NEW TREATMENTS FOR DISEASE PANEL

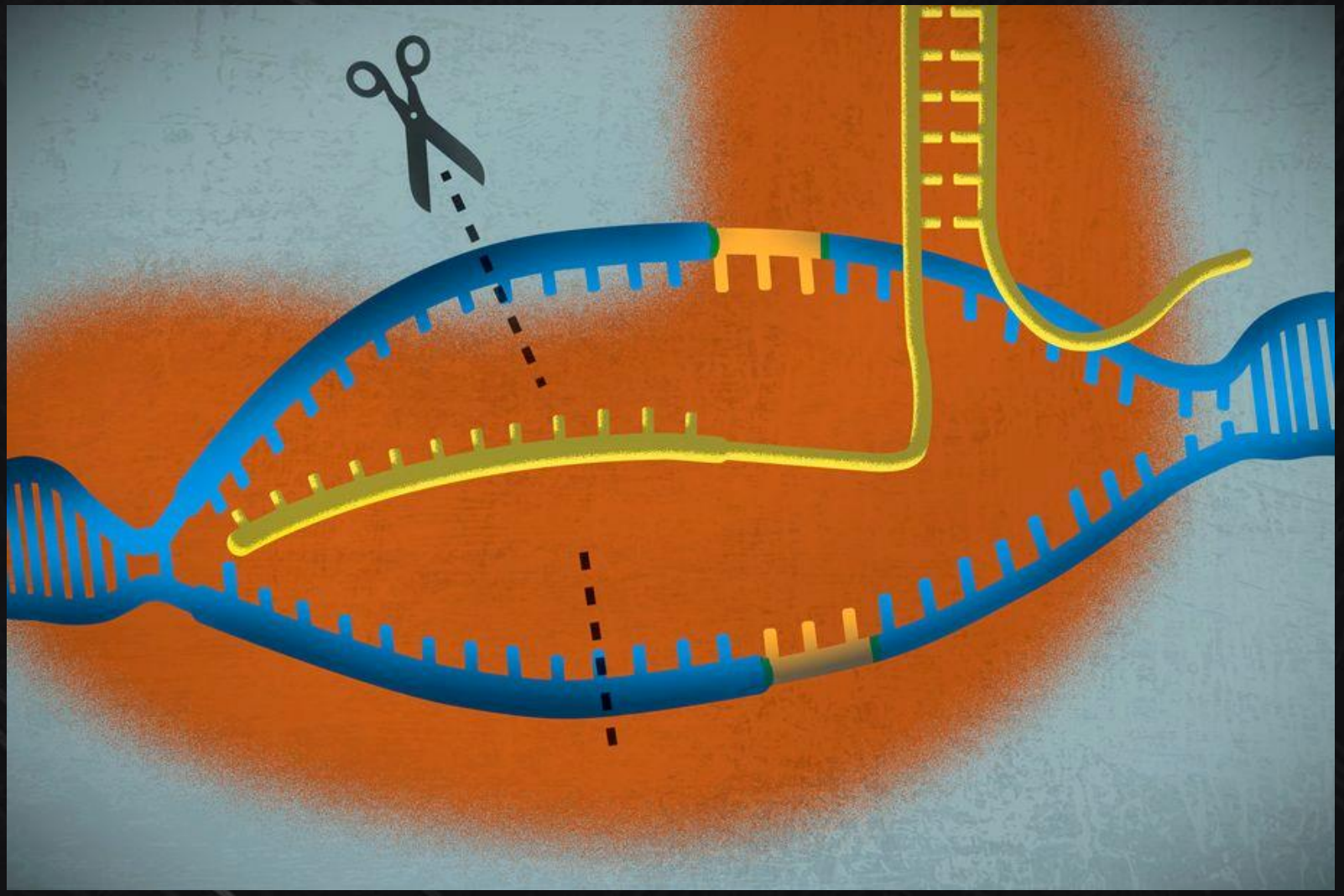
Februrary 29, 2020

Sickle-Cell Anemia/Beta-Thalassemia

Cystic Fibrosis

Parkinson's Disease

MS (PML actually)



Target single sequence in a genome (similar can be bound but less efficiently, and are called “off target.” One of the main technical objections to editing)

