

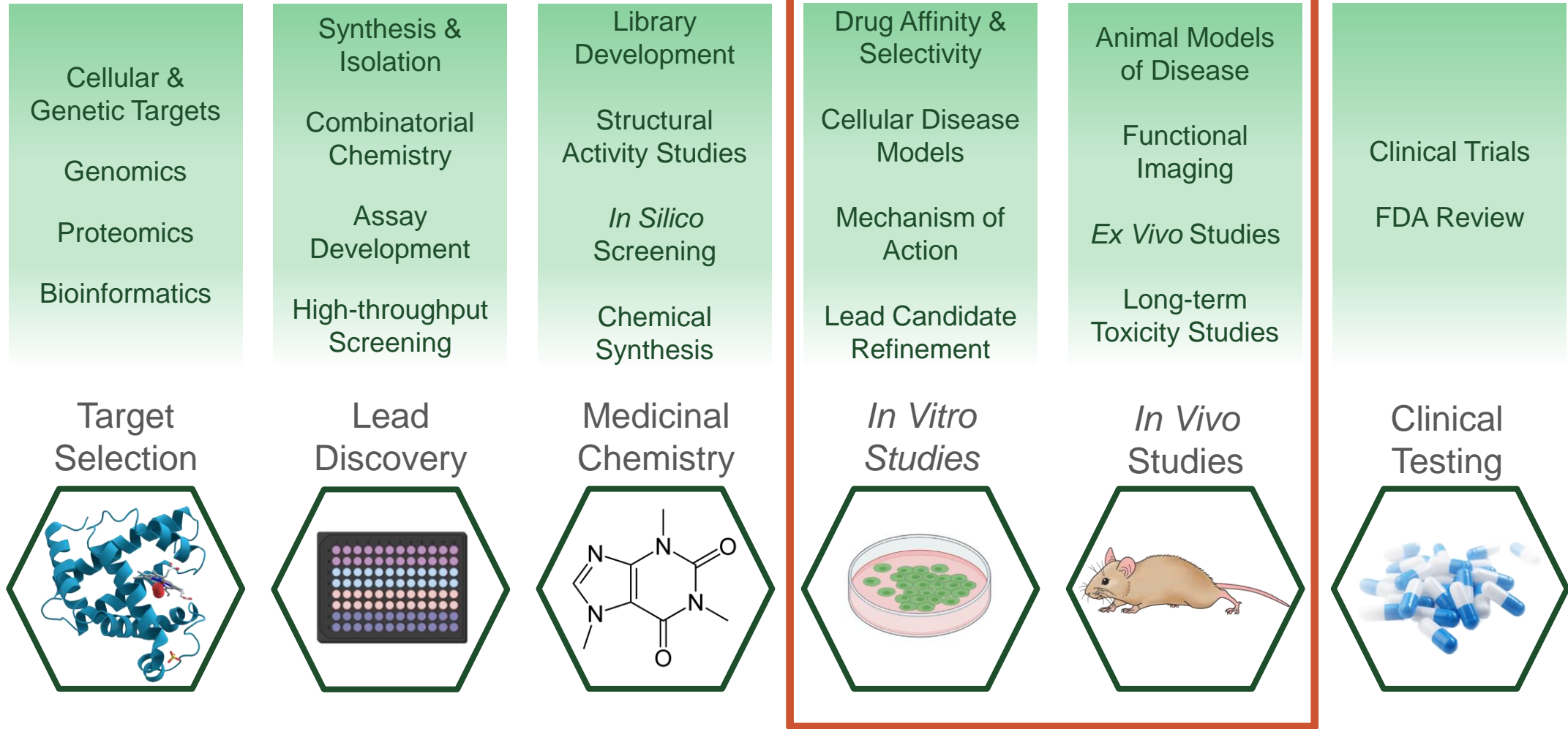
Cellular and animal models of prions and ADRD

