Macrophages and Exosomes Employ Brain Inflammation for CNS Delivery of Therapeutics

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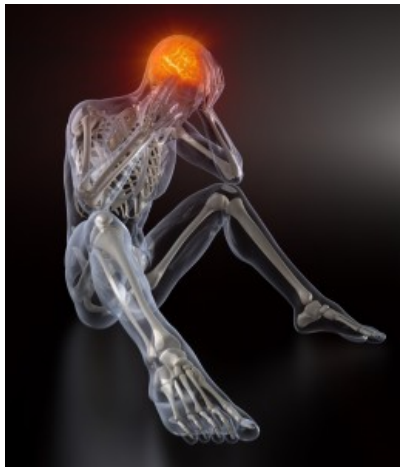
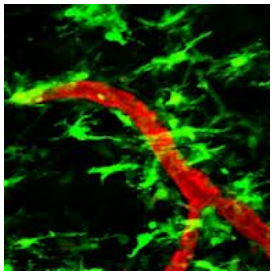
Targeting Brain Inflammation in Disease

- Biochemical studies of brains from individuals with many neurologic disorders provide clear evidence for an activation of inflammatory pathways in the brain.
- Activated microglial cells secrete a wide range of inflammatory factors, including reactive oxygen species, cytokines (IL-1β, IL-6, TNF-α, and INF-γ), chemokines (MIP1α), MIP1β, CXCL8), growth factors, and complement components (C1q, C3, C4, and C9).
- In addition, selectins, integrins and intercellular cell adhesion molecules (ICAM) are upregulated in the inflamed brain endothelium.

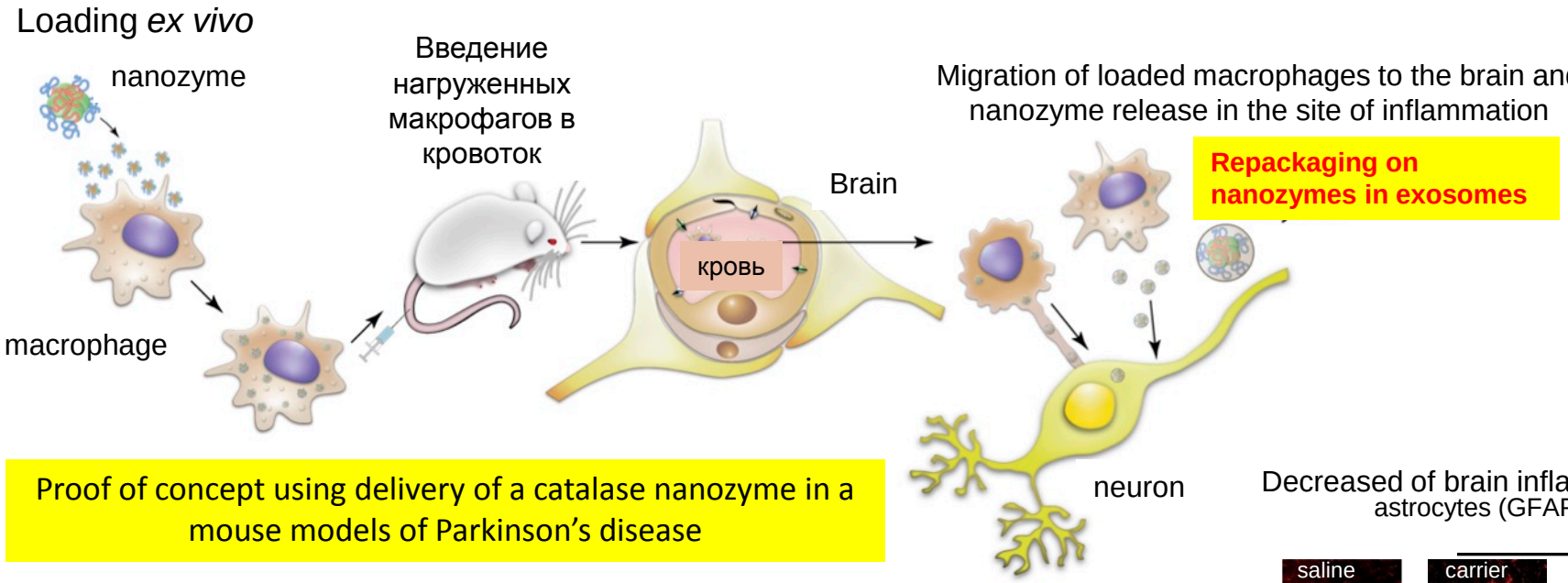
The inflammatory process in the brain provides an opportunity for targeting of therapeutics to the brain.





