

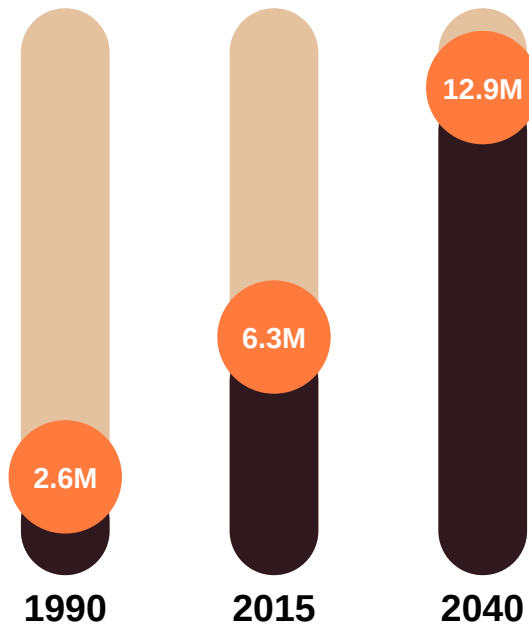
# Dopamine-modified Exosome : Autophagy Induction and Therapeutic Potential In Parkinson's Disease

# Parkinson's Disease : A growing global health challenge

## Parkinson's disease symptoms



## Number of people with Parkinson's disease globally



## number of deaths per 100,000 people due to Parkinson's disease in the United States

1976

1.6 people



1983

2.3 people



1990

3.2 people



1997

4.6 people



2004

6.2 people



2011

7.0 people



2017

8.4 people



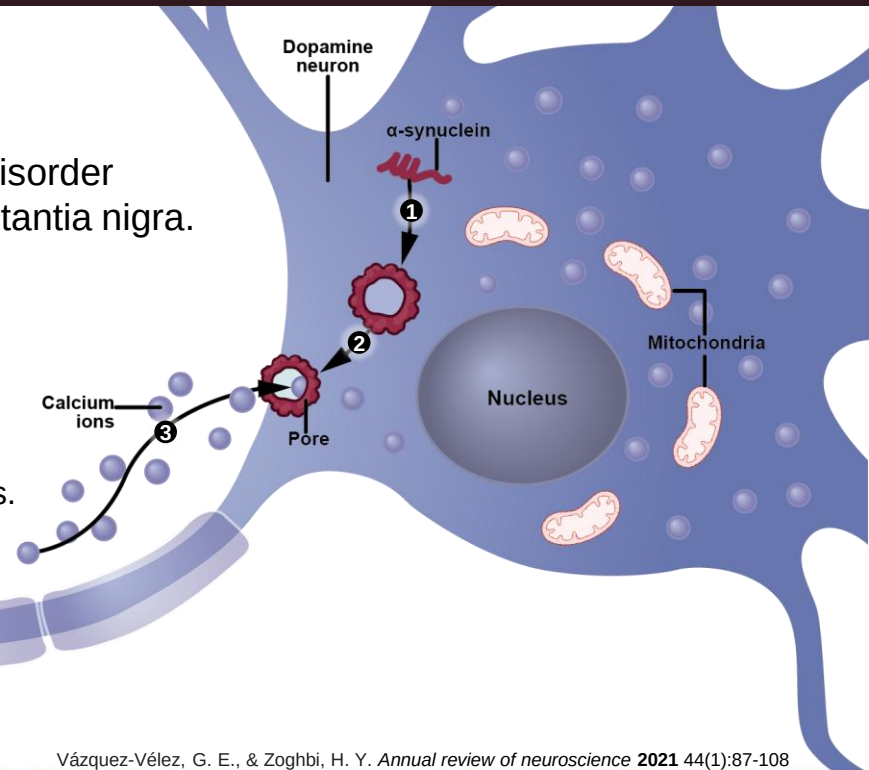
Dorsey, E. Ray, et al. *Journal of Parkinson's disease* 2018 8(s1):S3-S8

# 1 Introduction

## Death or damage of dopamine neurons

**Parkinson's disease (PD)** is a progressive neurodegenerative disorder resulting from the death of dopaminergic neurons in the substantia nigra.

- ① Single  $\alpha$ -synuclein molecules bind together in a doughnut shape
- ② They insert into the plasma membrane and form a pore
- ③ This pore allows calcium ions to accumulate in the cell at toxic levels.



Vázquez-Vélez, G. E., & Zoghbi, H. Y. *Annual review of neuroscience* **2021** 44(1):87-108

