights the therapeutic potential of these EVs in suppressing immune responses, particularly in conditions where an overactive immune system is a key driver of the disease.<br>• Figure 9C: This figure shows a Western blot analysis revealing that TGF-ß associated with EVs is primarily in a latent form. This finding is significant because it demonstrates that the TGF-ß carried by these EVs |

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| | requires activation to exert its biological effects. This information is important for developing therapies that aim to either enhance or inhibit the activity of these EVs by modulating the activation state of their TGF-ß cargo. |
| **VOCAB: (w/definition)** | • Transforming Growth Factor Beta (TGF-ß): This is a type of protein that plays a role in numerous cellular processes, including cell growth, differentiation, and immune regulation. It can have both stimulatory and inhibitory effects on cell behavior, depending on the context.<br>• Membrane-Tethered: This term means that a molecule, in this case, TGF-ß, is attached to the surface of a cell or vesicle's membrane. It is not floating freely. This attachment is often important for its biological activity.<br>• Biomarker: This is a measurable indicator of a particular biological state or condition. In the context of this patent, the level of TGF-ß tethered to EVs could be used as a biomarker to track disease activity or predict response to treatment.<br>• Immune Mediators: These are molecules that regulate immune responses. They can be produced by various cells of the immune system and act as signals to coordinate immune activity. The patent explores the use of immune mediators to stimulate the production of EVs with membrane-tethered TGF-ß.<br>• Immunomodulation: This refers to the ability to regulate or adjust the immune system's activity. It can involve either suppressing or enhancing immune responses, depending on the desired outcome. |
| **Cited references to follow up on** | - (Not cited but suggested) https://patents.google.com/scholar/12499123687201096535<br>- https://patents.google.com/patent/WO2012087241A1/en |
| **Follow up Questions** | • How can these EVs be used to target Tau proteins?<br>• Are there specific enzymes or microenvironmental cues that regulate this activation process?<br>• What is the baseline level of TGF-ß EBs? |

# Patent #2 Notes: Extracellular vesicles comprising membrane-tethered tgf-beta, compositions and methods of use thereof

Article notes should be on separate sheets

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| **Source Title** | Extracellular vesicles comprising membrane-tethered tgf-beta, compositions and methods of use thereof |
| **Source citation (APA Format)** | (Hoffman, 2020)<br>Hoffman, A. M. (2020). Extracellular vesicles comprising membrane-tethered tgf-beta, compositions and methods of use thereof (Patent No. 20200392219:A1). In *US Patent* (20200392219:A1). https://patents.google.com/patent/US20200392219A1/ |
| **Original URL** | https://patents.google.com/patent/US20200392219A1/en |
| **Source type** | Patent |
| **Keywords** | Extracellular Vesicles (EVs), Membrane-Tethered TGF-beta, Biomarkers, MSCs, Drug Delivery |
| **#Tags** | #Biomarkers #MSCs #MSC-EV #EVs #Mesenchymal_stem_cells |
| **Summary of key points + notes (include methodology)** | The patent employs a multi-pronged methodology to investigate the potential of MSC-derived EVs with membrane-tethered TGF-ß. The researchers first confirm the presence of TGF-ß on the EV surface using flow cytometry, as depicted in Figure 2. This technique allows for the identification and quantification of specific molecules on the surface of cells or vesicles. The researchers then demonstrate the functional effects of these EVs by assessing their impact on CD4+ T cell division, a key aspect of immune regulation. Figure 6A shows the dose-dependent suppression of T cell division by MSC-derived EVs, highlighting their potent immunosuppressive properties. The patent also explores methods for isolating and purifying EVs carrying membrane-tethered TGF-ß, including techniques like differential ultracentrifugation, density gradient centrifugation, and size exclusion chromatography. This emphasis on EV isolation and characterization is crucial for developing standardized and scalable therapeutic preparations.<br>The results presented in the US patent underscore the potential of |

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| | MSC-derived EVs with membrane-tethered TGF-ß as both therapeutics and diagnostics. The patent demonstrates the ability of these EVs to effectively suppress T cell responses in vitro, suggesting their potential application in treating conditions characterized by an overactive immune system, including cancer, autoimmune disorders, and inflammatory conditions. The patent also proposes using these EVs as biomarkers for disease diagnosis and prognosis. By quantifying the levels of EVs carrying membrane-tethered TGF-ß in biological samples, the patent suggests that clinicians could gain valuable insights into disease activity, treatment response, and potential recurrence. This dual focus on therapeutic and diagnostic applications highlights the multifaceted potential of this novel approach. |
| **Research Question/Problem/ Need** | Are there any other -- more bioactive and larger sample sizes – therapeutic drug delivery systems that target immune responses other than soluble TGF-ß? |
| **Important Figures** | Figure 2: Confirms the presence of TGF-ß on the surface of EVs using flow cytometry analysis. This figure provides direct evidence for the central concept of the patent – membrane-bound TGF-ß on EVs.<br><br>Figure 6A: Demonstrates the dose-dependent suppression of CD4+ T cell division by MSC-derived EVs. This figure highlights the therapeutic potential of these EVs in suppressing immune responses, a key aspect of the patent's focus. |
| **VOCAB: (w/definition)** | CD4+ T cells: T helper cells are crucial for immunomodulation. They coordinate the immune responses against pathogens and diseases. |
| **Cited references to follow up on** | • Yu et al, Exosomes Derived from Mesenchymal Stem Cells, Int. J. Mol. Sci. 15: 4142-4157, 2014 *<br>• https://patents.google.com/patents/US20100111916A1<br>• https://patents.google.com/patent/US20150190429A1 |
| **Follow up Questions** | • What are the methods for preparing exosomes or other EVs?<br>• Can these EVs be engineered for Tau proteins?<br>• What are the possible routes of administration for CDC-EVs, and what are the corresponding dosage ranges? |

# Article #11 Notes: Computational studies of tau protein : implications for the pathogenesis and treatment of neurodegenerative diseases

Article notes should be on separate sheets

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| **Source Title** | Computational studies of tau protein : implications for the pathogenesis and treatment of neurodegenerative diseases |
| **Source citation (APA Format)** | (Huang, 2009)<br>Huang, A. (2009). *Computational studies of tau protein : implications for the pathogenesis and treatment of neurodegenerative diseases* [Massachusetts Institute of Technology]. https://dspace.mit.edu/handle/1721.1/54453?show=full?show=full |
| **Original URL** | https://dspace.mit.edu/handle/1721.1/54453?show=full?show=full |
| **Source type** | Doctoral Thesis |
| **Keywords** | Tau protein, Implicit Solvent Models, Molecular Dynamics, Alzheimer's disease, Intrinsically disordered proteins |
| **#Tags** | #Tau_proteins #hyperphosphorylation #treatment |
| **Summary of key points + notes (include methodology)** | The structural properties of tau protein are studied as it is the main component of neurofibrillary tangles found in Alzheimer's disease (AD), which is a neurodegenerative disorder recognized for causing memory loss, cognitive dysfunction, and behavioral disturbances. Neurofibrillary tangles are established as a key feature of AD, which affects millions of individuals globally and is the most common cause of senile dementia. The investigation of tau protein poses challenges due to its classification as an intrinsically disordered protein (IDP). Unlike most proteins that possess fixed structures, IDPs exist in numerous conformations under physiological conditions, which complicates their study. However, despite this inherent disorder, IDPs may still exhibit some residual structural preferences that are crucial to understanding their propensity for forming protein aggregates. Molecular dynamics (MD) simulations are primarily employed to |