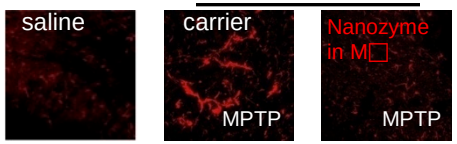
Microglia activation in MS brain

Use of macrophages (M□) as “Trojan horses” for delivery of therapeutic nanozymes in the areas of inflammation in the brain

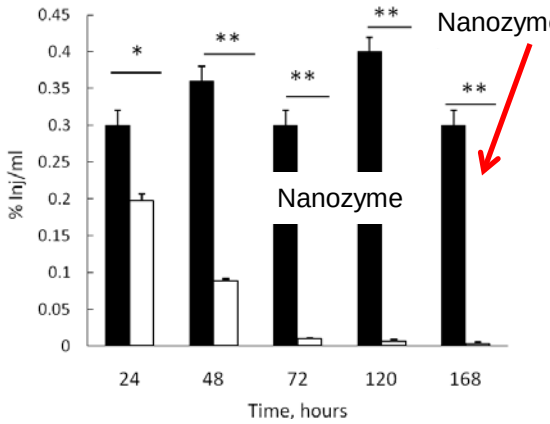


Proof of concept using delivery of a catalase nanozyme in a mouse models of Parkinson’s disease

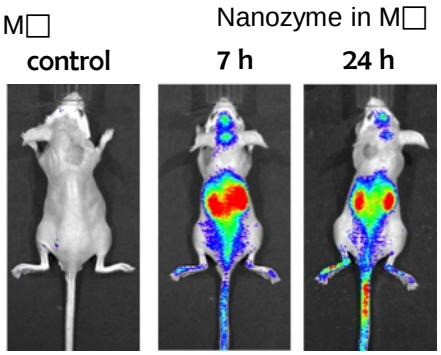
Decreased of brain inflammation
astrocytes (GFAP)



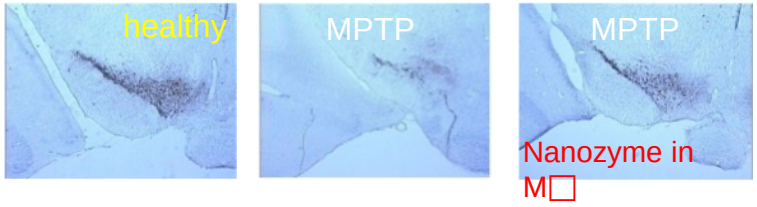
Increased blood circulation time compared to free nanozyme



