Nanotherapeutics for Immune Modulation in Parkinson's Disease

Hannah Calvelli, Nanxia Zhao, Nicola Francis, Prabhas V. Moghe
Rutgers University Department of Biomedical Engineering

Introduction

Parkinson's Disease (PD) is one of the most common neurodegenerative disorders in the United States, characterized by the loss of dopaminergic neurons in the substantia nigra of the midbrain. Neuronal death occurs due to the accumulation of toxic alpha synuclein (ASYN) aggregates, which are a hallmark of PD pathology [1]. ASYN aggregation ultimately results in the activation of microglia, the resident immune cells of the brain, due to oxidative stress. In this work, flash nanoprecipitation was used to fabricate two classes of nanoparticles (NPs) for immune modulation in PD.

Aim 1

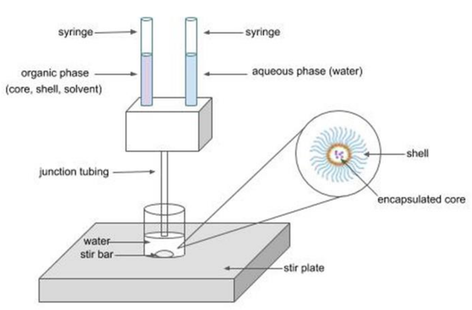
- To investigate dual-component FAATA NPs with a tannic acid (TA) core and a ferulic acid diacid (FAA) shell in reducing ASYN aggregation and attenuating microglia activation [2].

Aim 2

- To investigate amphiphilic macromolecule-based (AM) NPs in reducing ASYN aggregation and attenuating microglia activation via association with scavenger receptor CD36 [3].

Methods

Flash Nanoprecipitation Diagram. A confined impinging jet mixer was used to fabricate NPs within a narrow size distribution.



Dynamic Light Scattering Analysis. Hydrodynamic diameters and polydispersity index (PDI) values for different NP formulations fabricated were measured. Successful NP formation is indicated by PDI < 0.3.

FAATA NP Formulations

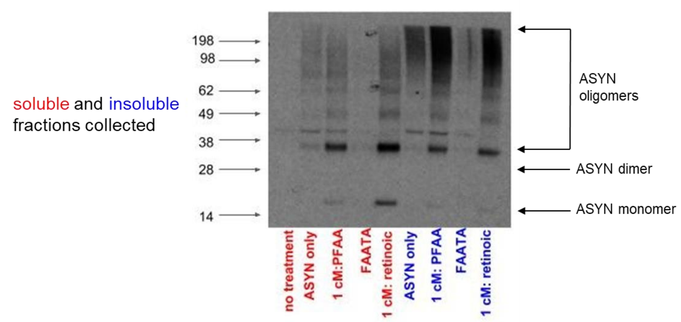
Diameter in nm (PDI)		FAA acid shell (mg/ml) 10	20	40
Tannic acid core (mg/ml)	5	361± 10 (0.43± 0.04)	392 ± 63 (0.36 ± 0.04)	331 ± 23 (0.40 ± 0.01)
	10	198 ± 5 (0.26 ± 0.01)	191 ± 3 (0.19 ± 0.02)	230 ± 15 (0.28 ± 0.02)
	20	594 ± 80 (0.51 ± 0.09)	260 ± 11 (0.30 ± 0.02)	430 ± 10 (0.24 ± 0.07)

AM NP Formulations

	1cMPS	1cTPS	1cToPS
Diameter in nm	149 ± 10	287 ± 68	221 ± 15
PDI	0.15 ± 0.01	0.24 ± 0.08	0.21 ± 0.05

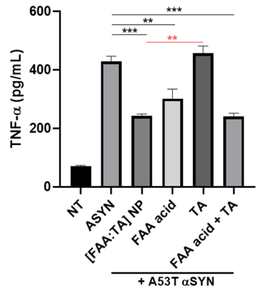
Aim 1: Effect of FAATA NPs on ASYN Aggregation

Western Blot for Microglia Treated with NPs and Monomeric ASYN. FAATA NPs decrease ASYN oligomer expression for both the soluble and insoluble fractions.



Aim 1: Effect of FAATA NPs on Microglia Activation

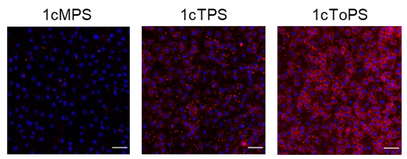
TNF-α ELISA for Microglia Treated with FAATA NPs and Oligomeric ASYN [4]. FAATA NPs, the FAA compound alone, and the mixture of FAA and TA significantly reduce production of the pro-inflammatory TNF-α cytokine.

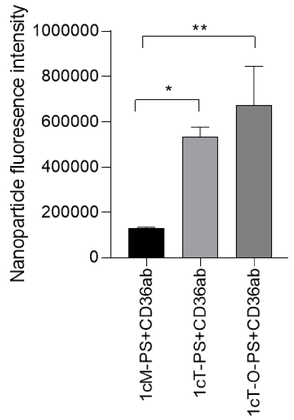


Aim 2: Competitive Binding of AM NPs to CD36

AM NP Fluorescence Intensity for CD36 Scavenger Receptor-Mediated Binding. Fluorescence intensity is significantly lower for microglia treated with 1cMPS NPs, suggesting that these NPs exhibit decreased binding to CD36 compared to 1cTPS and 1cToPS NPs.

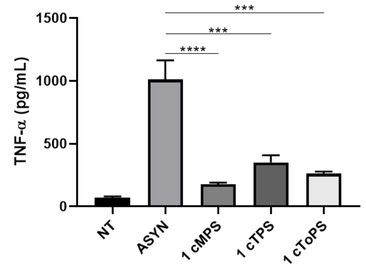
Microglia were treated with AM NPs and CD36 antibodies. Cells were visualized with nuclear stain Hoechst.
Scale bar = 50 µM.





Aim 2: Effect of AM NPs on Microglia Activation

TNF-α ELISA for Microglia Treated with AM NPs and Oligomeric ASYN. All 3 AM NP formulations significantly reduce production of the pro-inflammatory TNF-α cytokine.



Conclusions

Aim 1

- FAA and TA antioxidants can be combined into a multifunctional, dual-component antioxidant NP formulation with complementary effects on ameliorating ASYN aggregation and attenuating microglia activation.

Aim 2

- AM NPs ameliorate ASYN aggregation and attenuate microglia activation via association with scavenger receptor CD36.
- 1cTPS and 1cToPS NPs demonstrate the strongest binding to CD36.

Future Directions

- Elucidate the binding mechanisms between NPs and ASYN
- Investigate the molecular pathways involved in the action of NPs modulating neuroinflammation
- Test a wider range of NP formulations, including different antioxidant cores and AM shells

References

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