# 1 Introduction

## Exosome: Mediator of Cell-to-Cell communication

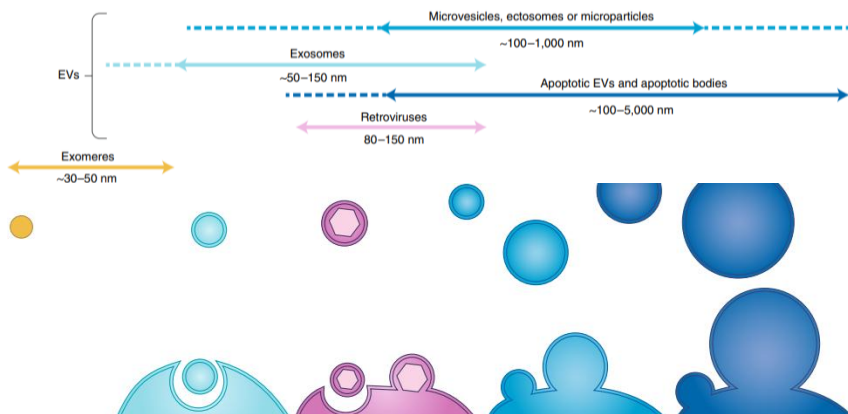
nature  
cell biology

FOCUS | PERSPECTIVE  
<https://doi.org/10.1038/n41556-018-0290-9>

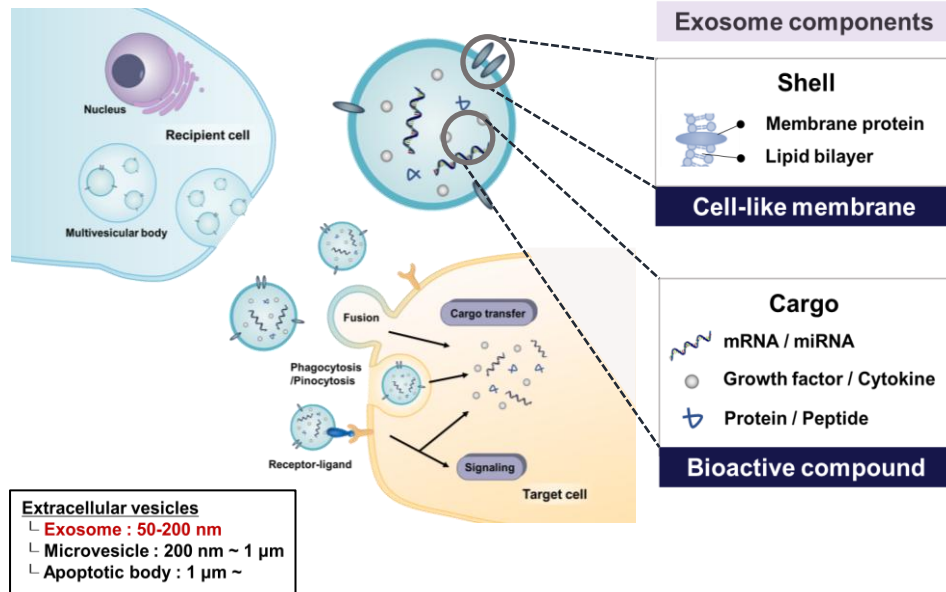
### Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication

Mathilde Mathieu<sup>1,2</sup>, Lorena Martin-Jaular<sup>1</sup>, Grégory Lavieu<sup>1</sup> and Clotilde Théry<sup>1\*</sup>

The ability of exosomes to transfer cargo from donor to acceptor cells, thereby triggering phenotypic changes in the latter, has generated substantial interest in the scientific community. However, the extent to which exosomes differ from other extracellular vesicles in terms of their biogenesis and functions remains ill-defined. Here, we discuss the current knowledge on the specificities of exosomes and other types of extracellular vesicles, and their roles as important agents of cell-to-cell communication.



### Mediator of Cell-to-cell Communication



Mathieu, Mathilde, et al. *Nature cell biology* 2019 21(1):9-17

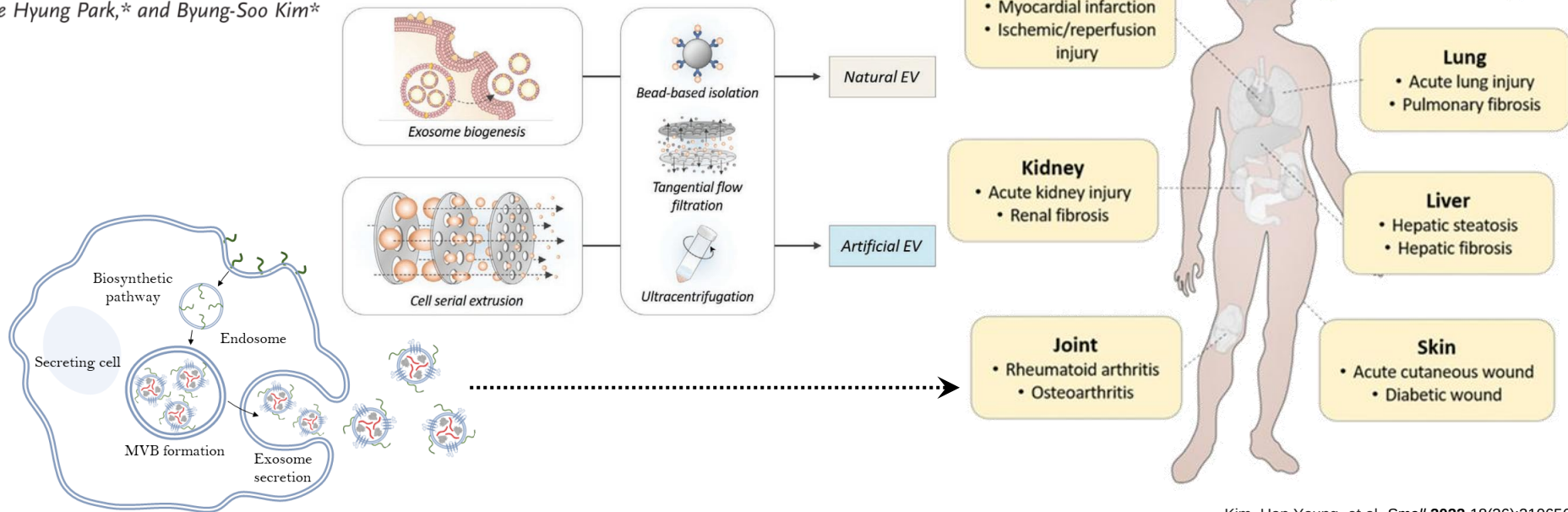


# 1 Introduction

## Stem cell-derived exosomes

### Functional Extracellular Vesicles for Regenerative Medicine

Han Young Kim, Seunglee Kwon, Wooram Um, Sol Shin, Chan Ho Kim,  
Jae Hyung Park,\* and Byung-Soo Kim\*