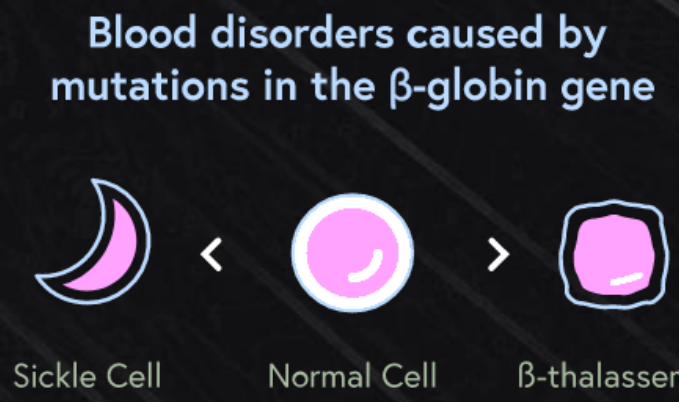
Only breaks DNA and then cell repair machinery “fix” but usually in a mutated way

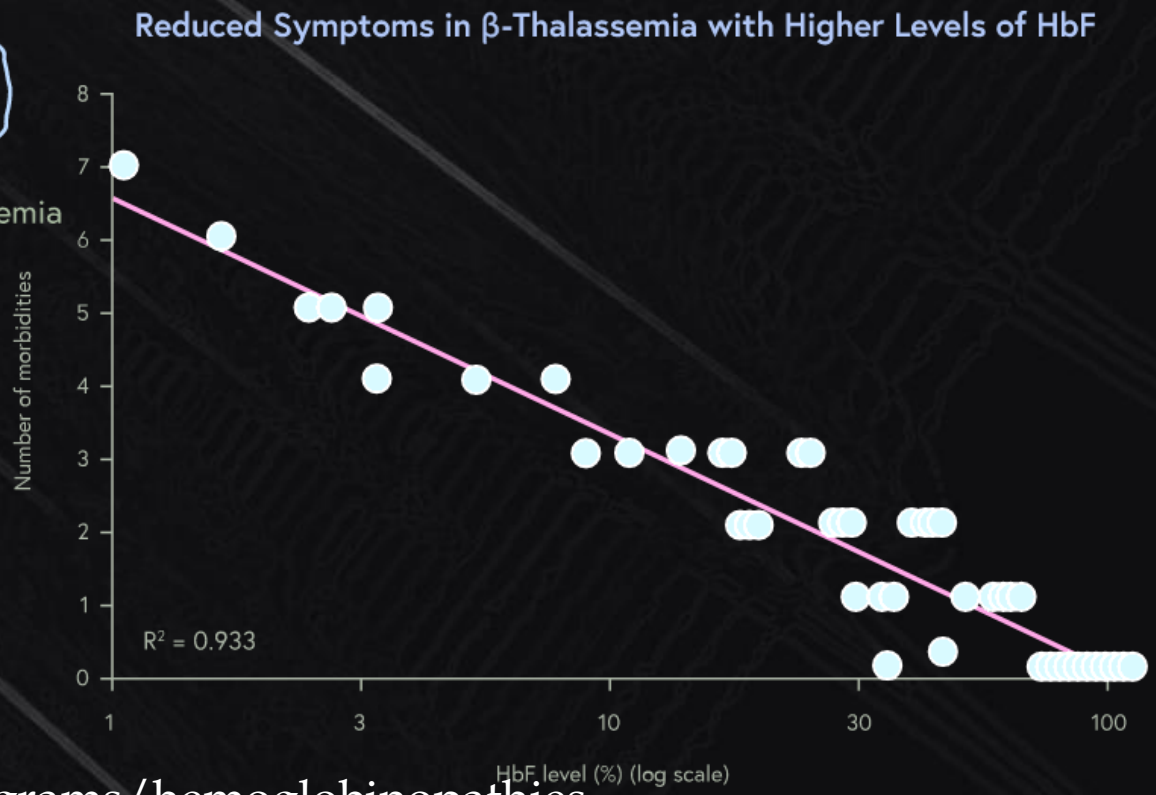
CRISPR IN DISEASE STUDY

- Mimic mutations in cells, tissues, model organisms
- Mutagenesis to discover interacting genes
- Unfortunately, clinical delivery of gene editing components remains a challenge
- Prime editing imparts more control

Sickle cell anemia and Beta thalassemia

CRISPR Therapeutics and Vertex Pharmaceuticals





http://www.crisprtx.com/programs/hemoglobinopathies

Adapted from Musallam, et al. Blood 2012.

