Examination of NP12 and BDNF nanoparticle combo-treatment as a potential therapeutic for Alzheimer Disease

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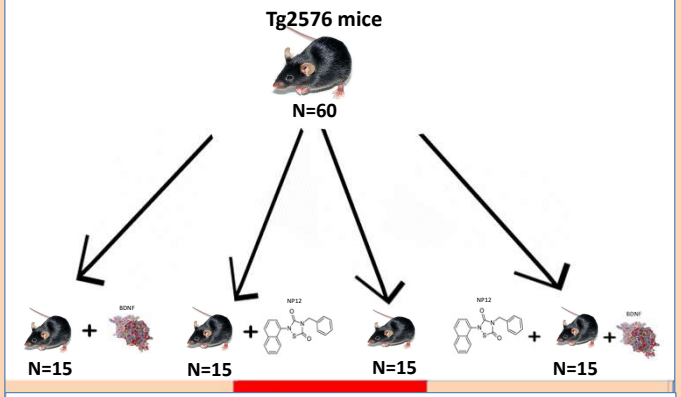
Alzheimer's Disease is a neurodegenerative disorder that afflicts approximately 44 million individuals worldwide. One of the most studied models of Alzheimer's Disease are Tg2576 mice, which progressively develop Alzheimer molecular markers such as AB plaques, as well as behavioral and cognitive deficits such as impaired spatial memory. Although previous research has shown that BDNF treatment may serve as an efficient treatment for reducing the progression of cognitive and behavioral deficits, the results suggest that such methods had little effect in decreasing the development of neurofibrillary tangles. Additionally, the methodology used for gene delivery has been criticized as being too "aggressive" of a technique for regular clinical use. To maximize both safety and treatment efficacy, Tg2576 mice were injected with nanoparticles coated with BDNF. To address the limitations that BDNF treatment had in diminishing neurofibrillary tangle accumulation, experimental mice were also treated with nanoparticles containing NP12, a GSK-3B inhibitor. Experimental groups consisted of mice injected with nanoparticles containing BDNF, NP12, both (combo) treatments, and an untreated group. BDNF, AB, and hyperphosphorylated tau were assessed using ELISA; spatial memory was assessed around the expected time of spatial memory deficit via a Morris water maze.

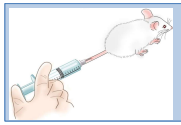


Procedure/Methodology

Initial housing conditions

- All mice were kept in cages in a lab setting under a 12-hour light/dark schedule. Food and water were provided ad libitum.

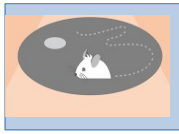
N=60 → 190 days



Nanoparticle injection

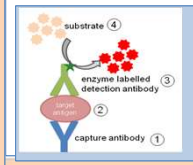
- Approximately 190 days following birth, mice received tail injections of poly(butyl cyanoacrylate) nanoparticles. Mice were injected with nanoparticles containing either no treatment, BDNF, NP12, or NP12 + BDNF combo-treatment.

80 days (270 total)



Morris Water Maze

- All experimental groups underwent water maze training two times a day for a total of five days. 24 hours later, probe trials were conducted. Video-tracking software was used to compute Mean Probe Scores.



ELISA/Molecular Analyses

Following proper handling and sedation procedure, Tg2576 mice were euthanized for brain and blood sample acquisition. Enzyme immunosorbent assays were performed to measure the level of BDNF, tau, and AB within each of the respective experimental groups.

