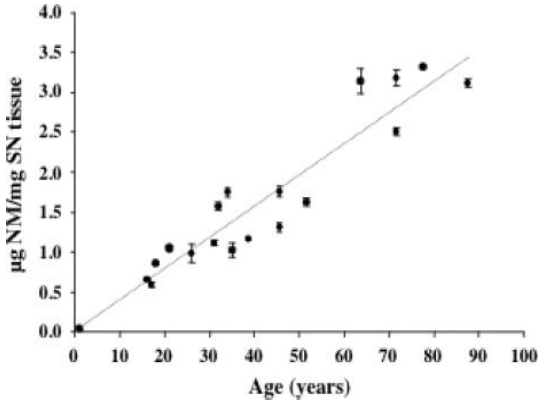
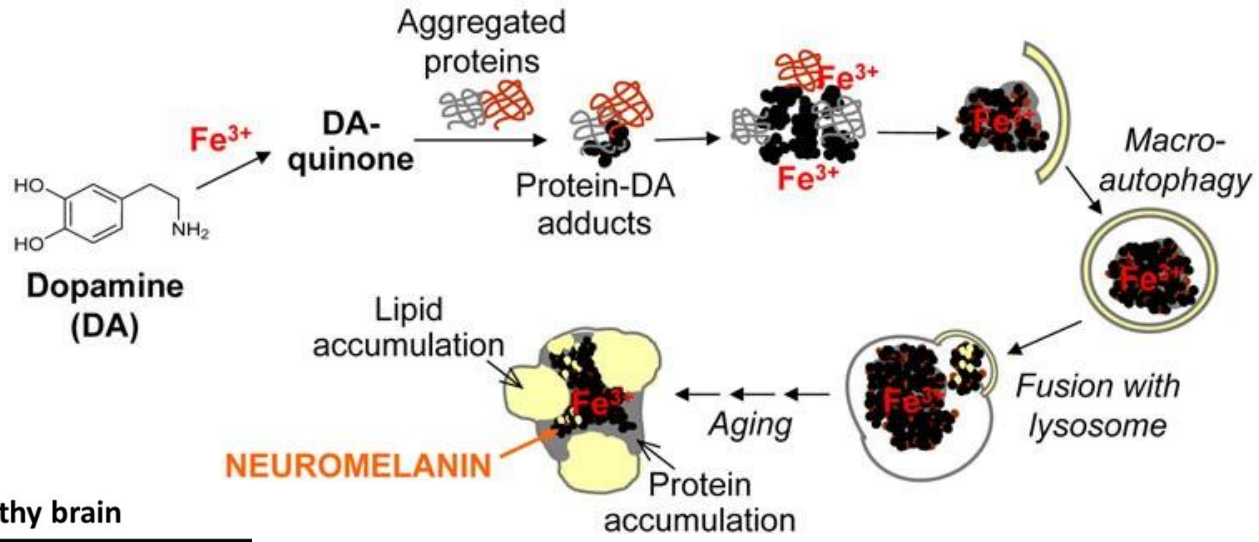
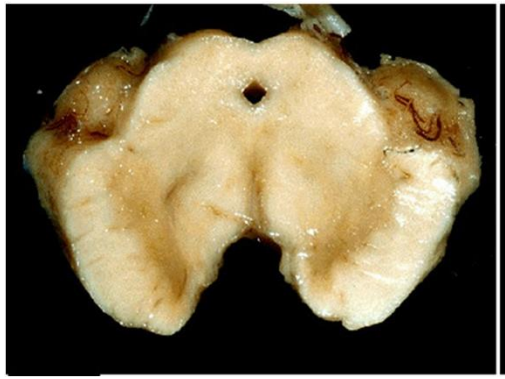
Vulnerability of dopaminergic neurons in Parkinson's disease: the role of neuromelanin