Sickle cell anemia and Beta thalassemia

CRISPR Therapeutics and Vertex Pharmaceuticals

Nov 19, 2019

CRISPR Therapeutics and Vertex Announce Positive Safety and Efficacy Data From First Two Patients Treated With Investigational CRISPR/Cas9 Gene-Editing Therapy CTX001® for Severe Hemoglobinopathies

https://investors.vrtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-positive-safety-and

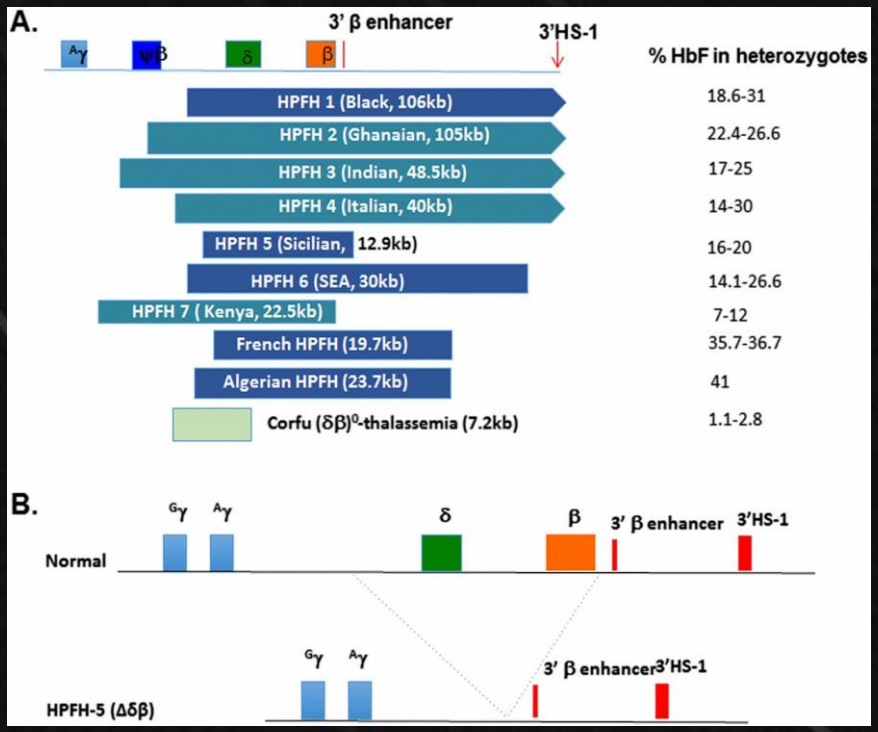


Fig. S1 Deletion type of hereditary persistence of fetal hemoglobin (HPFH).

Ye, Lin, et al. "Genome editing using CRISPR-Cas9 to create the HPFH genotype in HSPCs: An approach for treating sickle cell disease and β-thalassemia." Proceedings of the *National Academy of Sciences* 113.38 (2016): 10661-10665.

Cystic Fibrosis as a CRISPR Target

Hodges, Craig A., and Ronald A. Conlon. "Delivering on the promise of gene editing for cystic fibrosis." Genes & diseases 6.2 (2019): 97-108.