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| | explore the structural tendencies of tau protein, as this computational approach provides atomic-level details regarding protein behavior and interactions, extending insights beyond experimental limitations. Specific regions of tau protein, such as the PHF6* sequence—a six-amino-acid segment located within the third microtubule-binding repeat domain—are highlighted for their significance in aggregation. This sequence is identified as the minimal region required for in vitro aggregation and is found in the MTBR2 (second microtubule-binding repeat) domain, which harbors mutations linked to increased tau aggregation. A specific mutation, AK280, which replaces a lysine (K) residue with a neutral alanine (A) at position 280, is of particular interest due to its association with enhanced tau aggregation, suggesting that structural properties and aggregation propensity are influenced by such mutations. In the context of MD simulations, implicit solvent models are used to simulate the effects of surrounding water molecules on tau protein, which enhances computational efficiency by approximating solvent effects through a potential of mean force without the need for explicit simulation of individual water molecules. The accuracy of these implicit models is tested against explicit solvent simulations where water molecules are represented, leading to the evaluation of various implicit solvent models in their ability to reproduce the potential energy minima obtained from explicit solvent simulations. It is observed that implicit solvent models can accurately capture local energy minima for certain peptides, such as the PHF6 sequence, thereby demonstrating their utility in studying tau protein aggregation.<br><br>To model the residual structure in larger regions of tau protein, a novel method known as Energy-minima Mapping and Weighting (EMW) is developed, which samples energetically favorable conformations within an IDP and utilizes these structures to construct ensembles that align with experimental data, providing a comprehensive representation of the IDP's conformational space. The EMW method encompasses three primary steps: first, high-temperature MD simulations are performed, followed by energy minimization of the resulting structures, generating a library of diverse conformations; second, a subset of structures is selected from this library, and weights representing their relative prevalence are assigned, with these weights optimized to minimize discrepancies between calculated data and experimental results; finally, additional experimental data not used in model construction is employed to validate the resulting ensembles. This method offers a robust approach that accounts for the dynamic nature of IDPs, capturing the diversity of conformations present. Using the EMW method, it is found that disease-associated forms of tau, including those with the AK280 mutation, exhibit a preference for extended conformations near the aggregation-initiating region (PHF6*), which may facilitate the propagation of the cross-β structure |

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| | linked to aggregated forms of tau. The findings suggest that the aggregation capacity of tau protein is rooted in the inherent properties of its protein backbone, particularly its propensity to form intermolecular hydrogen bonds leading to the cross-β structure. This insight aligns with growing evidence that amyloidogenic proteins, such as tau, aggregate through partially folded intermediates exhibiting this specific structure. Acknowledged limitations in current methods for characterizing IDPs, including tau protein, arise from the vast conformational space available to IDPs and the challenges in correlating experimental data with specific conformations. Future research directions are proposed to refine implicit solvent models tailored for unfolded proteins, incorporate additional experimental data, and explore segment-based models that divide the protein into smaller segments for independent sampling, aiming to improve computational efficiency. Ultimately, the goal of this research is to leverage structural insights to design effective therapeutics targeting tau protein, including strategies to inhibit tau aggregation or stabilize non-aggregating conformations, contributing to the ongoing efforts to unravel the structural complexities of tau protein and its implications for Alzheimer's disease. Through the combination of molecular dynamics simulations, innovative modeling techniques, and experimental data, valuable insights into the conformational preferences of tau and their role in aggregation are obtained, with promising potential for developing effective strategies to combat neurodegenerative diseases in the future. |
| **Research Question/Problem/ Need** | How do the structural properties of tau protein's conformational preferences in the unfolded state, contribute to its aggregation and the formation of neurofibrillary tangles in Alzheimer's disease? |
| **Important Figures** | Figure 1 shows the primary structure of the common isoforms of proteins involved in neurodegenerative diseases, including Amyloid Precursor Protein (APP), Tau, and α-synuclein. This figure is important because key proteins implicated in these disorders are highlighted, emphasizing the role of intrinsically disordered proteins (IDPs) like Tau and α-synuclein.<br><br>Figure 5 shows the root-mean-square (RMS) fluctuations of the PHF6 peptide during molecular dynamics simulations in various solvent models. The significance of this figure lies in its demonstration that implicit solvent models can reasonably reproduce the dynamic behavior of the peptide observed in explicit solvent simulations, supporting their use for studying tau protein.<br><br>Figure 9 shows minimum pairwise distance (MPD) plots comparing the structural similarity between energy minima obtained from explicit solvent simulations and three different implicit solvent models (GB, GBSW, and EEF1). This figure is crucial as it shows that all three implicit |

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| | solvent models tested can effectively capture the major conformational states of the PHF6 peptide identified by explicit solvent simulations.<br><br>Figure 11 shows the potential of mean force (PMF) plots for the PHF6 peptide in various solvent models, revealing the free energy landscape of the peptide as a function of its radius of gyration. The importance of this figure is highlighted by its indication that all tested implicit solvent models predict an extended conformation as the most favorable state for the PHF6 peptide, consistent with explicit solvent simulations and suggesting their validity for studying IDP behavior.<br><br>Figure 13 shows the relative energies of minima obtained from simulations using different implicit solvent models, illustrating the energy distribution of various PHF6 conformations. This figure is significant because it shows that the EEF1 implicit solvent model can accurately predict the most stable conformation of PHF6 without the need for extensive umbrella sampling.<br><br>Figure 15 shows a schematic outline of the Energy-minima Mapping and Weighting (EMW) method developed to model IDPs. The importance of this figure is underscored by its introduction of the key steps involved in constructing ensembles of IDP conformations that are consistent with experimental data.<br><br>Figure 18 shows the amino acid sequences of the wild-type (WT) and AK280 mutant forms of the MTBR2 region of tau. This figure is important because the location of the AK280 mutation within the MTBR2 domain is highlighted, allowing for direct comparison of the PHF6* sequence in both the WT and mutant sequences.<br><br>Figure 23 shows the concept of sampling an unfolded protein conformation using peptide segments. This figure is significant as it shows the segment model as an alternative approach for modeling IDPs, offering a potentially more computationally efficient way to explore the conformational space of these proteins. |
| **VOCAB: (w/definition)** | • Intrinsically Disordered Proteins (IDPs): Proteins that lack a stable, well-defined three-dimensional structure in solution.<br>• Paired Helical Filament 6 (PHF6): A six-residue peptide sequence (VQIVYK) found in the tau protein that is essential for tau aggregation in vitro.<br>• Implicit Solvent Model: A computational model that simplifies the representation of solvent molecules, reducing computational cost while approximating solvent effects on the solute. |