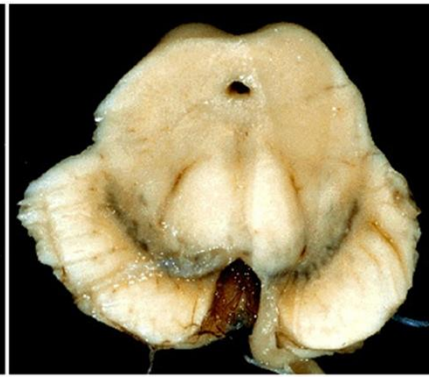




PD brain

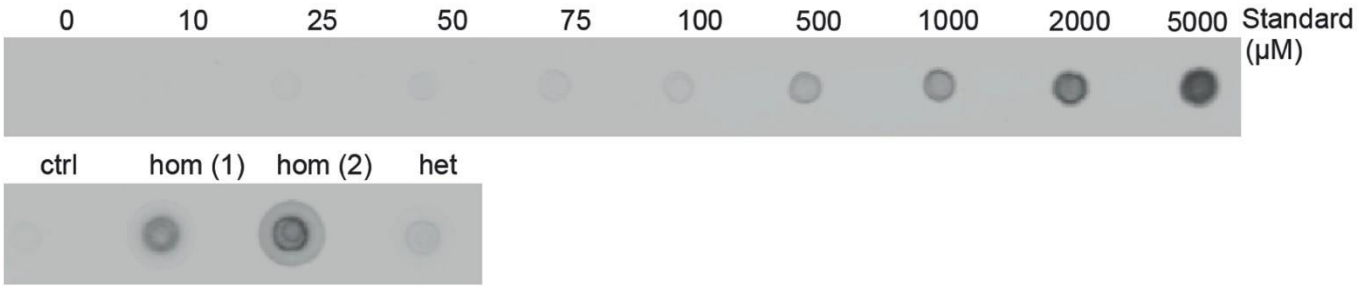


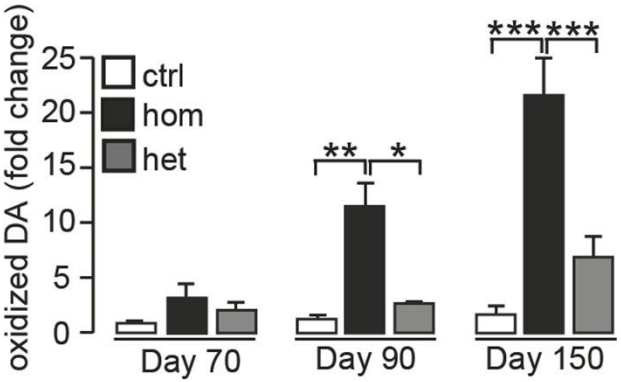
Healthy brain

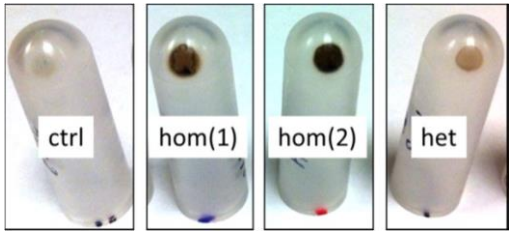


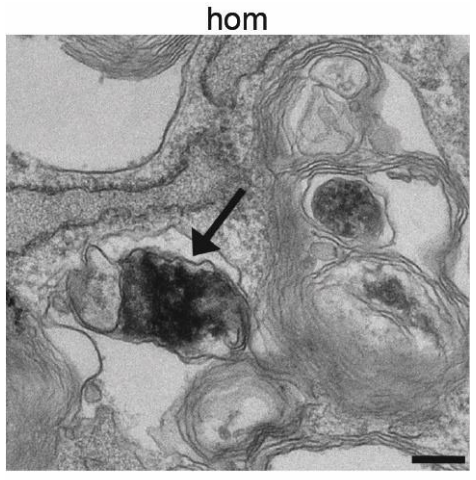
- Neuromelanin normally accumulates with age in nigral dopaminergic neurons
- Neuroprotective role - neuromelanin is chelator for metals, oxidized products
- Dopamine quinone-derived adducts not sequestered in neuromelanin considered toxic
- No neuromelanin detected in rodent substantia nigra

Accumulation of oxidized dopamine and neuromelanin in iPS-derived DA neurons from patients with Parkinson's disease