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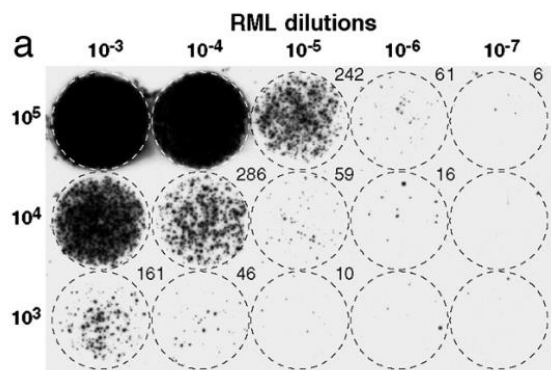
Colorado State University

Drug Discovery Process

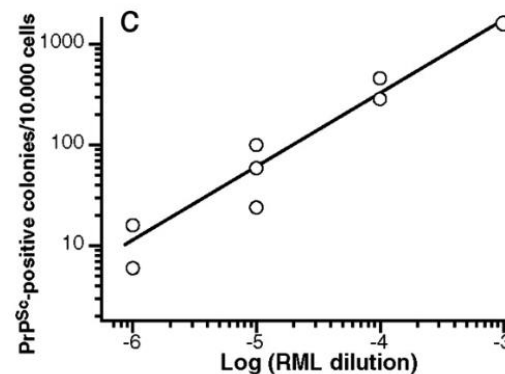
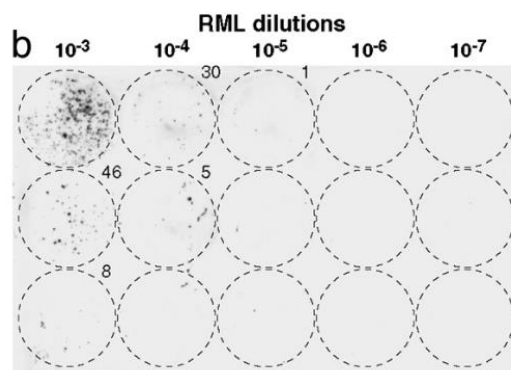


Induced cell models to investigate prion strain biology

Weissmann's scrapie cell assay



Klöhn, *et al.*, *PNAS*, 2003



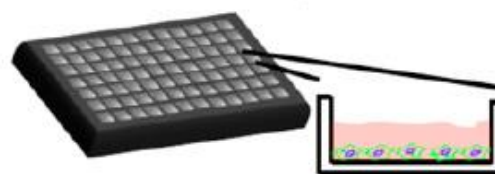
Overlapping approaches

- Primary neuronal cultures
- Differentiated iPSCs
- Organotypic slices
- Organoids



*Pol – Protein of Interest

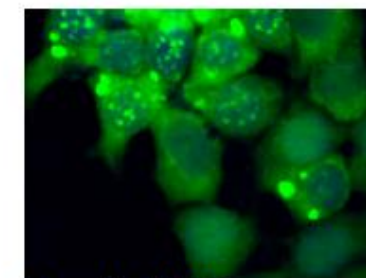
- Tau Sanders *et al.*, *Neuron*, 2014
- α -synuclein Woerman *et al.*, *PNAS*, 2015
- β -amyloid Aoyagi *et al.*, *Sci Transl Med*, 2019



1. HEK293T cells expressing protein-YFP + Hoechst 33342
2. Purified prions + Lipofectamine 2000 + OptiMEM
3. Incubate 4 days