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| | • Quenched Molecular Dynamics (QMD): A molecular dynamics simulation technique where the system's kinetic energy is periodically removed and the structure is minimized, allowing for efficient exploration of energy minima.<br>• Conformational Sampling: The process of exploring the different three-dimensional shapes a molecule can adopt, often using computational techniques like molecular dynamics simulations.<br>• Microtubule-Binding Repeat (MTBR): A repeated sequence in tau proteins that is responsible for binding to microtubules.<br>• |
| **Cited references to follow up on** | A. K. Dunker, I. Silman, V. N. Uversky, and J. L. Sussman, "Function and structure of inherently disordered proteins," Curr Opin Struct Biol, vol. 18, pp. 756-64, Dec 2008.<br><br>R. Bussell and D. Eliezer, "Residual structure and dynamics in Parkinson's disease-associated mutants of alpha-synuclein," Journal Of Biological Chemistry, vol. 276, pp. 45996-46003, Dec 7 2001.<br><br>M. Coles, W. Bicknell, A. A. Watson, D. P. Fairlie, and D. J. Craik, "Solution structure of amyloid beta-peptide(1-40) in a water-micelle environment. Is the membrane-spanning domain where we think it is?," *Biochemistry,* vol. 37, pp. 11064-77, Aug 4 1998. |
| **Follow up Questions** | • Beyond AD, which other neurodegenerative disorders are linked to the aggregation of IDPs, and what are the common themes in their pathogenesis?<br>• How do implicit solvent models affect the accuracy of conformational sampling for IDPs compared to explicit solvent models?<br>• What are the limitations of current methods in accurately predicting the conformations adopted by IDPs? |

# Article #12 Notes: Satellite repeat transcripts modulate heterochromatin condensates and safeguard chromosome stability in mouse embryonic stem cells

Article notes should be on separate sheets

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| **Source Title** | Satellite repeat transcripts modulate heterochromatin condensates and safeguard chromosome stability in mouse embryonic stem cells |
| **Source citation (APA Format)** | Novo, C. L., Wong, E. V., Hockings, C., Poudel, C., Sheekey, E., Wiese, M., Okkenhaug, H., Boulton, S. J., Basu, S., Walker, S., Kaminski Schierle, G. S., Narlikar, G. J., & Rugg-Gunn, P. J. (2022). Satellite repeat transcripts modulate heterochromatin condensates and safeguard chromosome stability in mouse embryonic stem cells. *Nature Communications*, *13*(1), 1–16. https://doi.org/10.1038/s41467-022-31198-3 |
| **Original URL** | https://www.nature.com/articles/s41467-022-31198-3 |
| **Source type** | Journal article |
| **Keywords** | Heterochromatin, MSR, MSR transcripts, HP1alpha, Phase separation, Embryonic stem cells, Chromocenters, FRAP, Chromatin compaction |
| **#Tags** | #Stem_cells #heterochromatin #MSR_transcript_levels |
| **Summary of key points + notes (include methodology)** | A study was conducted to examine the effects of major satellite repeat (MSR) transcripts on heterochromatin structure in mouse embryonic stem cells (ESCs). The study focused on the dynamic behavior of heterochromatin and the role of MSR transcripts in maintaining chromosome stability in ESCs. Findings showed that MSR transcripts were crucial for preserving a liquid-like, dynamic state in heterochromatin, which allowed chromocenters to coalesce and separate easily. Time-lapse imaging and fluorescence recovery after photobleaching (FRAP) were used to observe the mobility of molecules within chromocenters. A high degree of mobility was seen, suggesting that MSR transcripts facilitated a more fluid organization of heterochromatin. When MSR transcripts were depleted using specific locked nucleic acid (LNA) gapmers, molecular mobility within chromocenters was reduced. This result indicated a shift toward a |

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| | more static and compact heterochromatin state, which closely resembled the organization found in differentiated cells.<br><br>Further analysis revealed that MSR transcripts influenced heterochromatin organization through their interaction with HP1α, a protein known to play a role in phase separation. In vitro assays demonstrated that the addition of MSR RNA to HP1α prompted the formation of droplets, supporting the hypothesis that MSR transcripts regulate HP1α's behavior in chromocenters. When MSR transcripts were depleted, HP1α was observed to cluster into smaller, denser cores within chromocenters, while chromatin binding increased, indicating heightened chromatin compaction. Additionally, chromocenter organization in ESCs became altered, leading to an increase in chromocenter number and a decrease in size. This altered state mirrored that of differentiated cells and highlighted the significant role of MSR transcripts in maintaining the characteristic heterochromatin architecture of ESCs. Overall, the study demonstrated that MSR transcripts are essential for the unique heterochromatin dynamics and chromosome stability in ESCs, employing techniques such as live-cell imaging, FRAP, and RNA-FISH to confirm their impact on heterochromatin organization. |
| **Research Question/Problem/ Need** | What role do MSR transcripts play in regulating the dynamics and organization of constitutive heterochromatin in mouse ESCs? |
| **Important Figures** | • Figure 1: Heterochromatin forms liquid-like condensates in embryonic stem cells. This is important because it establishes the dynamic nature of heterochromatin in ESCs, setting the stage for investigating the role of MSR transcripts in modulating this behavior.<br>• Figure 3: Satellite RNA promotes the phase-separation of the heterochromatin protein HP1α. It provides a molecular mechanism by which MSR transcripts might contribute to the liquid-like properties of heterochromatin by enhancing the ability of HP1a to form phase-separated droplets.<br>• Figure 5: Shows chromocenter architecture protects chromosome stability in embryonic stem cells. Shows functional consequence of disrupting MSR transcript levels, linking the altered heterochromatin state to chromosome instability. |
| **VOCAB: (w/definition)** | • heterochromatin: a tightly packed form of DNA in the nucleus associated with gene silencing and structural chromosome organization.<br>• condensates: membraneless compartments within cells |

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| | that form through phase separation and concentrate specific molecules for various cellular processes.<br>• major satellite repeats (MSR): highly repetitive DNA sequences located in the centromeric regions of chromosomes in mice, usually silenced but transcribed in certain cell types like embryonic stem cells.<br>• chromocenters: dense, distinct nuclear structures where heterochromatin from different chromosomes clusters, enriched in HP1α and H3K9me3.<br>• fluorescence recovery after photobleaching (FRAP): a technique to study molecular mobility by bleaching a cell region with a laser and measuring the rate of fluorescence recovery in that region.<br>• ɣH2AX: a phosphorylated form of the histone protein H2AX, serving as a marker of DNA damage and identifying double-strand DNA breaks.<br>• TALE (transcription activator-like effector): DNA-binding proteins engineered to target specific sequences, often fused with fluorescent proteins or activators/repressors to study gene regulation and DNA visualization. |
| **Cited references to follow up on** | Rea, S. et al. Regulation of chromatin structure by site-specific histone H3 methyltransferases. *Nature* **406**, 593–599 (2000).<br><br>Lachner, M., O'Carroll, D., Rea, S., Mechtler, K. & Jenuwein, T. Methylation of histone H3 lysine 9 creates a binding site for HP1 proteins. *Nature* **410**, 116–120 (2001).<br><br>Larson, A. G. et al. Liquid droplet formation by HP1α suggests a role for phase separation in heterochromatin. *Nature* **547**, 236–240 (2017). |
| **Follow up Questions** | • What transcription factors regulate expression of MSR transcripts in ESCs and how do their levels change during differentiation?<br>• how does the unusual heterochromatin configuration in ESCs affect the expression of genes located near MSR regions?<br>• Given the link between MSR transcript depletion and chromosome instability, are there any compensatory |

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| | mechanisms in ESCs that can mitigate these effects in the short term? |