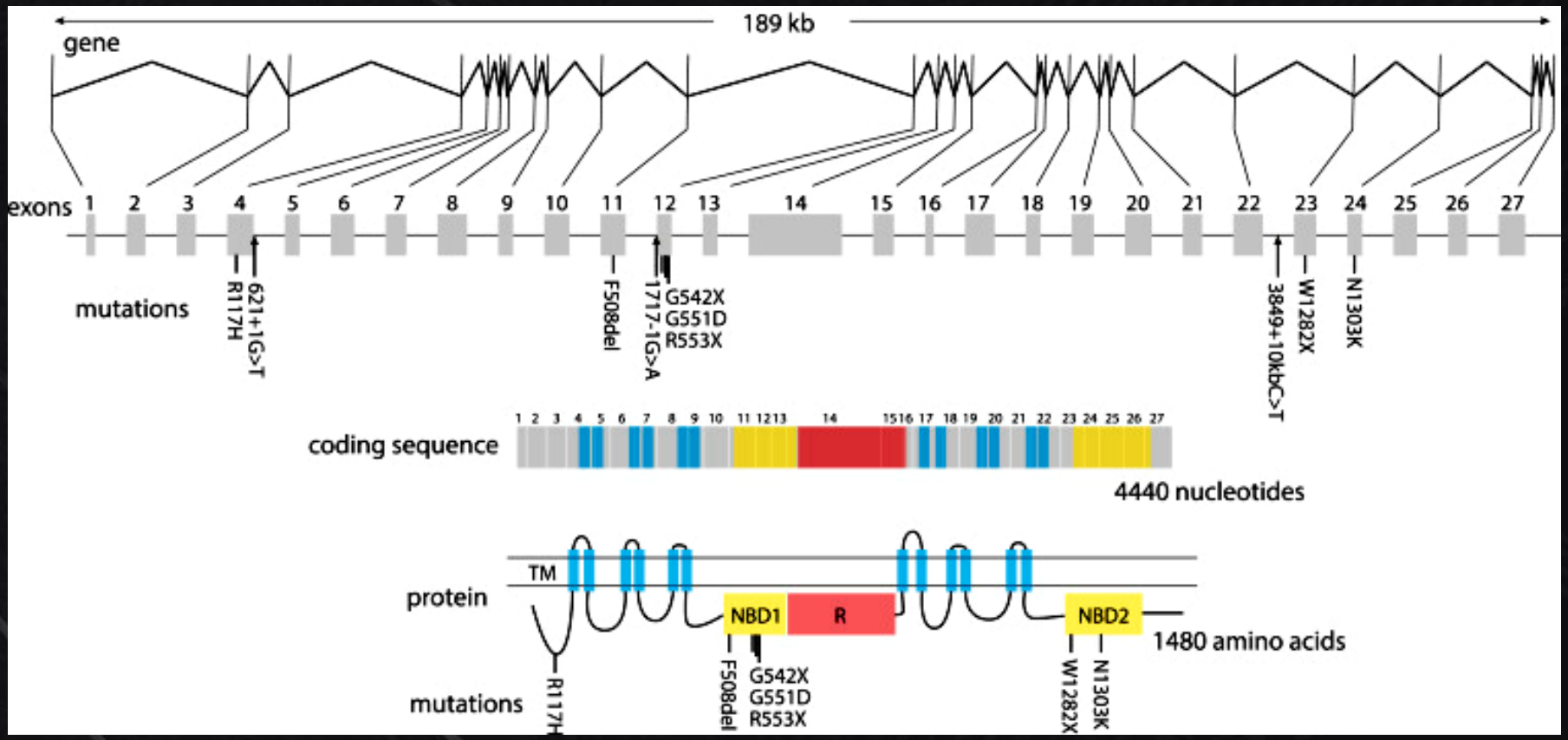


Figure 1. The structure of the human CFTR transcription unit, coding sequence and protein.

Cystic Fibrosis as a CRISPR Target

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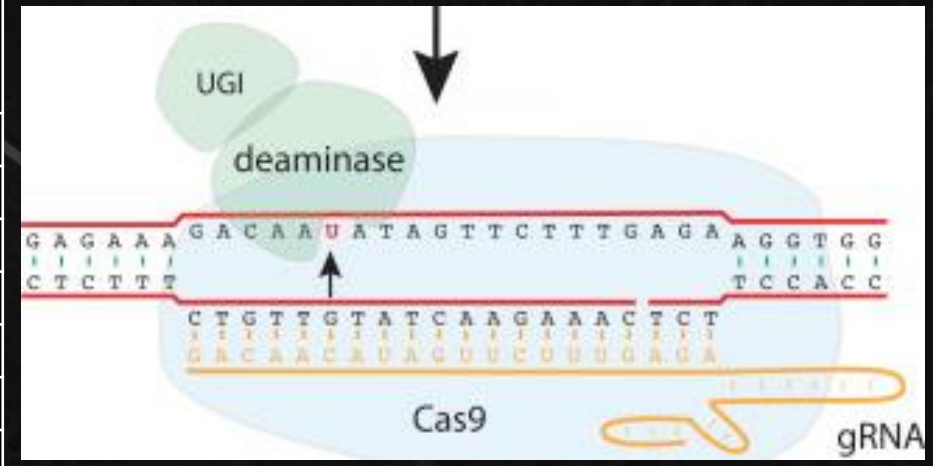
Table 1. The ten most common CF disease alleles.

