



Lowering alpha-synuclein as a Therapeutic Strategy for Parkinson's disease: Challenges & Possibilities

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Overview

Why is alpha-synuclein a therapeutic target for Parkinson's disease?

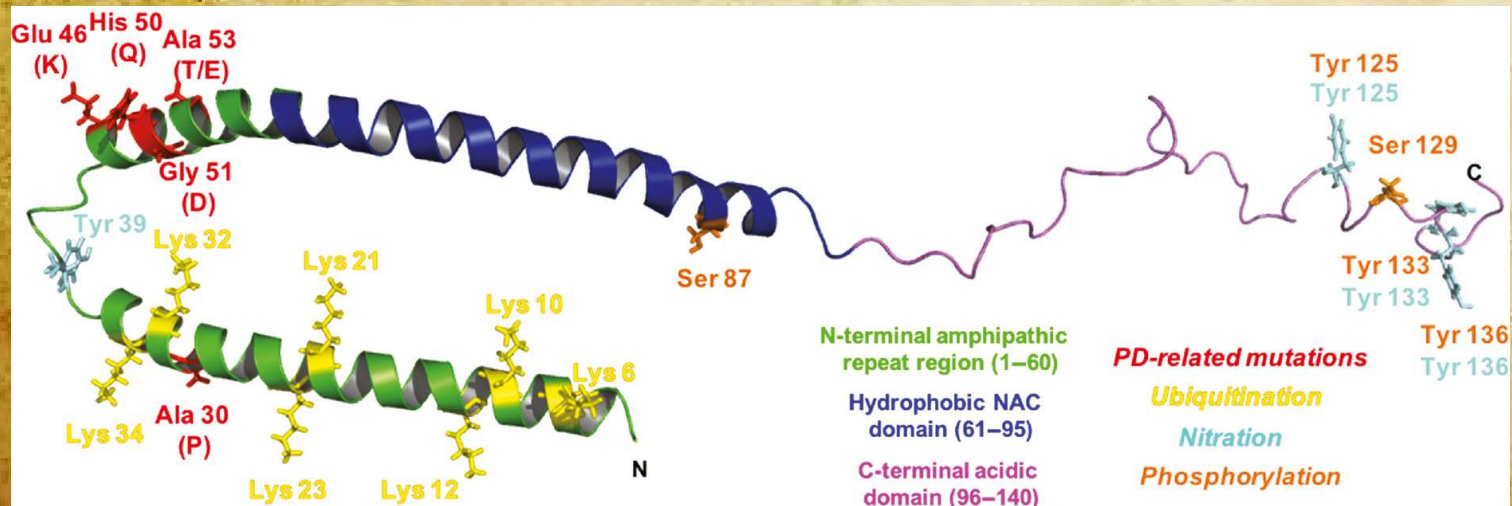
What are the different therapeutic concepts for targeting alpha-synuclein?

What are the challenges?

Where are the next breakthroughs?

WANTED!

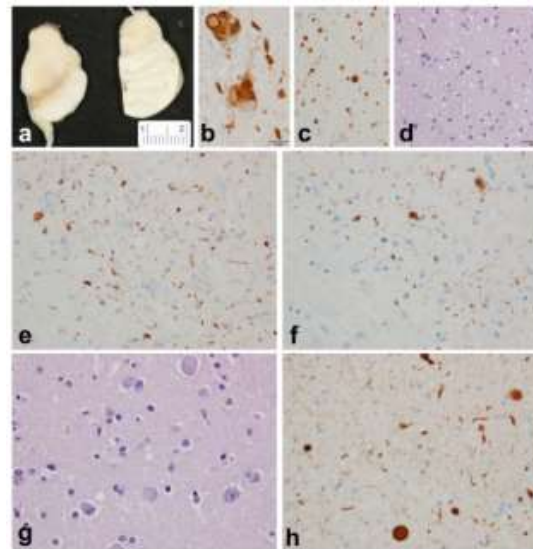
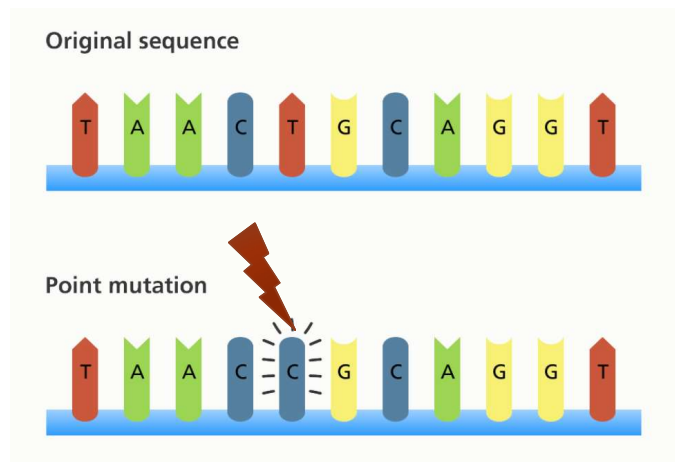
Name	Alpha-synuclein, alias: NACP, PARK1/PARK4
Address	Chromosome 4q22.1
Height/weight	140 amino acids, 14 kDa protein
Appearance	monomer, tetrameric α -helical oligomer, associates with biological membranes
Crime	aggregates can cause Parkinson's