# Article #13 Notes: ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans

Article notes should be on separate sheets

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| **Source Title** | ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans |
| **Source citation (APA Format)** | Haynes, C. M., Petrova, K., Benedetti, C., Yang, Y., & Ron, D. (2007). ClpP mediates activation of a mitochondrial unfolded protein response in C. elegans. *Developmental Cell*, *13*(4), 467–480. https://doi.org/10.1016/j.devcel.2007.07.016 |
| **Original URL** | https://pubmed.ncbi.nlm.nih.gov/17925224/ |
| **Source type** | Journal Article |
| **Keywords** | PROTEINS |
| **#Tags** | #Protein_folidng #c_elegans |
| **Summary of key points + notes (include methodology)** | The signaling pathway linking the mitochondrial folding environment to nuclear genes encoding mitochondrial chaperones was investigated, focusing on key genes involved in the mitochondrial unfolded protein response (UPRmt) in C. elegans. An epistatic relationship was identified among clpp-1, dve-1, and ubl-5, with these genes acting as major components in UPRmt signaling. Activation of the UPRmt involves communication between mitochondrial stress signals and transcriptional responses in the nucleus, enabling cells to address the buildup of unfolded proteins within mitochondria. Findings indicate that clpp-1 functions at an upstream step within mitochondria, while dve-1 and ubl-5 act in later nuclear stages. DVE-1 binds to promoters of chaperone genes in the nucleus, and ubl-5 forms a complex with DVE-1 that binds to the same promoters, enhancing chaperone expression under stress. Mitochondrial stress induces the relocation of DVE-1 to the nucleus, where it forms complexes with UBL-5. These findings suggest that clpp-1 aids in signal generation within mitochondria, while dve-1 and ubl-5 respond within the nucleus to help maintain mitochondrial integrity.<br><br>A genome-wide RNAi screening process identified UPRmt-related genes by targeting over 16,000 genes in a temperature-sensitive |

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| | mutant strain of C. elegans that activates the UPRmt at elevated temperatures. The RNAi screen used a strain with a fluorescent reporter gene linked to a chaperone, allowing observation of changes in fluorescence under mitochondrial stress. Stringent criteria selected RNAi clones specifically impairing the mitochondrial response without affecting responses to ER stress. Additional tests assessed candidate genes' effects on fitness under mitochondrial stress, selecting genes required for mitochondrial stress signaling. Only four genes passed these criteria, with three (later identified as dve-1, ubl-5, and clpp-1) identified as key players in the UPRmt. Further experiments, including gene localization, binding assays, and transcriptional activity assessments, confirmed the distinct but interdependent roles of these genes in responding to mitochondrial stress. |
| **Research Question/Problem/ Need** | What are the regulatory links between the protein folding environment in the mitochondrial matrix and the nuclear genes that encode mitochondrial chaperones? |
| **Important Figures** | Figure 1 shows that knocking down dve-1 reduces UPRmt activity by decreasing the expression of hsp-60pr::gfp in stressed zc32 mutant animals. It shows dve-1's specific role in the mitochondrial unfolded protein response, as its knockdown does not affect other stress responses.<br><br>Figure 2 shows that DVE-1 is a nuclear protein crucial for maintaining mitochondrial mass and morphology. It shows that dve-1 is essential for both developmental processes and mitochondrial function.<br><br>Figure 3 shows that DVE-1 relocates in response to mitochondrial stress, forming nuclear puncta and binding to promoters of mitochondrial chaperone genes. It shows DVE-1's role as a transcription factor that activates chaperone genes during mitochondrial stress.<br><br>Figure 4 shows that UBL-5 is required for the UPRmt, and it forms a complex with DVE-1 under mitochondrial stress. It shows a cooperative role between UBL-5 and DVE-1 in activating the mitochondrial unfolded protein response.<br><br>Figure 7 shows that the expression of ubl-5 in response to elevated temperatures depends on the proteolytic activity of CLPP-1. It shows the role of CLPP-1 in initiating the mitochondrial unfolded protein response through proteolysis. |
| **VOCAB: (w/definition)** | • CLPP-1: A protease that plays a critical role in the mitochondrial unfolded protein response by degrading misfolded proteins.<br>• UBL-5: Protein that regulates mitochondrial chaperone gene |

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| | expression during cellular stress.<br>• UPRmt: Maintains mitochondrial function and cellular homeostasis under stress conditions.<br>• HSP-60: Helps the proper folding of new mitochondrial proteins and is important for mitochondrial health.<br>• MitoTracker: Florescent die used to stain mitochondria.<br>• RNA interference (RNAi): Knocks down gene expression, facilitating the identification of key components involved in the UPRmt.<br>• Colocalization: observation of the spatial overlap between two (or more) different fluorescent labels with different emission wavelengths. To see if they are in the same area. |
| **Cited references to follow up on** | Van Gilst, M.R., Hadjivassiliou, H., Jolly, A., and Yamamoto, K.R. (2005). Nuclear hormone receptor NHR-49 controls fat consumption and fatty acid composition in C. elegans. PLoS Biol. 3, e53. |
| **Follow up Questions** | • Could dysregulation of ubl-5, potentially influenced by tau protein pathology, disrupt the delicate balance of the UPRmt and contribute to neuronal cell death?<br>• Could tau protein accumulation disrupt the function of dve-1, further exacerbating mitochondrial dysfunction?<br>• How does CLPP-1 function in the mitochondrial unfolded protein response (UPRmt) and what are its implications?<br>• |

# Article #14 Notes: Plant-Derived Nanovesicles: A Novel Form of Nanomedicine

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Plant-Derived Nanovesicles: A Novel Form of Nanomedicine |
| **Source citation (APA Format)** | Yu, L., Deng, Z., Liu, L., Zhang, W., & Wang, C. (2020). Plant-derived nanovesicles: A novel form of nanomedicine. *Frontiers in Bioengineering and Biotechnology*, *8*. https://doi.org/10.3389/fbioe.2020.584391 |
| **Original URL** | https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2020.584391/full |
| **Source type** | Journal Article |
| **Keywords** | plant-derived nanovesicles, cross-kingdom gene regulation, nanomedicine, bioeffects of nanomaterials, small RNAs |
| **#Tags** | #GDNVs #Ginver #nanovesicles #plant_derived_nanovesicles |
| **Summary of key points + notes (include methodology)** | The therapeutic potential of plant-derived nanovesicles (PDNVs) in inflammation regulation, cancer treatment, tissue regeneration, and microbiota modulation are explored through various studies. PDNVs, derived from dietary plants, were shown to carry bioactive molecules such as lipids, proteins, nucleic acids, and metabolites. Grapefruit nanovesicles reduced inflammation by modulating cytokine production, while ginger-derived nanoparticles inhibited the NLRP3 inflammasome and prevented colitis-associated cancer. Citrus limon nanovesicles induced cancer cell apoptosis through TRAIL/Dr5 upregulation, and ginseng-derived nanoparticles promoted anti-melanoma activity by polarizing macrophages to a tumoricidal phenotype. In tissue renewal, grape nanovesicles activated Wnt\ßcatenin signaling to enhance stem cell proliferation, and ginger-derived nanoparticles mitigated liver damage through Nrf2 activation. Ginger nanovesicles influenced bacterial gene expression, enhancing Lactobacillus growth and reducing the pathogenicity of *Porphyromonas gingivalis*.<br><br>Nanovesicle isolation was performed using techniques such as sucrose gradient centrifugation and size exclusion chromatography, with characterization achieved through dynamic light scattering. In vitro studies utilized cell culture models to examine effects on proliferation, |