Kim, Han Young, et al. *Small* 2022 18(36):2106569

# 1 Introduction

## In vivo Biodistribution of exosomes



Contents lists available at ScienceDirect

Journal of Controlled Release

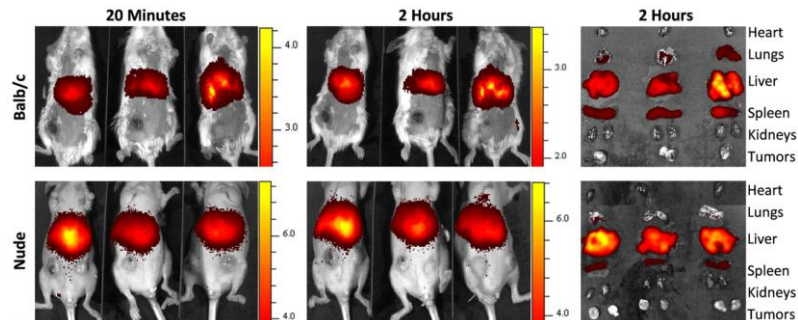
journal homepage: [www.elsevier.com/locate/jconrel](http://www.elsevier.com/locate/jconrel)



PEGylated and targeted extracellular vesicles display enhanced cell specificity and circulation time

S.A.A. Kooijmans<sup>a</sup>, L.A.L. Fliervoet<sup>b</sup>, R. van der Meel<sup>a,c</sup>, M.H.A.M. Fens<sup>a</sup>, H.F.G. Heijnen<sup>a</sup>, P.M.P. van Bergen en Henegouwen<sup>d</sup>, P. Vader<sup>a</sup>, R.M. Schiffelers<sup>a,\*</sup>

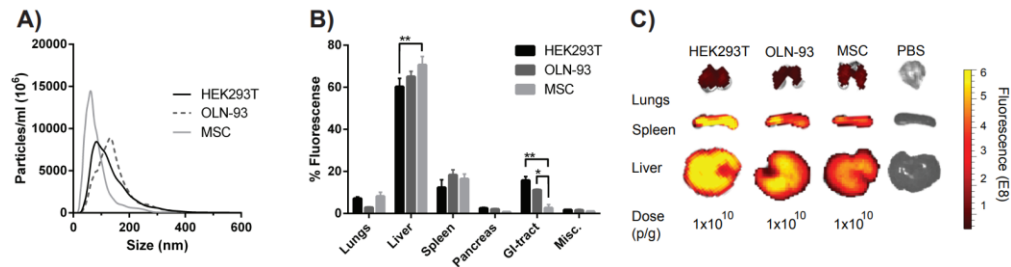
Extracellular vesicles (EVs) are increasingly being recognized as candidate drug delivery systems due to their ability to functionally transfer biological cargo between cells. However, the therapeutic applicability of EVs may be limited due to a lack of cell-targeting specificity and rapid clearance of exogenous EVs from the circulation. In order to improve EV characteristics for drug delivery to tumor cells, we have developed a novel method



Journal of  
Extracellular Vesicles

ORIGINAL RESEARCH ARTICLE

## Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting



Kooijmans, S. A. A., et al. *Journal of controlled release* **2016** 224:77-85  
Wiklander, Oscar PB, et al. *Journal of extracellular vesicles* **2015** 4(1):26316

# Dopamine receptor targeting



molecules

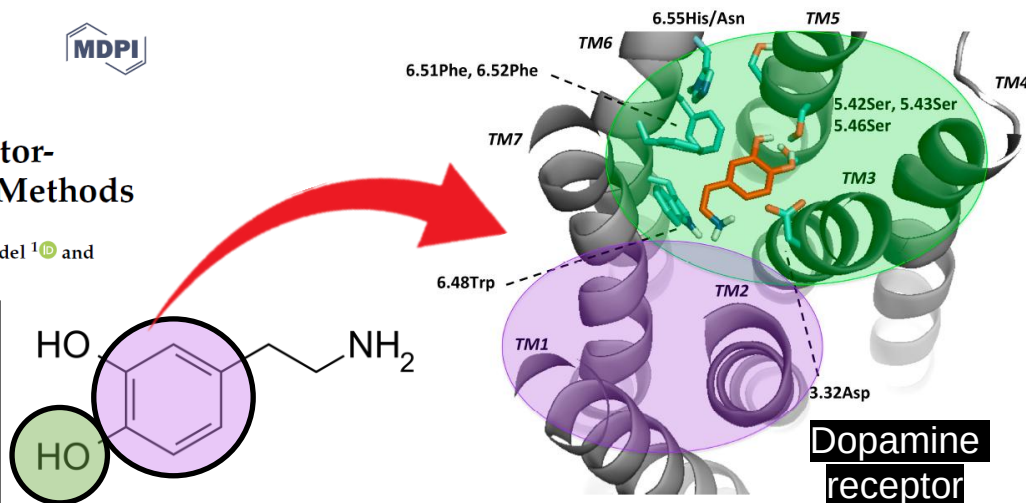
Article

## A Complete Assessment of Dopamine Receptor-Ligand Interactions through Computational Methods

Beatriz Bueschbell <sup>1</sup>, Carlos A. V. Barreto <sup>2</sup>, António J. Preto <sup>2</sup>, Anke C. Schiedel <sup>1</sup> and Irina S. Moreira <sup>2,3,\*</sup>