Imaging & Quantification of Prions

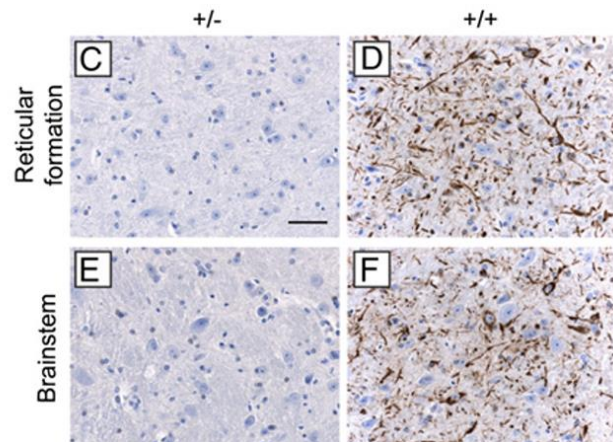
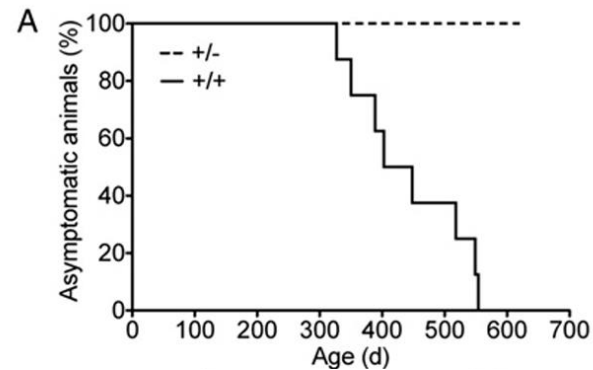


Hoechst YFP

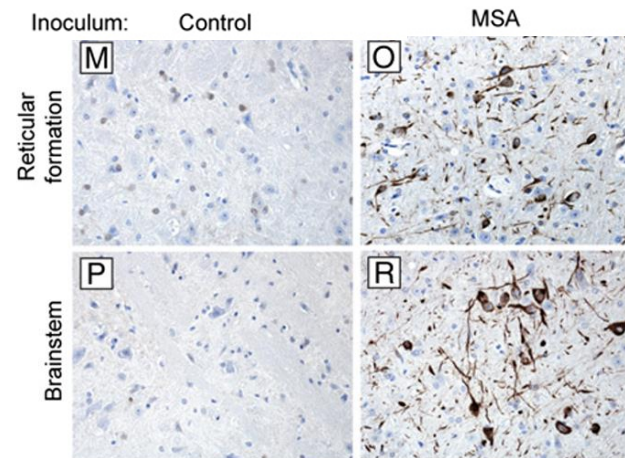
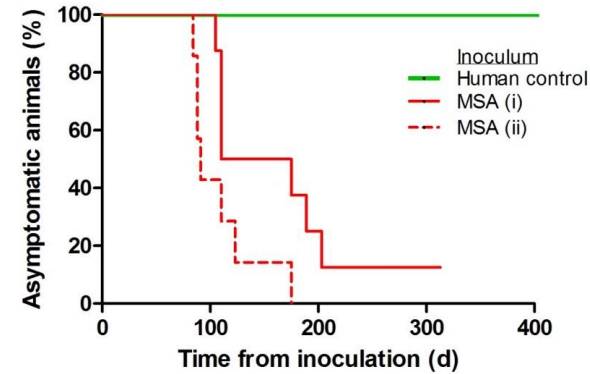
Woerman, *et al.*, *PNAS*, 2015