Delivery of nanozymes in cells to the brain in MPTP mouse model of PD



Neuronal survival in the PD mouse model

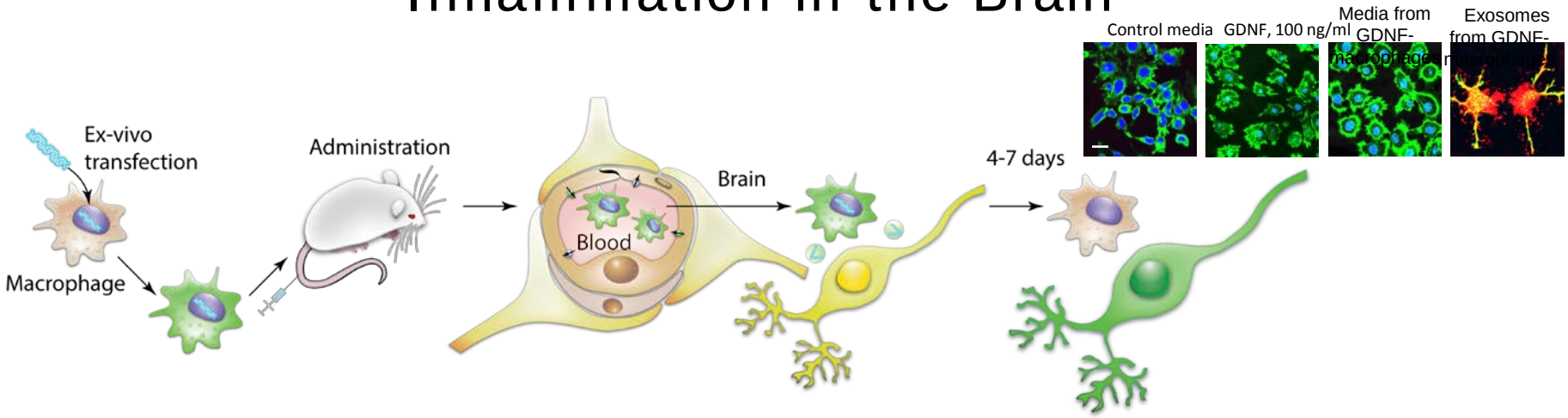


A. Brynskikh et al. *Nanomedicine (Lond.)* **2010**, 53:379

Y. Zhao et al. *Nanomedicine (Lond.)* **2011**, 6:25

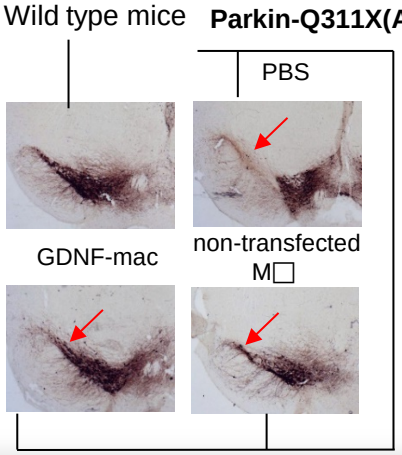
M. Haney et al. *Nanomedicine (Lond.)* **2012**, 7:815

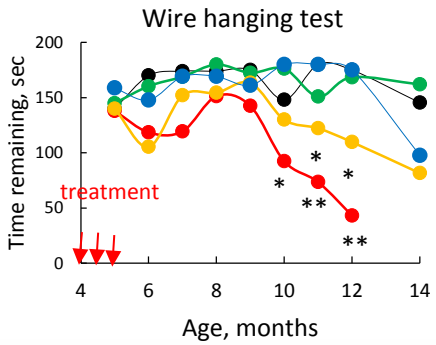
Adoptive Transfer of Genetically Modified M□ to Target Inflammation in the Brain

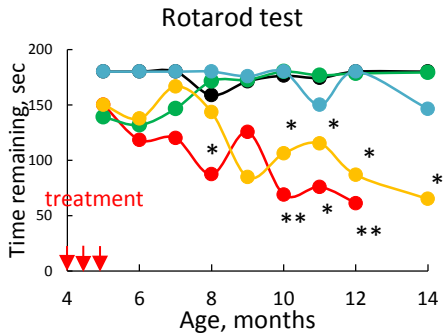


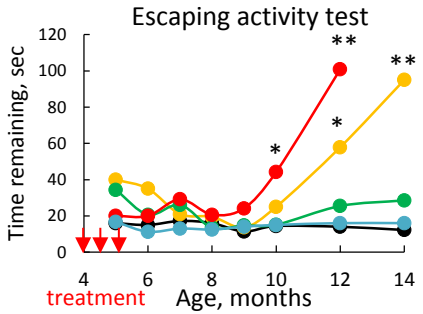
Haney et al. *PLoS ONE* 2013 8(4): e61852 Zhao et al. *PLoS ONE* 2014 9(9): e106867

Neuroprotective effects of GDNF-transfected macrophages in Parkin-Q3111X(A) mouse model