**TM5 (5.42Ser, 5.43Ser, 5.46Ser)=(Ser193, 194, 197)**

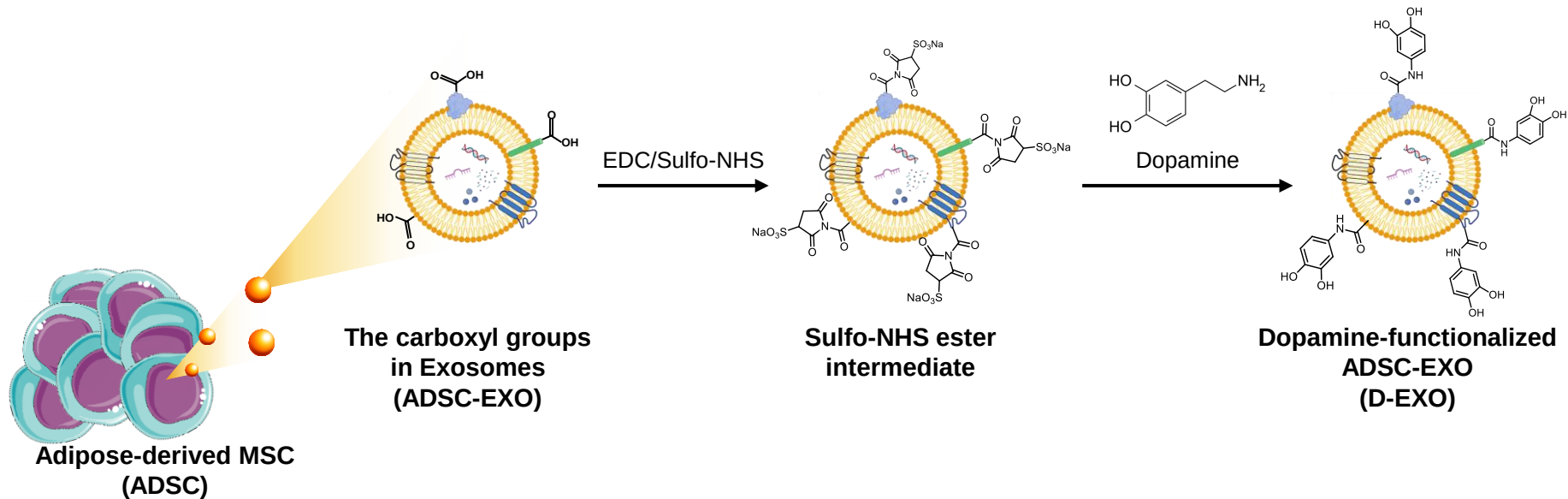
important feature for dopaminergic binding in all DRs the serines form hydrogen bonds with the catechol hydroxyls of dopamine increasing the binding affinity and orienting ligands in the orthosteric binding pocket the aromatic microdomain, consisting of 6.48Trp, 6.51Phe, 6.52Phe and 6.55His/Asn was reported to trigger the activation of the dopamine receptor.



**Figure 2.** Key residues for molecular docking of Dopamine to DR models. Residues were designated in bold and colored in cyan, TMs in bold and italic. This set-up was kept for Figures S3–S7 and highly corresponds to the definition of the binding pocket of Floresca and Schnetz [47]. The area of the orthosteric and secondary binding pockets were colored and violet, respectively.

Bueschbell, Beatriz, et al. *Molecules*, **2019** 24(7):1196

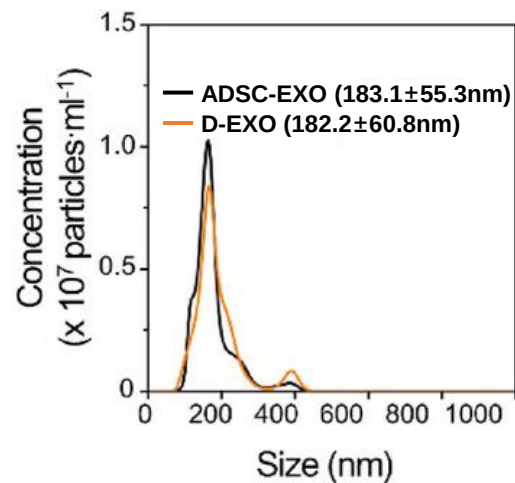
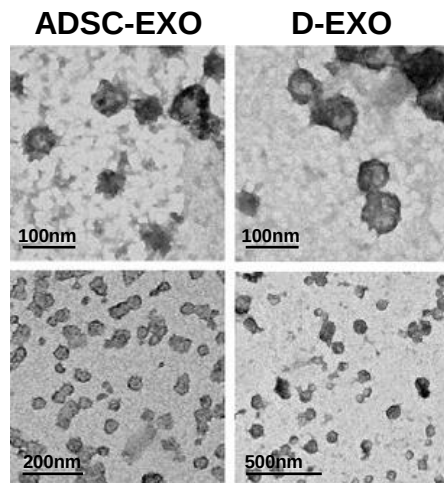
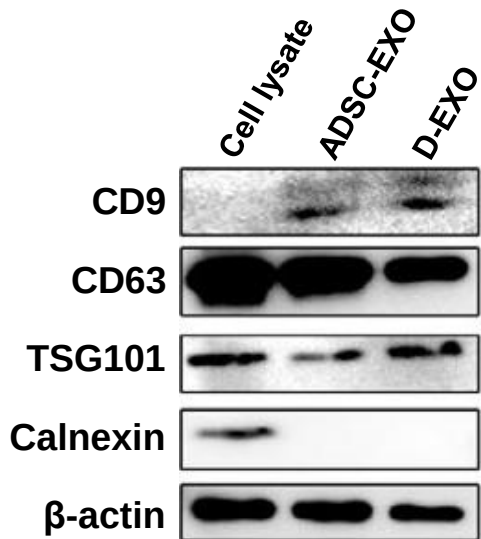
## 2 Strategy Surface Engineering Strategies