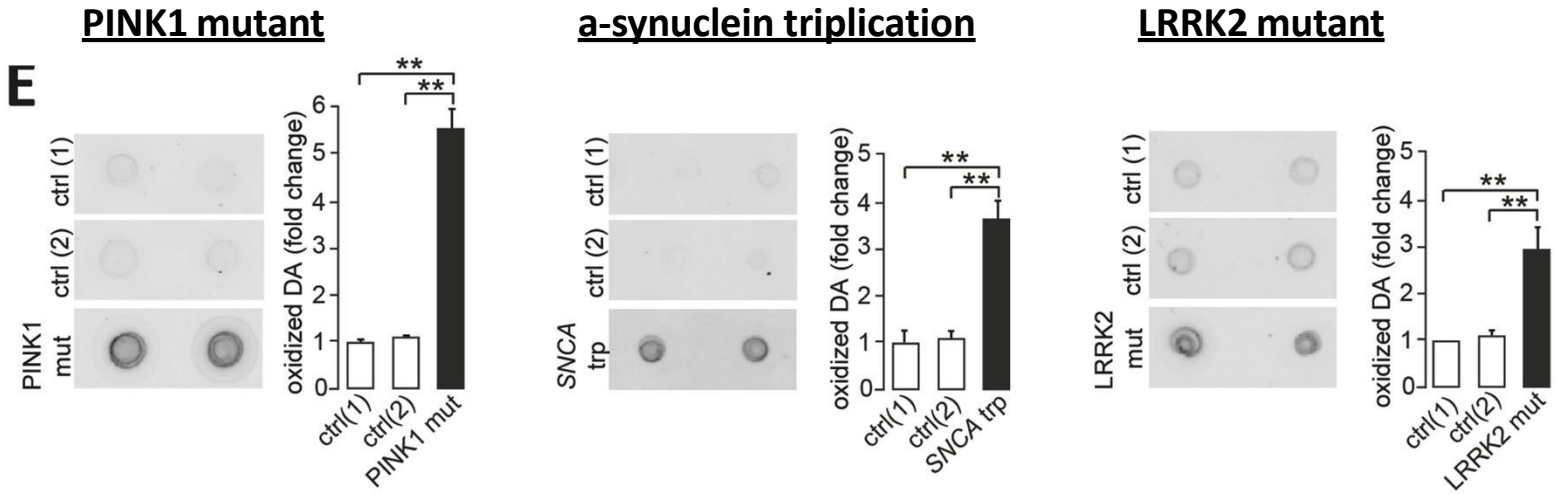




Lena Burbulla

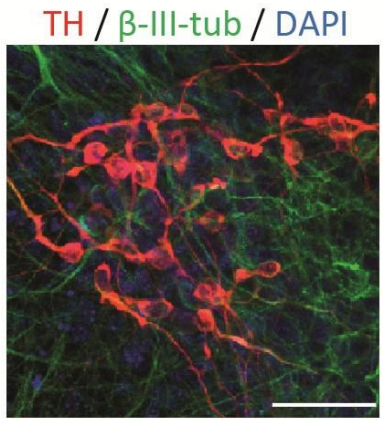
Burbulla et al., *Science*, 2017

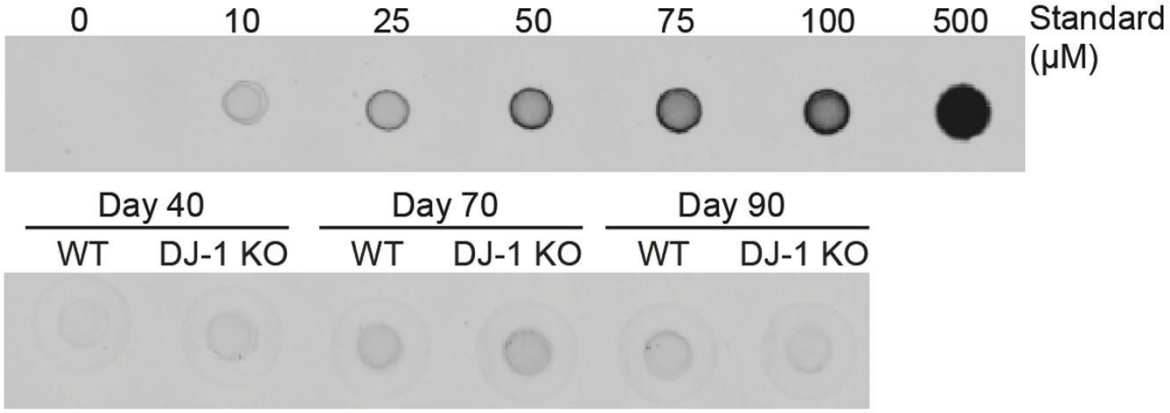
Accumulation of oxidized dopamine in neurons from patients with genetic forms of PD



Burbulla et al., *Science*, 2017

No accumulation of oxidized dopamine in iPS-derived dopaminergic neurons from PD mouse models