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| | apoptosis, and signaling pathways, while in vivo studies employed animal models, including DSS-induced colitis and xenograft tumors, to assess therapeutic effects. Molecular biology methods, such as RNA sequencing and Western blotting, were used to analyze mechanisms of action. Emphasis was placed on advancing the field through further characterization of PDNV small RNA content, elucidation of molecular pathways, and development of synthetic mimics to enhance therapeutic applications. |
| **Research Question/Problem/ Need** | How can properties of Plant Derived nanovesicles be used as a nanomedicine technique?<br>What are their potentials and limitations? |
| **Important Figures** | Figure 1: Therapeutic applications of plant-derived nanovesicles across four key areas: inflammation regulation, anticancer treatment, tissue renewal and remodeling, and modulation of commensal microbiota. Grapefruit, broccoli, and ginger-derived nanoparticles suppress inflammation through mechanisms like cytokine modulation and inflammasome inhibition. |
| **VOCAB: (w/definition)** | • Porphyromonas gingivalis (P. gingivalis): Bacteria associated with periodontal disease. Ginger-derived nanovesicles have been found to inhibit the growth and pathogenicity of P. gingivalis, suggesting potential applications in oral health<br>• Wnt/ß-catenin signaling pathway: This is a critical signaling pathway involved in cell growth, development, and tissue renewal. Grape-derived nanovesicles have been found to activate this pathway in intestinal stem cells, promoting their proliferation and contributing to intestinal tissue repair.<br>• Ulcerative colitis: This is a chronic inflammatory bowel disease that affects the lining of the colon. It can cause symptoms like abdominal pain, diarrhea, and rectal bleeding. Plant-derived nanovesicles have shown promise in treating UC by reducing inflammation and promoting tissue repair<br>• Cross-kingdom gene regulation: This refers to the ability of plant nanovesicles to enter mammalian cells and influence gene expression in animals<br>• Lactobacillus rhamnosus (LGG): A bacterium commonly found in the human gut. Ginger-derived nanovesicles can promote the growth of LGG and alter its gene expression |
| **Cited references to follow** | Zhang, M., Wang, X., Han, M. K., Collins, J. F., and Merlin, |

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| **up on** | D. (2017). Oral administration of ginger-derived nanolipids loaded with siRNA as a novel approach for efficient siRNA drug delivery to treat ulcerative colitis. *Nanomedicine (Lond)* 12, 1927–1943. doi: 10.2217/nnm-2017-0196<br><br>Zhang, M., Viennois, E., Prasad, M., Zhang, Y., Wang, L., Zhang, Z., et al. (2016a). Edible ginger-derived nanoparticles: a novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials* 101, 321–340. doi: 10.1016/j.biomaterials.2016.06.018 |
| **Follow up Questions** | • Beyond NLRP3, are there other inflammasomes or inflammatory pathways that ginger-derived nanovesicles target?<br>• How can the production of ginger-derived nanovesicles be standardized to ensure consistent therapeutic efficacy? |

# Article #15 Notes: Effect of Ginger on Inflammatory Diseases

Article notes should be on separate sheets

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| **Source Title** | Effect of Ginger on Inflammatory Diseases |
| **Source citation (APA Format)** | Ballester, P., Cerdá, B., Arcusa, R., Marhuenda, J., Yamedjeu, K., & Zafrilla, P. (2022). Effect of ginger on inflammatory diseases. *Molecules (Basel, Switzerland)*, *27*(21), 7223. https://doi.org/10.3390/molecules27217223 |
| **Original URL** | https://pmc.ncbi.nlm.nih.gov/articles/PMC9654013/# |
| **Source type** | Journal Article |
| **Keywords** | inflammatory diseases, ginger, bioactive compounds |
| **#Tags** | #GDVNs #inflammation |
| **Summary of key points + notes (include methodology)** | Ginger has anti-inflammatory properties that benefit inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, lupus, psoriasis and cancer. Key bioactive compounds in ginger such as gingerols, shogaols, paradols, and zingerone demonstrate strong antioxidant and anti-inflammatory effects. 6-gingerol converts into shogaols and paradols through heating and metabolism which are even more stable and effective in reducing inflammation and oxidative stress.<br><br>These compounds protect cells from damage by preventing lipid peroxidation and reducing the buildup of harmful reactive oxygen species in the body. Increased antioxidant enzymes like catalase and superoxide dismutase are observed along with a reduction in markers of oxidative stress such as MDA and nitric oxide limiting tissue damage and inflammatory responses in diseases with high levels of inflammatory cytokines. Specific effects on inflammatory diseases reveal that ginger compounds reduce inflammation and improve symptoms across several conditions.<br><br>In rheumatoid arthritis compounds like 6-shogaol and zingerone reduce tissue inflammation and inhibit inflammatory molecules. In inflammatory bowel disease ginger modulates the gut microbiota and suppresses multiple inflammatory pathways leading to a decrease in cytokine activity. Ginger's anti-inflammatory effects also extend to |

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| | systemic lupus erythematosus and psoriasis where it decreases cytokine expression and controls inflammatory responses. Anticancer effects are also noted with ginger reducing tumor-promoting factors and inhibiting tumor cell growth supporting its potential role in cancer prevention and treatment. While ginger shows promise for alleviating symptoms across these conditions additional research is essential to fully understand its therapeutic effects and explore possible synergies with conventional treatments for inflammation-related diseases. |
| **Research Question/Problem/ Need** | How effective are ginger's bioactive compounds in managing/suppressing inflammatory illnesses? |
| **Important Figures** | Figure 1: Shows a detailed explanation of what exactly causes inflammation, how ginger is involved in preventing it, and different consequences of inflammation. This is important because this shows ginger helps with inflammation, furthering their research goals.<br><br>Figure 2: Provides a detailed break-up of the properties and structures of the 4 main compounds in ginger. Highlights how all the compounds aid in reducing inflammation. |
| **VOCAB: (w/definition)** | • 6-gingerol: A compound found in ginger, known for its anti-inflammatory, antioxidant, and anticancer properties.<br>• ß-bisabolene: A natural sesquiterpene found in various plants, including ginger, with anti-inflammatory and antimicrobial activities.<br>• NF-kβ: A natural sesquiterpene found in ginger with anti-inflammatory and antimicrobial activities.<br>• Psoriasis: A skin disorder with the buildup of skin cells, leading to scaling, inflammation, and redness.<br>• COX2: An enzyme involved in the production of pro-inflammatory hormones.<br>• LOX Pathway: Produces lipids (eicosanoids) like leukotrienes from arachidonic acid. Eicosanoids mainly aid in hemostasis.<br>• Nonsteroidal Anti-inflammatory Drugs (NSAIDs): Help reduce inflammation. It has a negative effect on stomach mucosa. |
| **Cited references to follow up on** | 30.Joshi D., Srivastav S.K., Belemkar S., Dixit V.A. Zingiber officinale and 6-gingerol alleviate liver and kidney dysfunctions and oxidative stress induced by mercuric chloride in male rats: A protective approach. Biomed. Pharmacother. 2017;91:645–655. doi: 10.1016/j.biopha.2017.04.108. |

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| | 85.Habib S.H.M., Makpol S., Abdul Hamid N.A., Das S., Ngah W.Z.W., Yusof Y.A.M. Ginger extract (Zingiber officinale) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. Clinics. 2008;63:807–813. doi: 10.1590/S1807-59322008000600017. |
| **Follow up Questions** | • What other problems are caused by inflammation?<br>• |