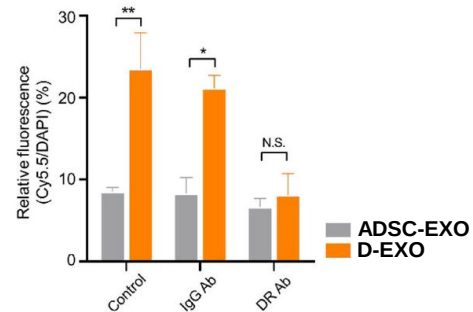
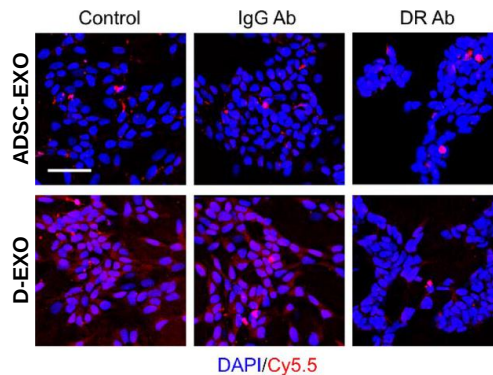
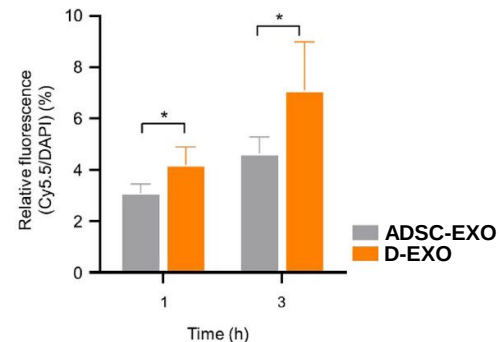
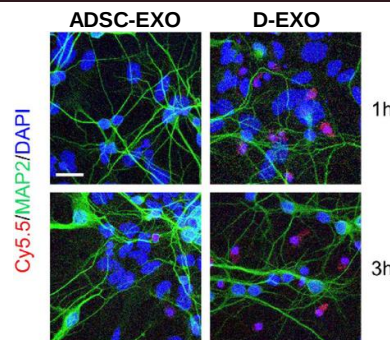
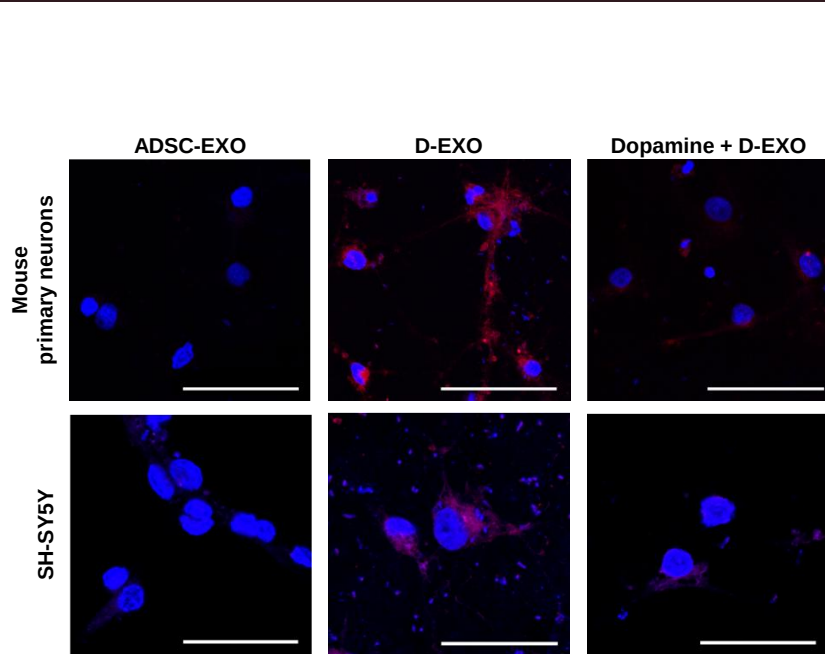