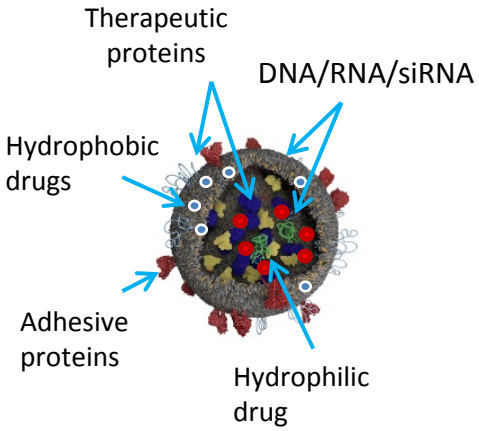


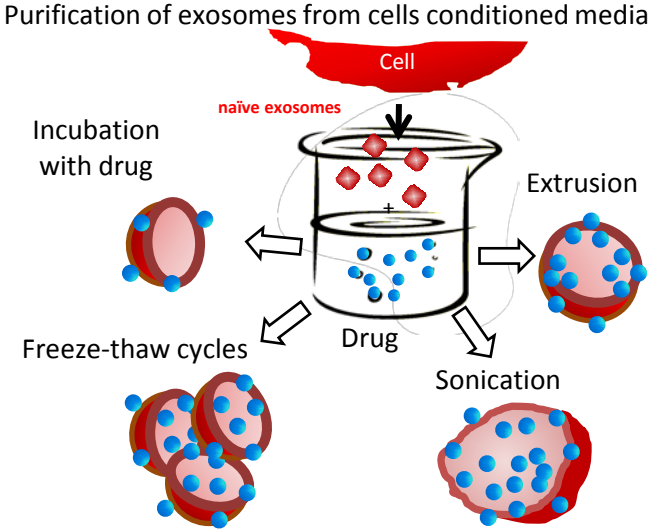




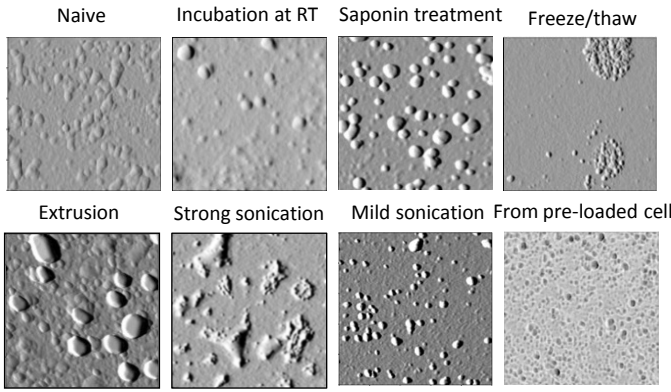


Exosome as protein carriers to brain in inflammation

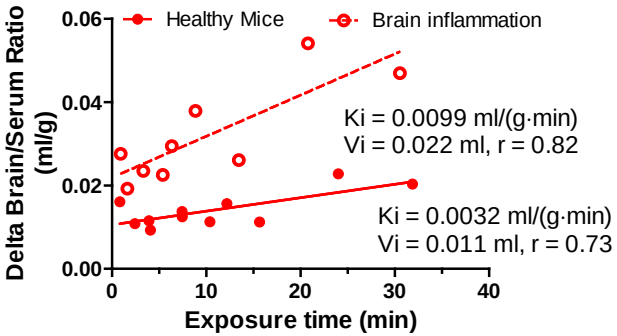


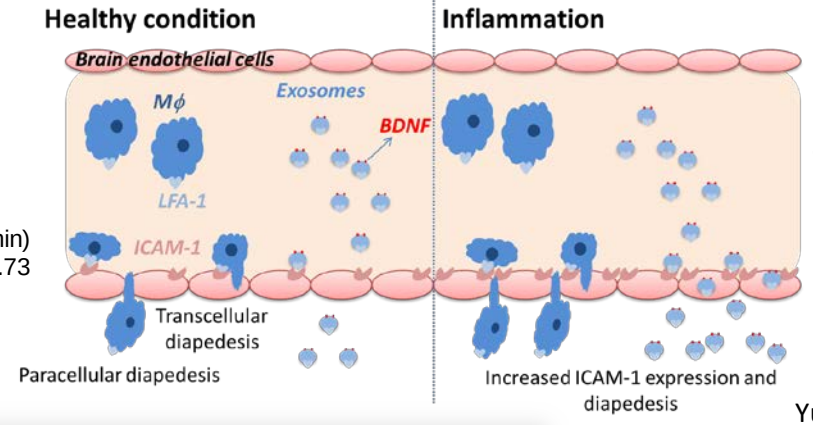


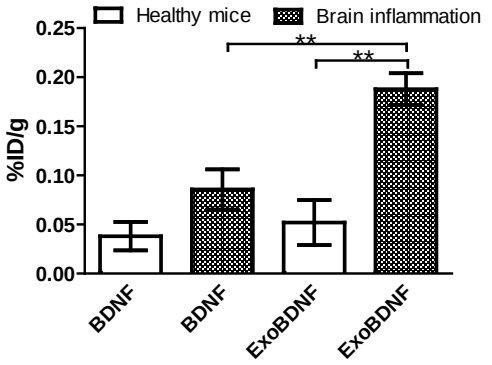
Exosome-based drug formulations



Increased brain accumulation of exosomes and neurotrophin (BDNF) under brain inflammation



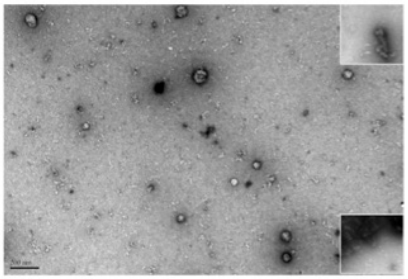




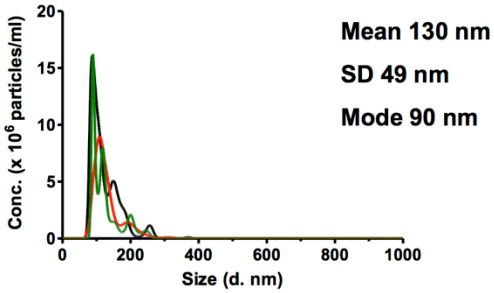
Yuan, et al. *Biomaterials* 142 (2017) 1e12