# Article #16 Notes: Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau)

Article notes should be on separate sheets

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| **Source Title** | Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau) |
| **Source citation (APA Format)** | Wood, J. G., Mirra, S. S., Pollock, N. J., & Binder, L. I. (1986). Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). *Proceedings of the National Academy of Sciences of the United States of America*, *83*(11), 4040–4043. https://doi.org/10.1073/pnas.83.11.4040 |
| **Original URL** | https://www.pnas.org/doi/abs/10.1073/pnas.83.11.4040 |
| **Source type** | Journal Article |
| **Keywords** | Neurofibrillary Tangles, Tau, Phosphorylation |
| **#Tags** | #Tau #hyperphosphorylation |
| **Summary of key points + notes (include methodology)** | The study focused on the presence of tau in neurofibrillary tangles (NFTs) found in Alzheimer's disease (AD) brain tissue. By using a monoclonal antibody that specifically binds to tau, brain samples from AD patients and age-matched controls were analyzed and showed tau as a major component of NFTs and neurotic plaques (NPs). In healthy brains, tau immunoreactivity is not typically seen in neuronal cell bodies, but in AD tissue, tau labeling intensifies within NFTs, particularly in regions such as the hippocampus. Tau accumulates or redistributes in AD, disrupting its usual location and function.<br><br>The phosphorylation of tau masks the tau epitopes that this antibody recognizes, because phosphatase digestion reveals tau labeling in both NFTs and NPs. Abnormal phosphorylation thus interrupts the normal functioning of tau, probably interfering with axonal transport and instead promoting the build-up of tau within the neuronal cell bodies, as opposed to transporting tau down the length of the axon. |
| **Research** | What is the relationship between tau and NFTs? |

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| **Question/Problem/ Need** | **Whether tau protein is present in NFTs primarily located in the neuronal cell body (perikaryon).** |
| **Important Figures** | • Figure 1: immunoblot data showing that the T-1 antibody detects tau in both control and AD brain samples, with increased tau labeling in AD tissue suggesting tau upregulation in Alzheimer's. This supports the T-1 antibody's effectiveness for studying tau in human tissue.<br>• Figure 2: Light and electron micrographs showing tau protein in NFTs and NPs, with a linear tau pattern in hippocampal NFTs and tau closely associated with PHFs. These images show a visual representation of tau's role in NFTs and suggest that phosphorylation may mask tau in NPs. |
| **VOCAB: (w/definition)** | • Microtubule-Associated Protein (MAP): A type of protein that binds to and stabilizes microtubules, which are long, hollow structures that provide structural support and transport pathways within cells.<br>• Kinase: Enzymes that catalyze the transfer of a phosphate group from a donor molecule to a substrate molecule, often involved in cellular signaling and regulation.<br>• Neuritic Plaques (NPs): Abnormal clusters of protein fragments and cellular debris found in the brains of individuals with Alzheimer's disease, often surrounding dying neurons. |
| **Cited references to follow up on** | No relevant sources cited |
| **Follow up Questions** | • Could targeting NFTs reduce effects of AD? |

# Article #17 Notes: Inflammation and Alzheimer's disease

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Inflammation and Alzheimer's disease |
| **Source citation (APA Format)** | Akiyama, H. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging*, *21*(3), 383–421. https://doi.org/10.1016/s0197-4580(00)00124-x |
| **Original URL** | https://www.sciencedirect.com/science/article/pii/S019745800000124X |
| **Source type** | Journal Article |
| **Keywords** | Alzheimer's disease; Inflammation; Nervous system; Neuroinflammation; Complement; Cytokine; Chemokine; Acute phase protein; Microglia; Astrocyte; Neuron |
| **#Tags** | #AD #inflammation #amyloid_beta |
| **Summary of key points + notes (include methodology)** | The role of inflammation in Alzheimer's disease is explored, with a focus on how inflammatory processes contribute to both the onset and worsening of the disease. Inflammation in Alzheimer's is caused by neurofibrillary tangles and degenerating neurons, which collectively activate a range of inflammatory responses in the brain. These involve inflammatory mediators such as the complement system, various cytokines and chemokines, acute phase proteins, and free radicals. The complement system, for example, becomes activated by Aß plaques and other pathological features in Alzheimer's brains, which can lead to neuronal damage through the formation of membrane attack complexes.<br>Cytokines and chemokines, many of which are upregulated in Alzheimer's brains compared to non-demented brains, play a crucial role in modulating inflammation. They are produced by multiple cell types, including microglia, astrocytes, neurons, and endothelial cells, which are all involved in the inflammatory environment observed in Alzheimer's. Additionally, free radicals, which indicate oxidative damage, are also abundant in Alzheimer's affected brains and amplify inflammation through the production of inflammatory molecules. Elevated inflammatory mediators in regions with significant Alzheimer's pathology, such as the frontal and limbic cortices, suggests a direct correlation between inflammation and disease severity.<br>Although inflammation is generally thought to worsen Alzheimer's, the |

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| | specific roles of certain inflammatory mediators like TNF-α and complement anaphylatoxins, which may have both protective and damaging effects under different circumstances, are possible. The complexity of inflammatory processes in Alzheimer's and suggest that further research is needed to fully understand the interplay of these mediators. Anti-inflammatory therapies are proposed as potential adjunct treatments alongside approaches targeting the primary causes of Alzheimer's, reflecting the view that reducing inflammation could alleviate disease progression. |
| **Research Question/Problem/ Need** | What is the role of inflammation in the development of AD? |
| **Important Figures** | No figures in paper |
| **VOCAB: (w/definition)** | • Free Radicals: Free radicals are highly reactive molecules that can damage cells and contribute to inflammation.<br>• Cytokines: Signaling molecules produced by cells that regulate immune and inflammatory responses. |
| **Cited references to follow up on** | [590] Weiner MF, Vobach S, Olsson K, Svetlik D, Risser RC. Cortisol secretion and Alzheimer's disease progression. Biol Psychiatry 1997;42:1030–8.<br><br>[635] Zlokovic BV, Martel CL, Matsubara E, et al. Glycoprotein 330/ megalin: probable role in receptor-mediated transport of apolipoprotein J alone and in a complex with Alzheimer disease amyloid beta at the blood-brain and blood-cerebrospinal fluid barriers. Proc Natl Acad Sci USA 1996;93:4229–34.<br><br>[416] Papassotiropoulos A, Bagli M, Jessen F, et al. A genetic variation of the inflammatory cytokine IL-6 delays the initial onset and reduces the risk for sporadic Alzheimer's disease. Ann Neurol 1999;45: 666–8. |
| **Follow up Questions** | • Can Tau proteins cause inflammation?<br>• How might NSAIDs delay inflammation in AD?<br>• How do cytokine and chemokine production interact with each other in AD inflammatory? |