Spontaneous vs induced disease in transgenic mice

Spontaneous TgM83^{+/+} mice



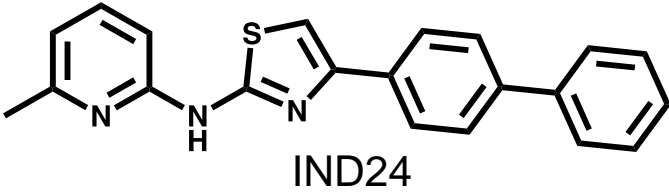
MSA inoculated TgM83^{+/-} mice



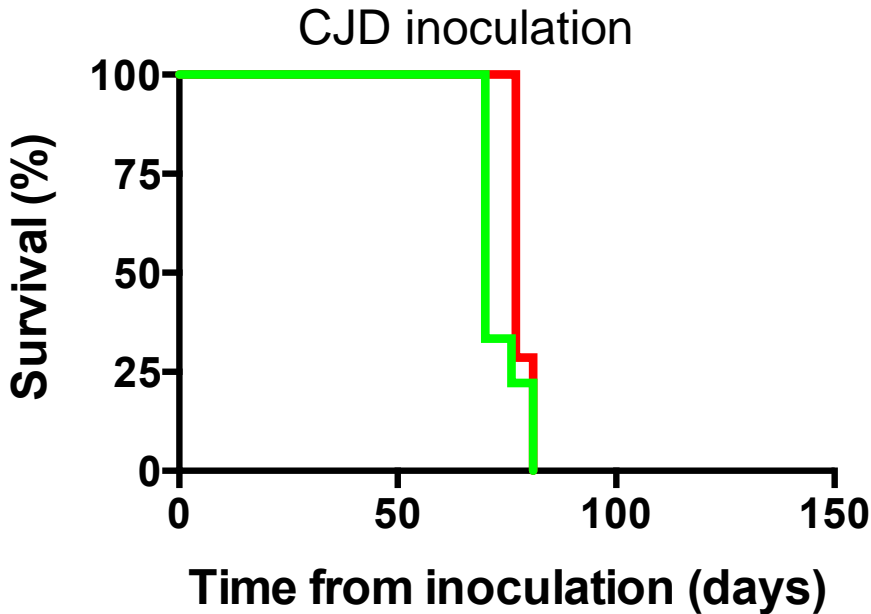
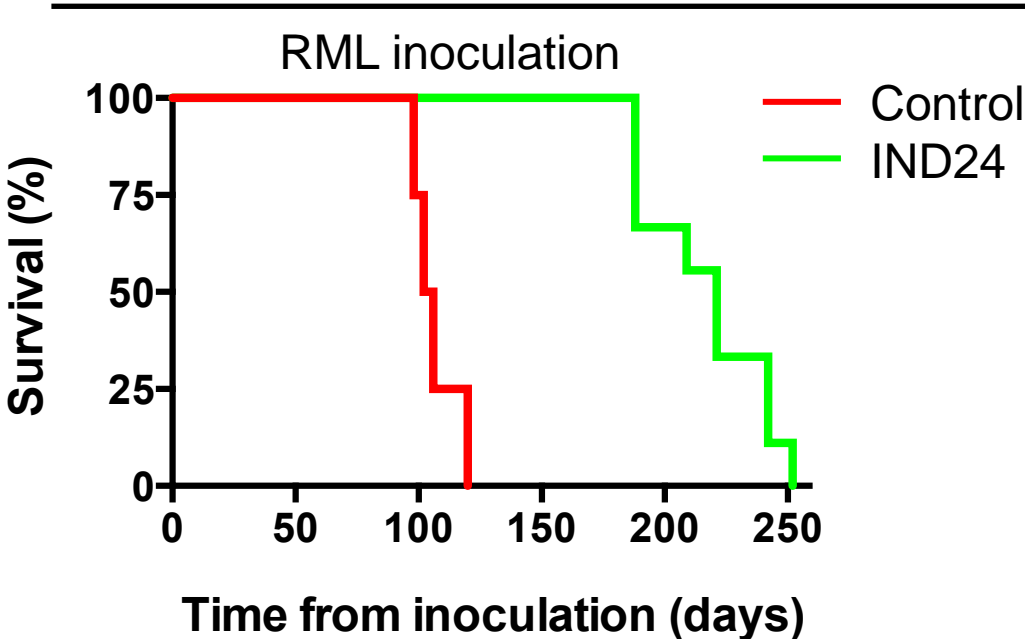
Overlapping aspects to consider

- Inoculation site
- Overexpression vs gene-targeted
- Species barriers

Effect of IND24 treatment is prion strain specific

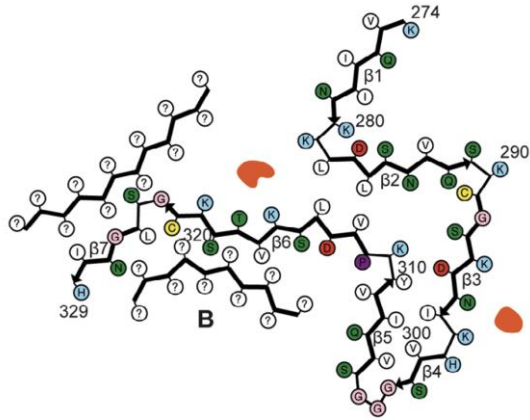


Tg(Hu/MoPrP)