### 3 Result

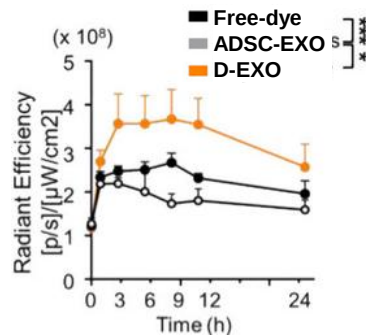
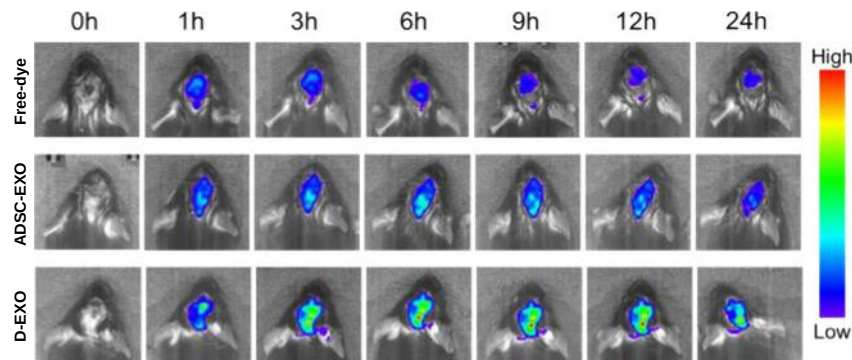
## Characterization of D-EXO



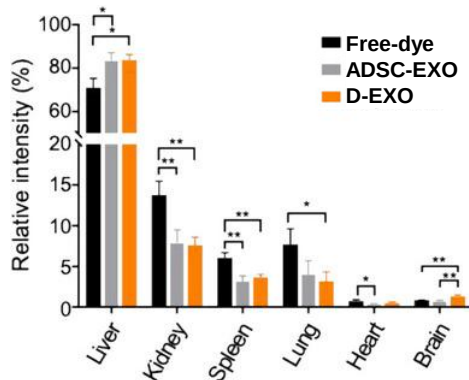
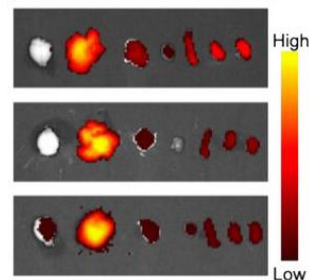
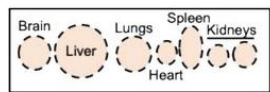
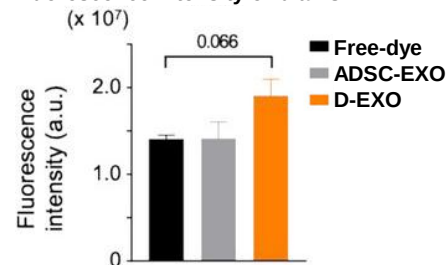
# Neuronal delivery of D-EXO *in vitro*



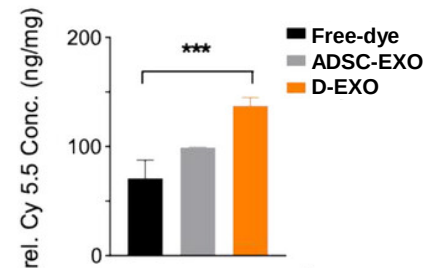
# Neuronal delivery of D-EXO *in vivo*



Quantification of fluorescence intensity of brains

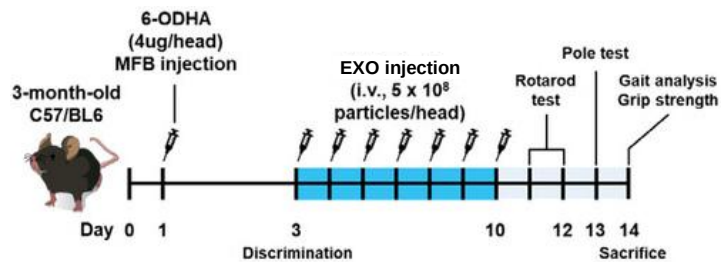


Quantification of fluorescence of brain homogenates

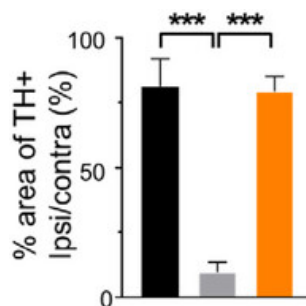
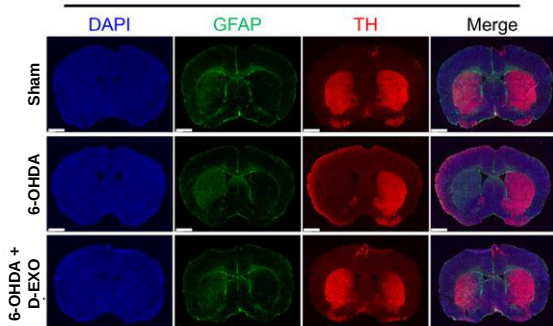


# 3 Result

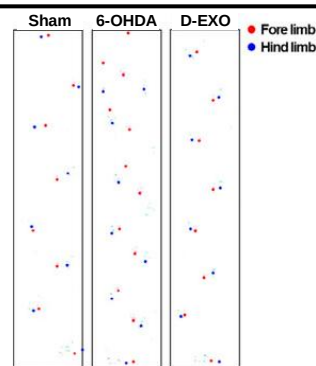
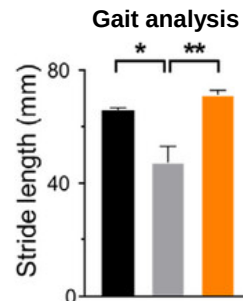
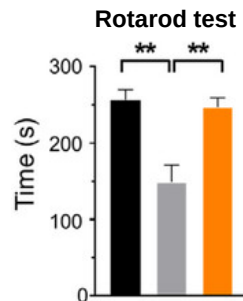
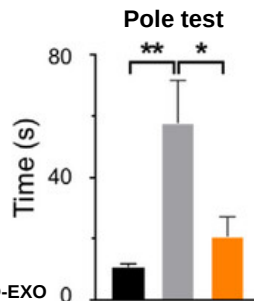
## Therapeutic efficacy of D-EXO