# Article #18 Notes: Structure-based inhibitors of tau aggregation

Article notes should be on separate sheets

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|---|---|
| **Source Title** | Structure-based inhibitors of tau aggregation |
| **Source citation (APA Format)** | (Seidler et al., 2018)<br>Seidler, P. M., Boyer, D. R., Rodriguez, J. A., Sawaya, M. R., Cascio, D., Murray, K., Gonen, T., & Eisenberg, D. S. (2018). Structure-based inhibitors of tau aggregation. *Nature Chemistry*, *10*(2), 170–176. https://doi.org/10.1038/nchem.2889 |
| **Original URL** | https://www.nature.com/articles/nchem.2889 |
| **Source type** | Journal Article |
| **Keywords** | Tau aggregation inhibition, VQIINK, VQIVYK |
| **#Tags** | #Tau_structure #tau |
| **Summary of key points + notes (include methodology)** | Tau aggregation is a hallmark of neurological disorders such as Alzheimer's disease (AD). In its normal state, tau stabilizes microtubules within neurons, but in tauopathies, it aggregates into amyloid fibrils, forming intracellular tangles linked to cognitive decline in AD. Two key hexapeptide segments, VQIINK and VQIVYK, drive this aggregation through steric zippers, tightly interlocked structures critical to fibril formation. Focus on the VQIINK segment revealed its structure through micro-electron diffraction (MicroED), using nanocrystals too small for traditional methods. VQIINK forms a more extensive steric zipper interface than VQIVYK, making it a potent driver of tau aggregation. Engineered tau constructs with only VQIINK aggregated faster than wild-type tau.<br><br>Inhibitors designed based on the VQIINK structure effectively disrupted aggregation. Phase 1 inhibitors, such as MINK and WINK, targeted interfaces identified in the first polymorph, while Phase 2 inhibitors addressed additional interfaces from the second polymorph. These inhibitors reduced tau40 aggregation in vitro and blocked tau seeding in HEK293 biosensor cells, preventing the spread of tau aggregates. VQIINK inhibitors outperformed VQIVYK inhibitors, challenging the view of VQIVYK as the primary driver of tau seeding. |

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| | Targeting VQIINK offers a promising approach to combating tauopathies, with its polymorphs potentially explaining the structural basis for distinct tau strains associated with diverse clinical presentations. |
| **Research Question/Problem/ Need** | What is the role of the VQIINK segment in tau aggregation, and can targeting this segment lead to effective inhibitors of tau aggregation? |
| **Important Figures** | Figure 1: Shows the atomic structure of amyloid fibrils formed by segments of tau. The formation of steric zipper interfaces by both VQIINK and VQIVYK segments, highlighting the structural basis of tau aggregation. The figure also depicts how a specific mutation (ΔK280) can enhance fibril formation by altering these interfaces.<br>Figure 2: Shows the time dependence of fibrillization and oligomerization for different tau constructs, providing evidence that VQIINK drives aggregation more strongly than VQIVYK. The 2xIN construct forms fibrils more rapidly than wild-type tau and the 2xVY construct, with a shift in equilibrium toward fibril formation, indicating VQIINK's role in promoting rapid aggregation.<br>Figure 4: Shows the inhibition of tau aggregation by Phase 2 inhibitors, showing the discovery of a second VQIINK polymorph and the development of inhibitors targeting multiple interfaces. The structures of the two VQIINK polymorphs are compared, revealing distinct steric zipper interfaces. Data on Phase 2 inhibitors demonstrate their effectiveness in blocking tau seeding and the importance of targeting multiple interfaces for improved inhibition. |
| **VOCAB: (w/definition)** | • Amyloid fibrils: Insoluble protein aggregates with a highly ordered cross-β sheet structure.<br>• Steric zipper: A tightly interlocked structure formed by amino acid side chains in amyloid fibrils, giving them stability and promoting aggregation.<br>• Polymorph: A different structural form of a molecule or aggregate, such as the two distinct VQIINK fibril structures.<br>• Tauopathies: neurodegenerative diseases caused by the aggregation of tau protein in the brain.<br>• Micro-electron diffraction (MicroED): A cryo-electron microscopy method that determines high-resolution structures from nanocrystals too small for X-ray crystallography.<br>• HEK293 biosensor cells: Genetically modified human kidney cells used to study tau protein and related processes.<br>• Seeding: Pre-formed amyloid fibrils that accelerate the aggregation of soluble proteins into new fibrils. |

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| | • Thioflavin T (ThT): A fluorescent dye that binds amyloid fibrils and shows enhanced fluorescence, allowing measurement of fibril formation.<br>• Tau strains: Different conformations of aggregated tau protein linked to various tauopathies.<br>• Fuzzy coat: The disordered region around the structured core of amyloid fibrils that may contain segments involved in seeding.<br>• Structure-based inhibitor design: A drug development method targeting a protein based on its 3D structure.<br>• Gel filtration chromatography: A technique that separates molecules by size, used to analyze tau species like monomers and oligomers.<br>• Half-maximum inhibitory concentration (IC50): The concentration of an inhibitor needed to reduce activity by 50%.<br>• K18: A truncated tau protein form with four microtubule-binding repeats used in studies.<br>• ΔK280 mutant: A tau variant with a deleted lysine at position 280, which speeds up fibril formation and is linked to tauopathies.<br>• Shape complementarity (Sc): A measure of how well two surfaces fit, with higher values indicating a tighter fit, as in steric zippers.<br>• Solvent-accessible surface area buried (Ab): The protein surface area buried when interacting with another molecule, like in steric zippers. |
| **Cited references to follow up on** | Kaufman, S. K. et al. Tau prion strains dictate patterns of cell pathology, progression rate, and regional vulnerability in vivo. Neuron 92, 796–812 (2016). |
| **Follow up Questions** | What are the potential implications of the discovery of two separate VQIINK polymorphs for the development of tau aggregation inhibitors? |

# Article #19 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

Article notes should be on separate sheets

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| **Source Title** | 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 citation (APA Format)** | (Chagas et al., 2017)<br>Chagas, A. M., Godino, L. P., Arrenberg, A. B., & Baden, T. (2017). The 100 € lab: A 3-D printable open source platform for fluorescence microscopy, optogenetics and accurate temperature control during behaviour of zebrafish, Drosophila and C. elegans. *bioRxiv*. https://doi.org/10.1101/122812 |
| **Original URL** | https://github.com/amchagas/Flypi/tree/v1.0.0 |
| **Source type** | Journal Article |
| **Keywords** | Drosophila melanogaster Larvae Zebrafish Cameras Fluorescence imaging Light emitting diodes 3D printing Optogenetics |
| **#Tags** | #FlyPI #Florescence_microscope #mCherry |
| **Summary of key points + notes (include methodology)** | FlyPi is a 3D-printable, open-source platform for neuroscience research using small model organisms like zebrafish, fruit flies, and nematodes. The hardware includes a 3D-printed frame, a Raspberry Pi 3 with a camera module, an Arduino-Nano microcontroller, a custom PCB, and various sensors and actuators. Optical components consist of an adjustable focus lens, LEDs, and low-cost theater filters for illumination, fluorescence imaging, and optogenetic stimulation. Temperature control is achieved using a Peltier element and thermistor, and behavioral tracking is supported through video monitoring and analysis software like Ctrax. A Python-based graphical user interface (GUI) controls the hardware and enables data acquisition. The platform's cost ranges from under €100 for basic |