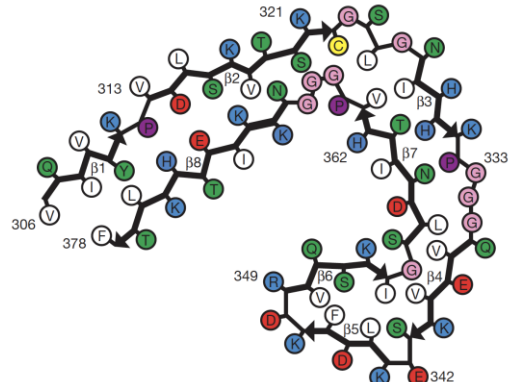


Spontaneous tau models do not develop human tau strains

Tg2541^{+/+}

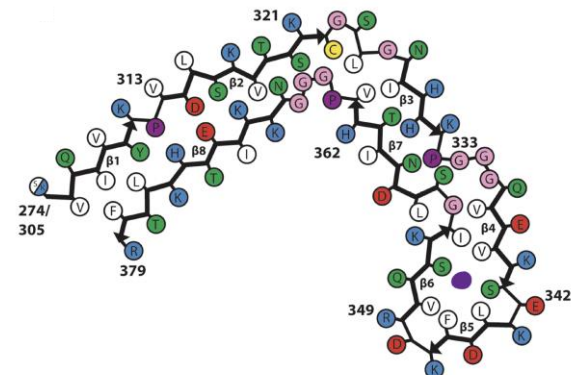


Alzheimer's



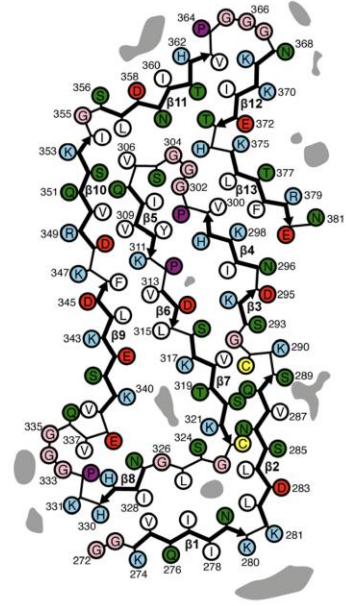
Fitzpatrick *et al.*, *Nature*, 2017

CTE



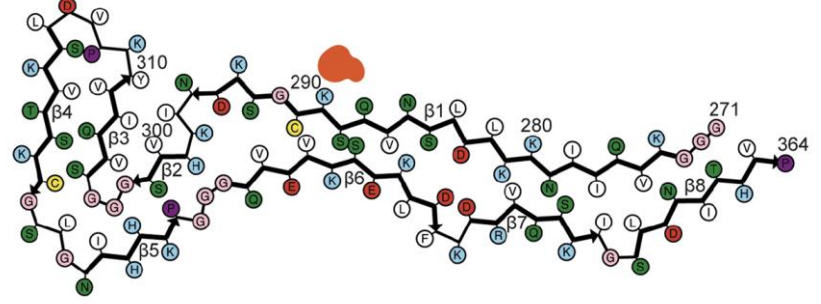
Falcon *et al.*, *Nature*, 2019

PSP



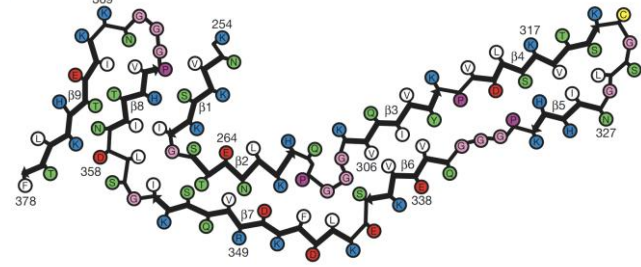
Shi *et al.*, *Nature*, 2021

PS19



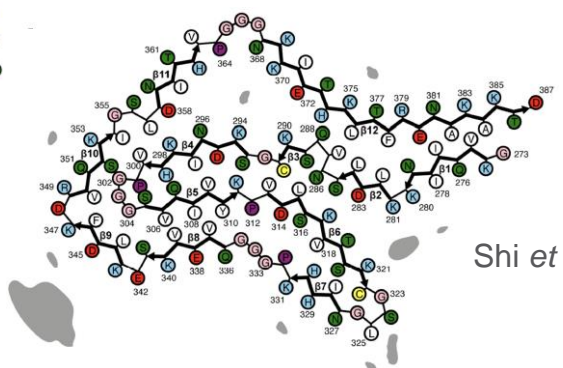
Schweighauser *et al.*, *Acta Neuropathol Comm*, 2023

Pick's Disease



Falcon *et al.*, *Nature*, 2018

AGD

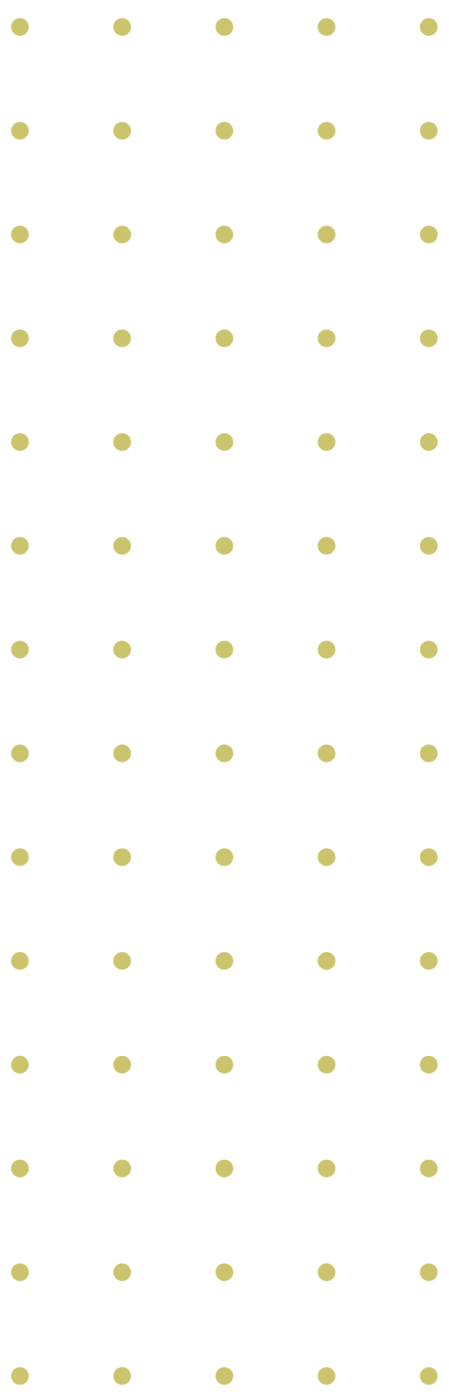


A-synuclein strains adapt or evolve in the TgM83^{+/-} host during primary passage

Mutation	Control	MSA16	MSA inoculum	Passaged MSA		PFF* inoculum	Passaged PFFs
				i.c	sc.n.		
A30G	Red	Blue	Red	Red	Red	Blue	Red
E46K	Red	Red	Red	Red	Red	Blue	Red
K80E	Red	Red	Red	Red	Red	Blue	Red
G51D	Red	Blue	Red	Red	Red	Blue	Red
A53E	Red	Red	Red	Red	Red	Blue	Red
A53T	Red	Blue	Blue	Blue	Blue	Blue	Blue
A53V	Red	Blue	Blue	Blue	Blue	Blue	Blue
V55Y	Red	Blue	Red	Red	Red	Blue	Blue
V66F	Red	Blue	Red	Red	Red	Blue	Red
V74P	Red	Blue	Red	Red	Red	Blue	Red

**PFFs contain the A53T mutation.*

Red, negative infection; Blue, positive infection.



Major discoveries and advancements in strain biology and disease pathogenesis for PrP and non-PrP amyloids must continue to inform one another to move research in each field forward.