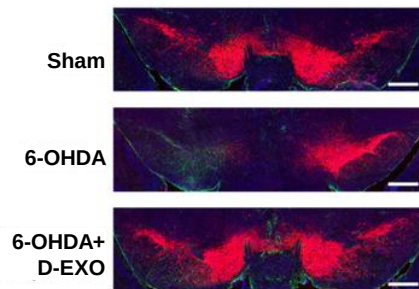
Striatum



### Behavioral assessment

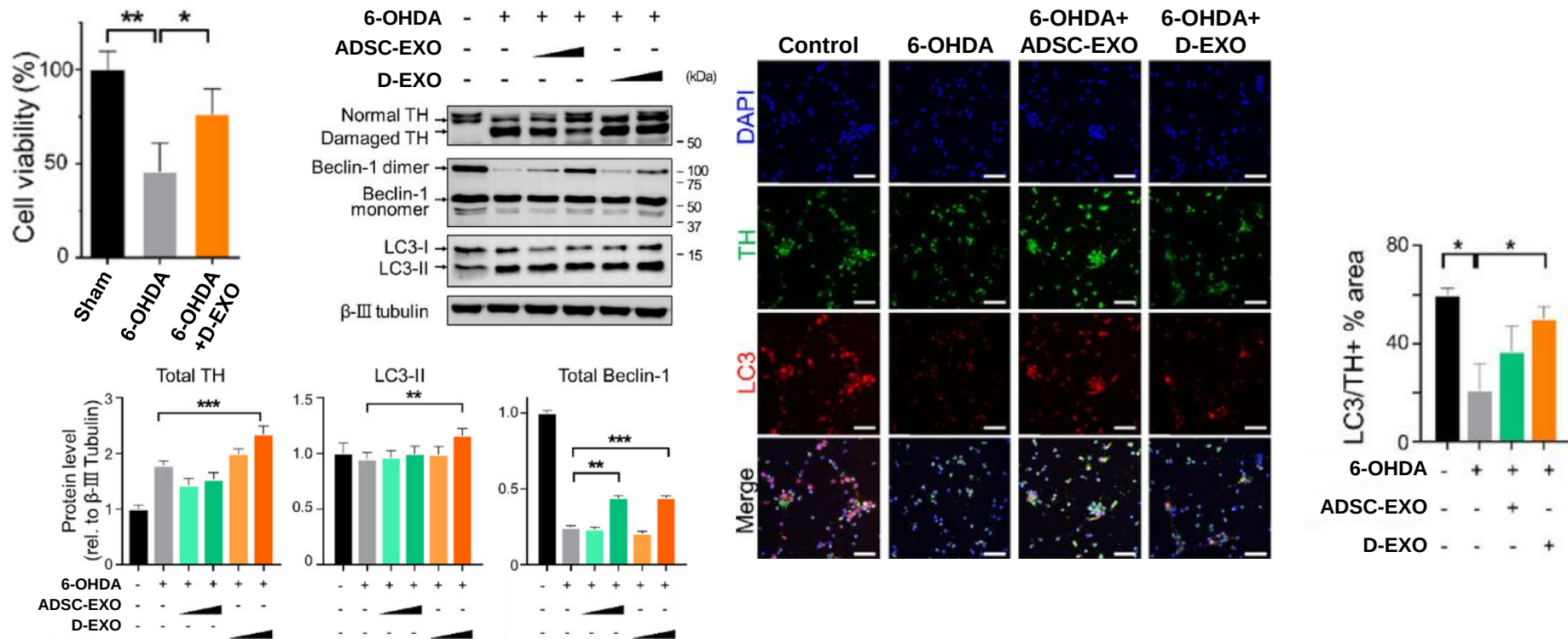


Substantia nigra

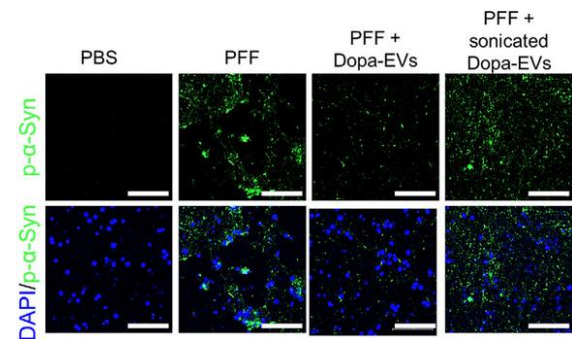
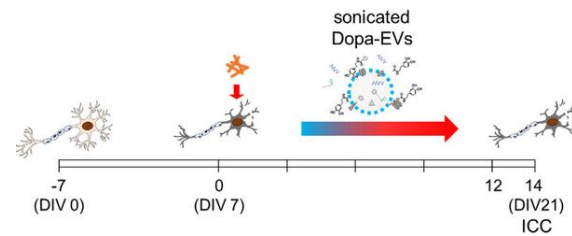
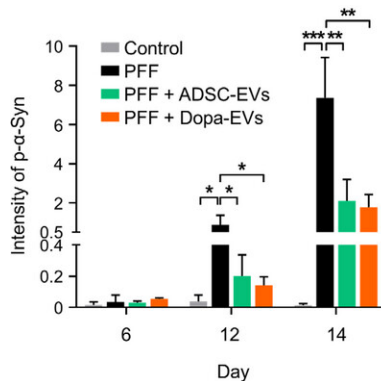
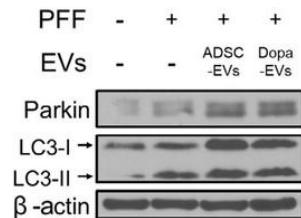
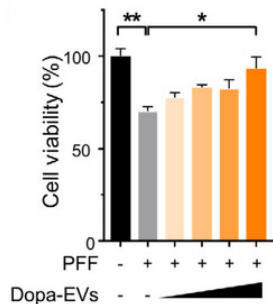
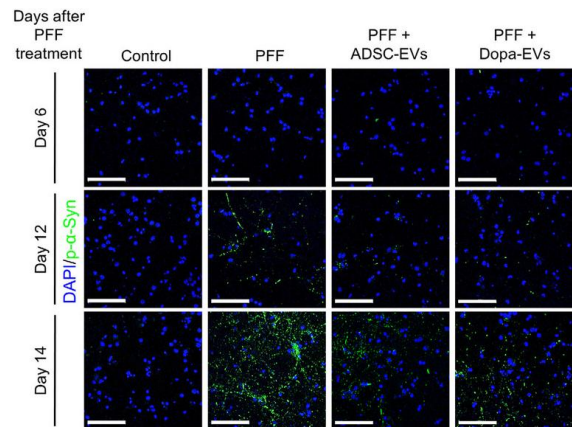
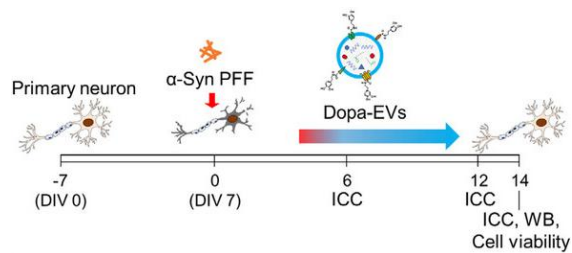




# Neuroprotective effect of D-EXO via autophagy induction

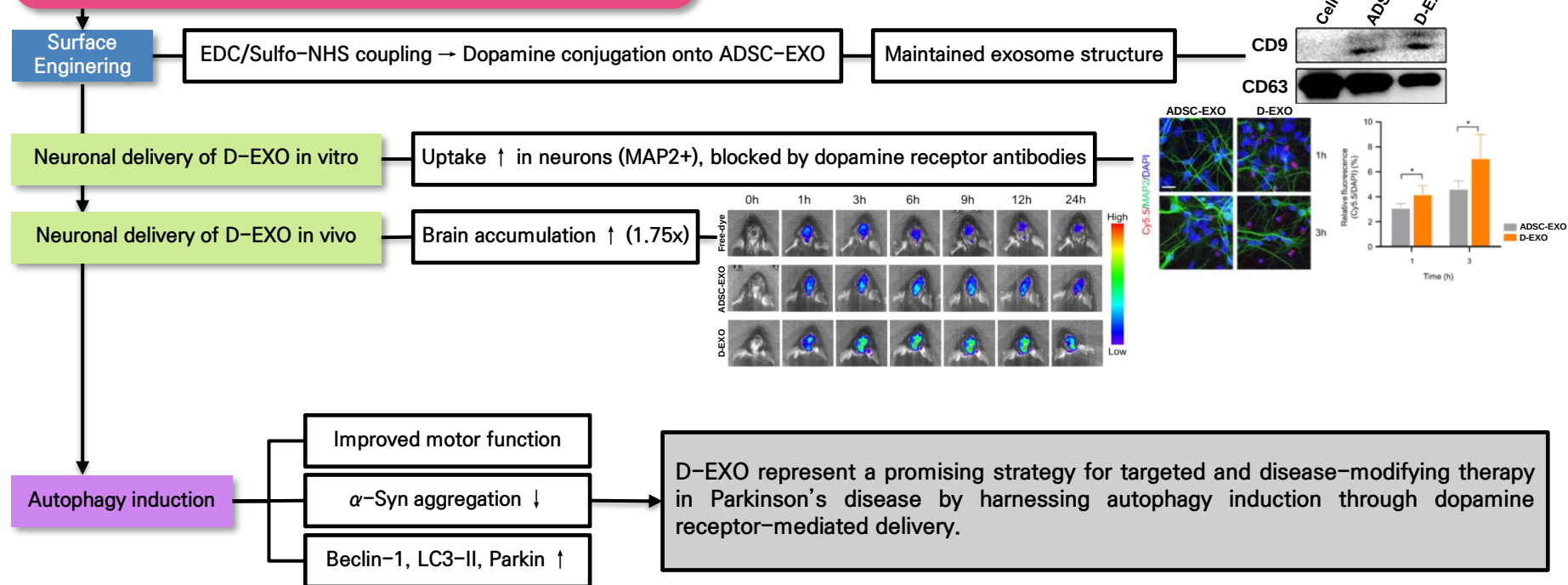


# Neuroprotective effect of D-EXO via autophagy induction



# Summary of D-EXO strategy in Parkinson's Disease

Can Exosomes be directed to dopamine receptors for specific delivery?





A whimsical illustration of a man with dark hair and a purple shirt, looking upwards. He is surrounded by a variety of floating objects: a grey cat, a brown and white dog, a bee, a fried egg, a bowl of soup, a bottle of laundry detergent, a box of milk, a slice of pizza, a shrimp, and various colorful flowers and leaves. The background is a light yellow with stylized clouds.

**Thank you for listening**