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| | illumination and optogenetic stimulation to €200 for a fully equipped setup, including fluorescence imaging and automated focus. FlyPi is modular, allowing users to assemble only the required components for specific experiments, and all 3D models, source code, and PCB designs are openly available for modification.<br><br>FlyPi supports basic light and fluorescence microscopy, demonstrating its capabilities with GFP-expressing samples, calcium imaging in zebrafish and fruit fly larvae, and imaging parasites in human tissue. Optogenetic functions include activating proteins like Channelrhodopsin 2 in zebrafish, fruit fly larvae, and adult flies. The Peltier-based system enables precise temperature control for thermogenetics, working with temperature-sensitive proteins. Suggested improvements include enhancing spatial resolution with higher-quality lenses, improving fluorescence contrast with better filters, integrating monochrome cameras, and adding features like auto-focusing, motorized stages, and wireless networking. FlyPi has been successfully used in workshops in African universities, training students to assemble and use the platform for basic neuroscience experiments. Its modular design can substitute malfunctioning equipment in laboratories, and detailed assembly instructions ensure reproducibility. Researchers encourage further development and sharing of modifications within the open-source community to expand FlyPi's applications and improve its design. |
| **Research Question/Problem/ Need** | A cheap microscope that can capture videos for a long term as well as capture florescence emissions. |
| **Important Figures** | Figure 2: Shows FlyPi's light microscopy capabilities are shown with both upright and inverted camera setups, a micromanipulator for sample positioning, and an LED ring for illumination. Images include parasites in human tissue, demonstrating its utility for medical diagnostics.<br>Figure 3: The fluorescence microscopy setup uses a 410 nm LED, excitation and emission filters, and a test slide. Imaging examples include live zebrafish larvae, Drosophila larvae, and point spread functions measured with fluorescent beads.<br>Figure 5: Optogenetic stimulation capabilities are demonstrated with zebrafish larvae, showing the LED spectrum and power used for activation. Behavioral responses are illustrated for zebrafish larvae, Drosophila larvae, and adult Drosophila.<br>Figure 6: It shows the Peltier element used for temperature control, the CPU fan for heat dissipation, and a graph illustrating the performance of the Peltier-thermistor feedback loop in maintaining stable temperatures. |
| **VOCAB: (w/definition)** | |

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| **Cited references to follow up on** | Wei Q, Qi H, Luo W, Tseng D, Ki SJ, Wan Z, et al. Fluorescent Imaging of Single Nanoparticles and Viruses on a Smart Phone. ACS Nano 2013;7: 9147–9155. pmid:24016065 |
| **Follow up Questions** | • What frequencies of light work best on the FlyPi?<br>• How could this be built for cheaper (less parts)? |

# Article #20 Notes: Inhibition of tau aggregation in a novel Caenorhabditis elegans model of tauopathy mitigates proteotoxicity

Article notes should be on separate sheets

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| **Source Title** | Inhibition of tau aggregation in a novel Caenorhabditis elegans model of tauopathy mitigates proteotoxicity |
| **Source citation (APA Format)** | (Fatouros et al., 2012)<br>Fatouros, C., Pir, G. J., Biernat, J., Koushika, S. P., Mandelkow, E., Mandelkow, E.-M., Schmidt, E., & Baumeister, R. (2012). Inhibition of tau aggregation in a novel Caenorhabditis elegans model of tauopathy mitigates proteotoxicity. *Human Molecular Genetics*, *21*(16), 3587–3603. https://doi.org/10.1093/hmg/dds190 |
| **Original URL** | https://academic.oup.com/hmg/article-abstract/21/16/3587/2901004?redirectedFrom=fulltext |
| **Source type** | Journal Article |
| **Keywords** | Phenotype, caenorhabditis elegans, tauopathies, mapt gene |
| **#Tags** | |
| **Summary of key points + notes (include methodology)** | Tau aggregation is a major contributor to neuronal dysfunction in tauopathies, with soluble oligomers considered the most toxic form. Researchers developed a *Caenorhabditis elegans* model expressing human Tau with the pro-aggregation DK280 mutation and full-length Tau V337M to isolate the toxic effects of Tau aggregation. They created a control strain with anti-aggregant Tau mutations (I277P, I308P) that prevent aggregation. This allowed direct comparison of aggregation-driven toxicity versus non-aggregation effects. The model showed severe locomotion defects, indicating that Tau aggregation disrupts neuronal function.<br><br>Multiple assays were used to evaluate the effects of Tau aggregation, including locomotion analysis, neuronal morphology, synaptic integrity, and mitochondrial transport. Pro-aggregant worms exhibited motor neuron damage, with axonal gaps and disorganized synaptic vesicle markers, indicating structural and functional neuronal deficits. |

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| | Mitochondrial transport was impaired, with mitochondria accumulating in the proximal axon and frequently pausing during movement, suggesting disrupted axonal transport caused by Tau aggregates.<br><br>To explore therapeutic potential, several Tau aggregation inhibitors were tested, including methylene blue (MB), BSc3094, bb14, and cmp16. MB improved locomotion and reduced insoluble Tau levels. BSc3094 and cmp16 significantly lowered Tau aggregation, while bb14 shifted Tau toward more soluble forms. These findings underscore the critical role of Tau aggregation in neuronal toxicity and highlight the C. elegans model as a valuable platform for drug discovery targeting tauopathies |
| **Research Question/Problem/ Need** | What is the role of Tau aggregation in neuronal dysfunction, and can inhibiting this aggregation mitigate the associated damage in C. Elegans? |
| **Important Figures** | Figure 1: Connection between pro-aggregant Tau expression, Tau aggregation, and locomotion defects in C. elegans. Worms expressing pro-aggregant Tau move significantly slower than those expressing anti-aggregant Tau or wild-type worms. Thioflavin S staining reveals extensive Tau aggregates in the nerve ring of the pro-aggregant strain, while the anti-aggregant strain shows minimal staining, linking aggregation to impaired movement.<br><br>Figure 7: Shows that axonal transport is disrupted in mechanosensory neurons of the pro-aggregant strain. Kymographs of mitochondria labeled with GFP in PLM neurons display frequent pauses in mitochondrial movement in the pro-aggregant strain compared to the anti-aggregant and wild-type strains. This shows that amyloidogenic Tau interferes with mitochondrial transport, contributing to neuronal dysfunction. |
| **VOCAB: (w/definition)** | None |
| **Cited references to follow up on** | Sirangelo, I. and Irace, G. (2010) Inhibition of aggregate formation as therapeutic target in protein misfolding diseases: effect of tetracycline and trehalose. Expert Opin. Ther. Targets, 14, 1311–1321.<br><br>Landau, M., Sawaya, M.R., Faull, K.F., Laganowsky, A., Jiang, L., Sievers, S.A., Liu, J., Barrio, J.R. and Eisenberg, D. (2011) Towards a pharmacophore for amyloid. PLoS Biol., 9, e1001080.<br><br>Kraemer, B.C., Zhang, B., Leverenz, J.B., Thomas, J.H., Trojanowski, J.Q. and Schellenberg, G.D. (2003) Neurodegeneration and defective Human Molecular Genetics, 2012, Vol. 21, No. 16 3601 by guest on |

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| | April 10, 2015 http://hmg.oxfordjournals.org/ Downloaded from neurotransmission in a Caenorhabditis elegans model of tauopathy. Proc. Natl Acad. Sci. USA, 100, 9980–9985. |
| **Follow up Questions** | • What techniques could be used to further characterize the biochemical properties of these different Tau species, such as their size and conformation?<br>• What other cellular processes could be studied to understand mechanisms underlying Tau-mediated neurotoxicity in this model?<br>• How to identify Tau aggregation inhibitors using this model system, such as genetic screens or high-throughput drug screening? |