Allele Frequency	Mutation	DNA Change	Class
70%	F508del	delCTT	deletion
2.50%	G542X	G > T	transversion
2.10%	G551D	G > A	transition
1.50%	N1303K	C > G	transversion
1.30%	R117H	G > A	transition
1.20%	W1282X	G > A	transition
0.93%	R553X	C > T	transition
0.93%	621+1G > T	G > T	transversion
0.86%	1717-1G > A	G > A	transition
0.82%	3849 + 10kbC > T	C > T	transition



Spacing is important
As is type of base change
C to T, or A to G
G to A, or T to C are only options

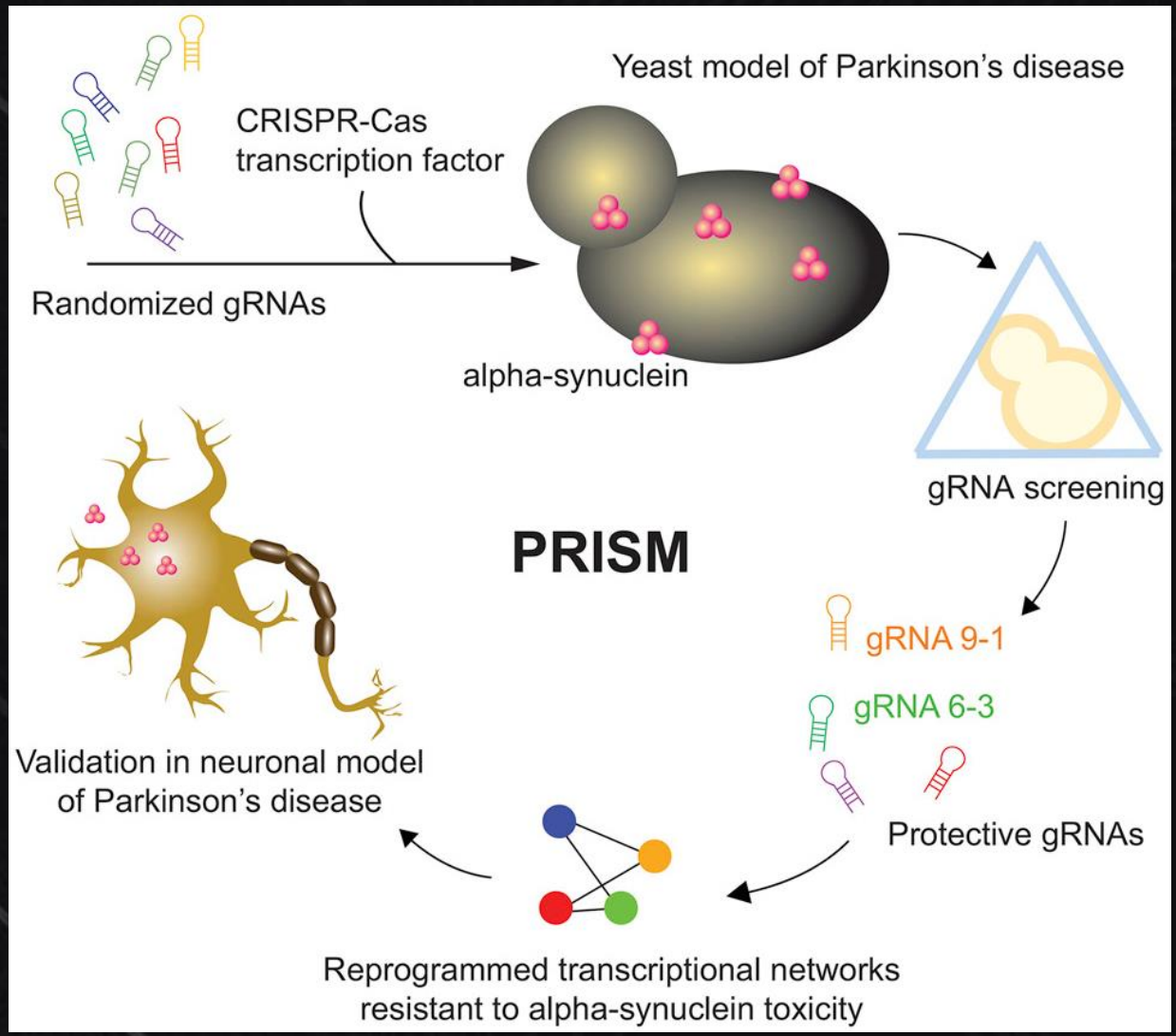
Parkinson's Disease

Chen, Ying-Chou, et al. "Randomized CRISPR-Cas transcriptional perturbation screening reveals protective genes against alpha-synuclein toxicity." Molecular cell 68.1 (2017): 247-257.