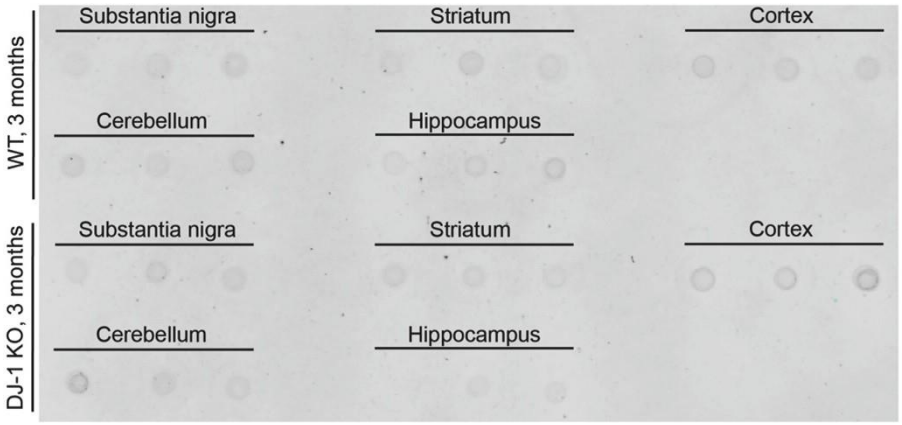




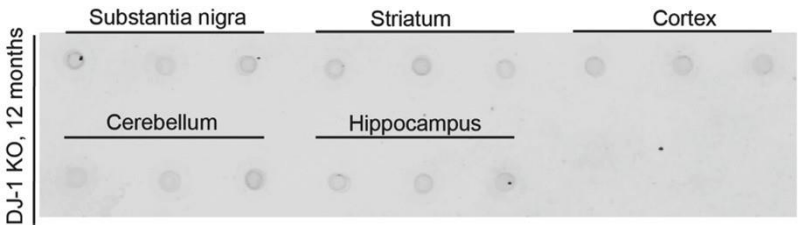
Burbulla et al., *Science*, 2017

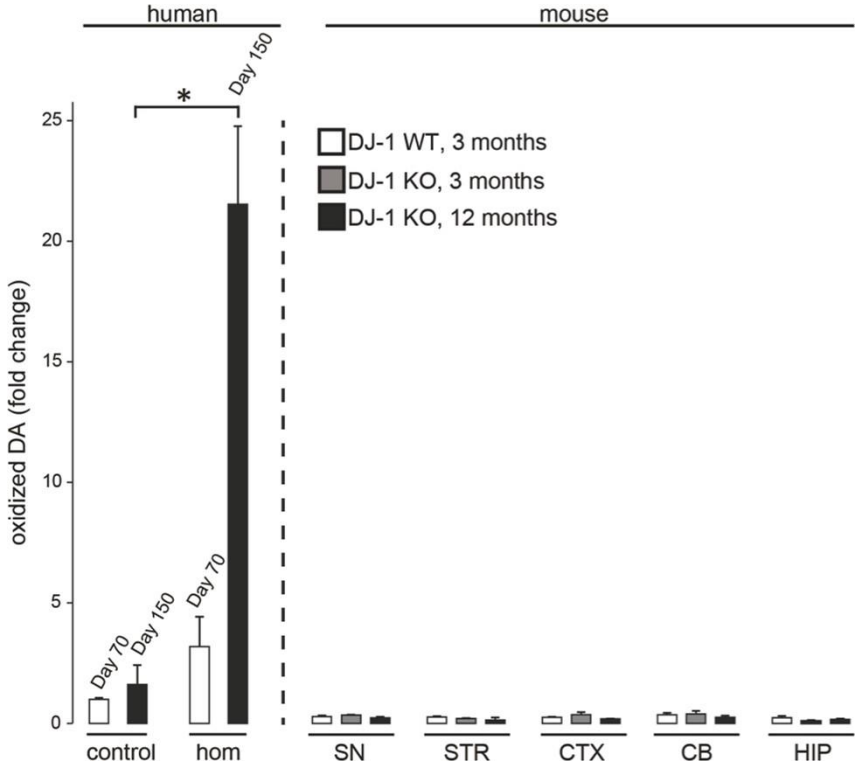
No accumulation of oxidized dopamine in PD mouse models