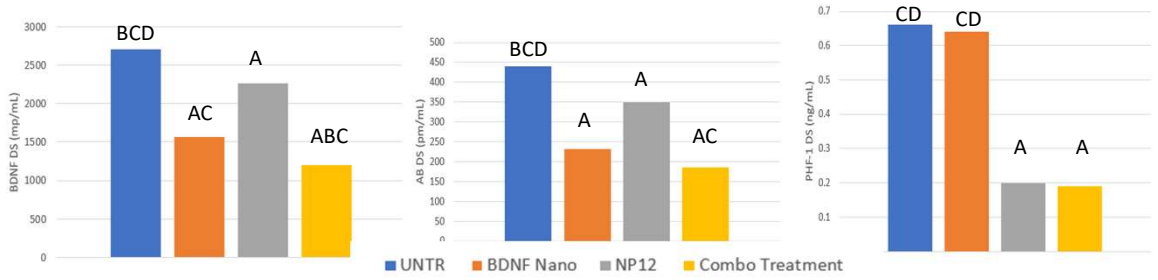


Figure 1: **a)** Effect of BDNF-coated nanoparticles on endogenous BDNF concentration. **b**.) AB concentration differences in 9-month-old Tg2576 mice. **c.)** Concentration of PHF-1 (hyperphosphorylated tau) in 9-month-old Tg2576 mice. Difference scores computed by calculating the absolute difference between the concentrations in baseline mice (9 weeks) and the experimental groups. A, B, C, D correspond to UNTR (untreated), BDNF Nano, NP12, and Combo Treatment, respectively; letters on bars indicate significant difference.

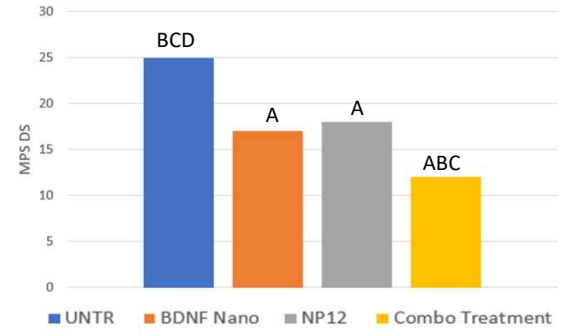
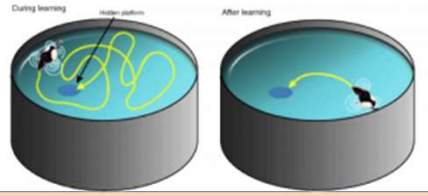


Figure 2: **Computed Probe Difference Scores.** Mean Probe Scores were calculated for baseline mice and experimental groups. Probe Difference Scores were then calculated by taking the absolute value of the difference between the experimental and baseline mice. A, B, C, D correspond to UNTR (untreated), BDNF Nano, NP12, and Combo Treatment, respectively; letters on bars indicate significant difference.



Future Directions/Conclusions:

- If combo-treatment proves more effective than BDNF or NP12 individual treatments, the results of the study may prove useful in providing further insight on the potential of nanoparticles in treating Alzheimer's and other neurodegenerative disorders.
- To truly assess the efficacy of BDNF nanoparticle treatment and more "traditional" approaches, methodology should also include an experimental group that receives BDNF gene therapy.
- In the current study, mice were treated with BDNF, NP12, or a combo therapy to see whether the examined therapeutics can attenuate the onset and severity of Alzheimer Disease. Future directions should examine the efficacy of saving spatial memory after disease onset has already occurred.

References:

Angelova, A., & Angelov, B. (2017). Dual and multi-drug delivery nanoparticles towards neuronal survival and synaptic repair. *Neural regeneration research*, *12*(6), 886–889. https://doi.org/10.4103/1673-5374.208546. Castillo-Carranza, D. L., Guerrero-Muñoz, M. J., Sengupta, U., Hernandez, C., Barrett, A. D., Dineley, K., & Kayed, R. (2015). Tau immunotherapy modulates both pathological tau and upstream amyloid pathology in an Alzheimer's disease mouse model. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *35*(12), 4857–4868. https://doi.org/10.1523/JNEUROSCI.4989-14.2015DeTure, M.A., Dickson, D.W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegeneration* 14, 32. https://doi.org/10.1186/s13024-019-0333-5. Elder, G. A., Gama Sosa, M. A., & De Gasperi, R. (2010). Transgenic mouse models of Alzheimer's disease. *The Mount Sinai journal of medicine, New York*, *77*(1), 69–81. https://doi.org/10.1002/msj.2015. Forest, S. K., Acker, C. M., d'Abramo, C., & Davies, P. (2013). Methods for measuring tau pathology in transgenic mouse models. Journal of Alzheimer's disease : JAD, 33(2), 463–471. https://doi.org/10.3233/JAD-2012-121354.