Perturbing Regulatory Interactions by Synthetic Modulators (PRISM) Overview

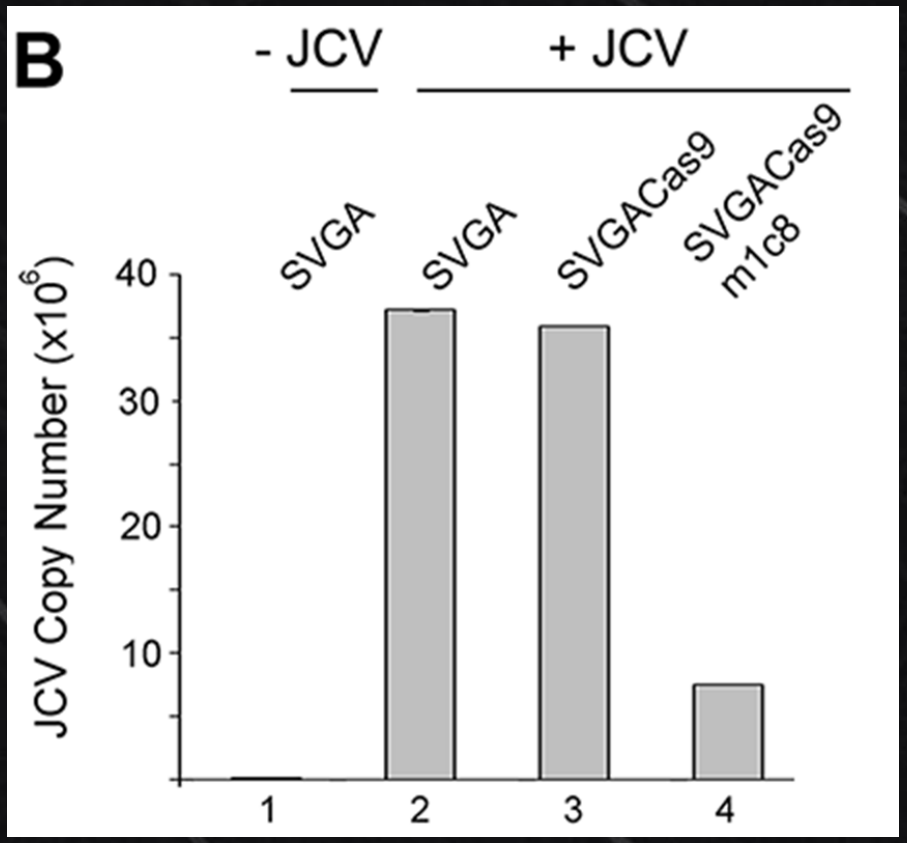
Validated the target in a human cell line model

Alpha-synuclein aggregates are identified as pathological hallmark in PD



Progressive multifocal leukoencephalopathy (PML)

Wollebo, Hassen S., et al. "CRISPR/Cas9 system as an agent for eliminating polyomavirus JC infection." PloS one 10.9 (2015): e0136046.



fatal demyelinating disease of the central nervous system (CNS) caused by reactivation of the human polyomavirus JCV gene expression

Infects 90% of people

Healthy immune systems keep it suppressed

Using Cas9 to mutate and inactivate a viral gene important for replication