Use of macrophage (M□) exosomes for delivery of proteins to the sites of inflammation in the brain

Exosomes

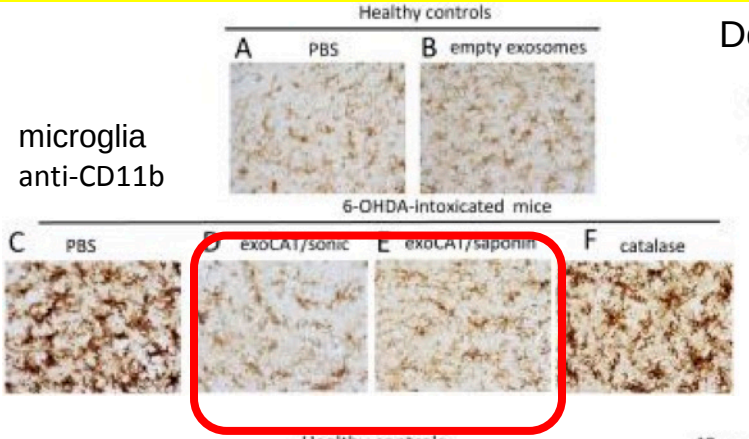


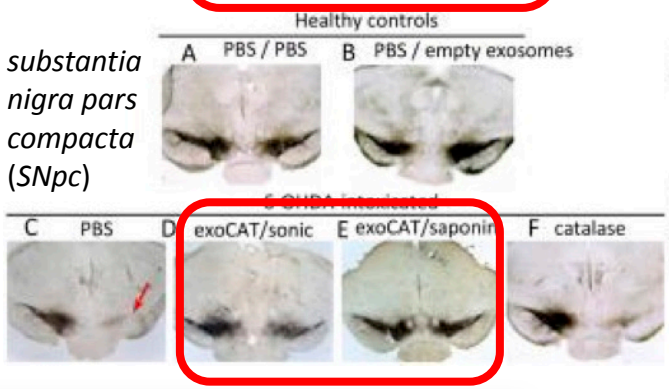
Exosomes are isolated from macrophages (M2) and loaded with catalase



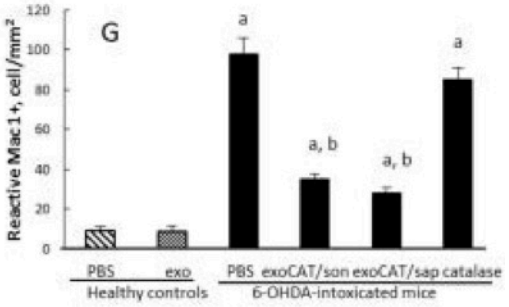
Particle size before and after loading

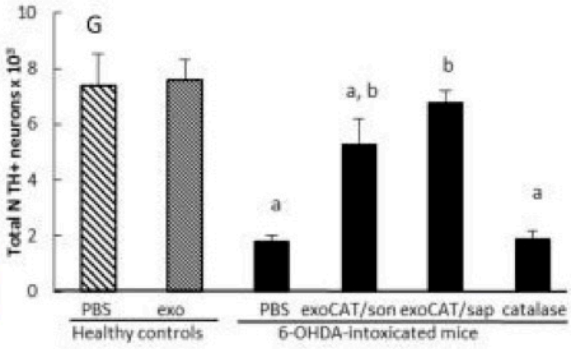
Anti-inflammatory and neuroprotective effects of macrophage (M2) exosomes loaded with catalase and administered intranasal in a mouse model of Parkinson's disease (6-OHDA in SNpc)





Decrease of brain inflammation





Journal of Controlled Release **2015**, 207:18–30

Value proposition

- A) To deliver **therapeutic proteins** to the brain by using engineered exosomes to target to target sites of inflammation associated with the disease

  Potential upside “in the works”: to deliver DNA, siRNA, and mRNA using exosomes

- B) To deliver proteins, nucleic acids and nanoparticles to the brain and develop respective therapeutic using genetically engineered macrophages after adoptive transfer to target to target sites of inflammation associated with the disease