3 months old mice



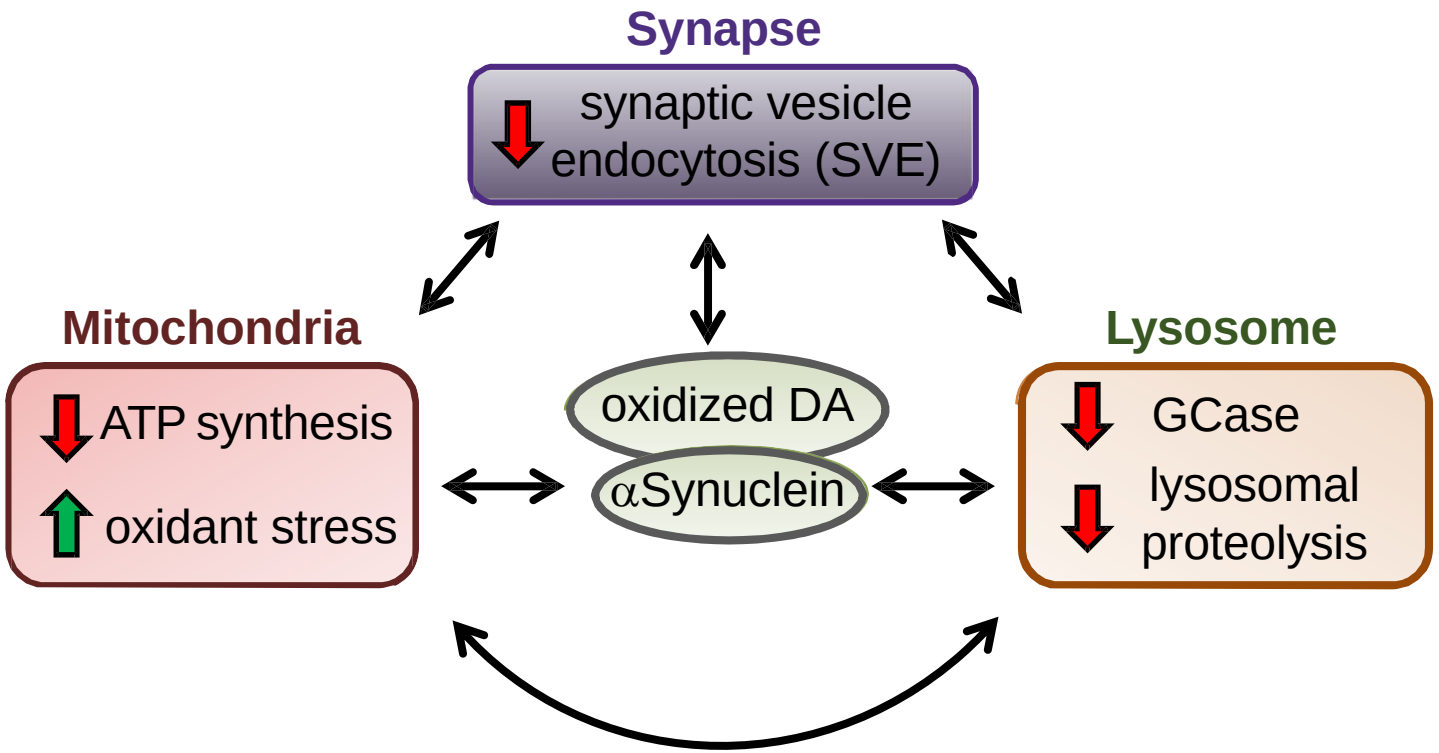
12 months old mice





Burbulla et al., *Science*, 2017

Mitochondrial, lysosomal and synaptic dysfunction in human dopaminergic neurons in PD



Burbulla et al., *Science,* 2017
Wong et al. *Nature*, 2018
Nguyen & Krainc, *PNAS*, 2018
Burbulla et al., *Sci Transl Med,* 2019
Wong, Peng et al, *Dev Cell*, 2019
Kim et al, *Nature Commun (2021)*
Mazzulli et al., *Cell*, 2011

Session 3- Key Discussion Questions:

- What is the role of different animal and human model systems for discovery and validation?
- How can these approaches be used to gain a better understanding of different variants' impact on the disease state (e.g., variant to function), including phenotypic expression and differential vulnerability.
- How can greater ancestral diversity and the incorporation of environmental influences in genetic studies provide better insight into the phenotypic expression of neuropsychiatric disease states, and what are the implications for target validation?
- What scientific findings and lessons learned from rare variants and monogenetic diseases can be applied to more genetically complex common disorders?
- What criteria do different decision makers use when deciding how to validate biomarkers and select which targets to invest in and advance to clinic?

Speakers

Helen Willsey, University of California, San Francisco
Fenna Krienen, Harvard Medical School
Paola Arlotta, Harvard University
Martin Kampmann, University of California, San Francisco
Daphne Koller, Insitro
Alice Zhang, Verge Genomics