Ottolini et al. 2016

Alpha-synuclein genetics, part 1: point mutations

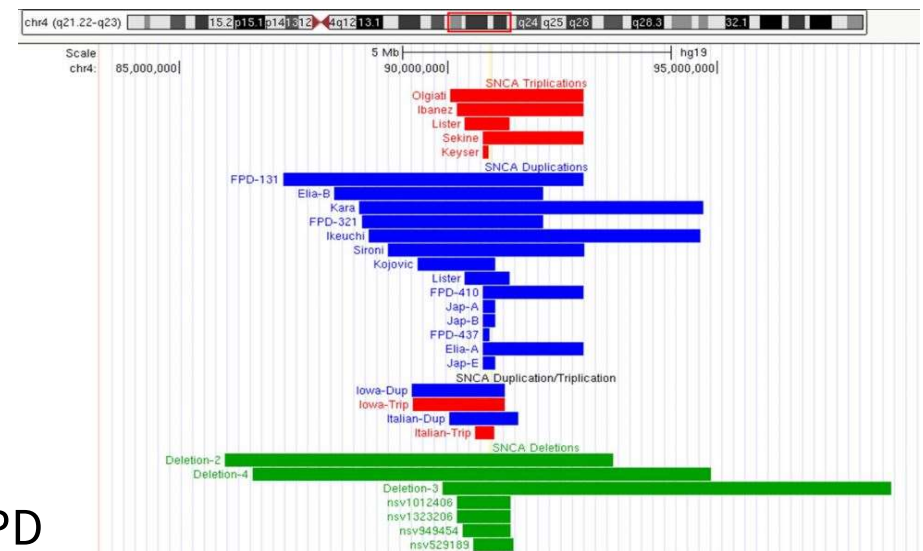
- First point mutation discovered in 1997
- Major component of Lewy bodies
- Frequency 0.5% in familial and sporadic cases
- Only a few point mutations
- Mutations cause PD by increasing aggregation propensity



*Alpha-synuclein
staining in human
brain*

Alpha-synuclein genetics, part 2: copy number mutations

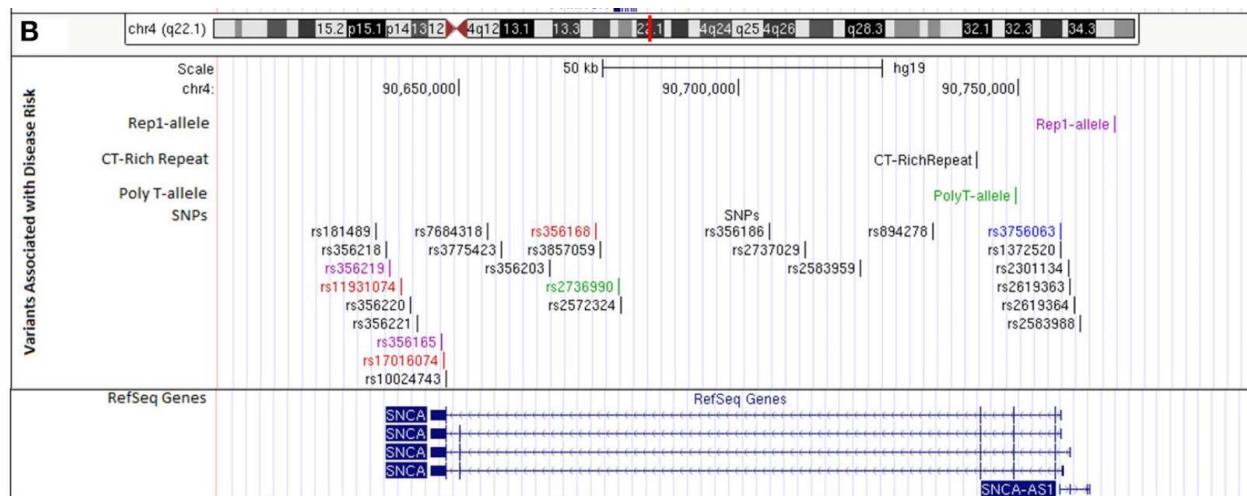
- Larger genomic regions multiplied (duplication or triplication)
= copy number (mutation) variant
- Discovered in 2003
- Regions may include many genes
- Alpha-synuclein is common ‘denominator’
- Too much normal alpha-synuclein causes PD



Piper, Sastre & Schüle 2018, *Front. Neurosci.* 12:199.

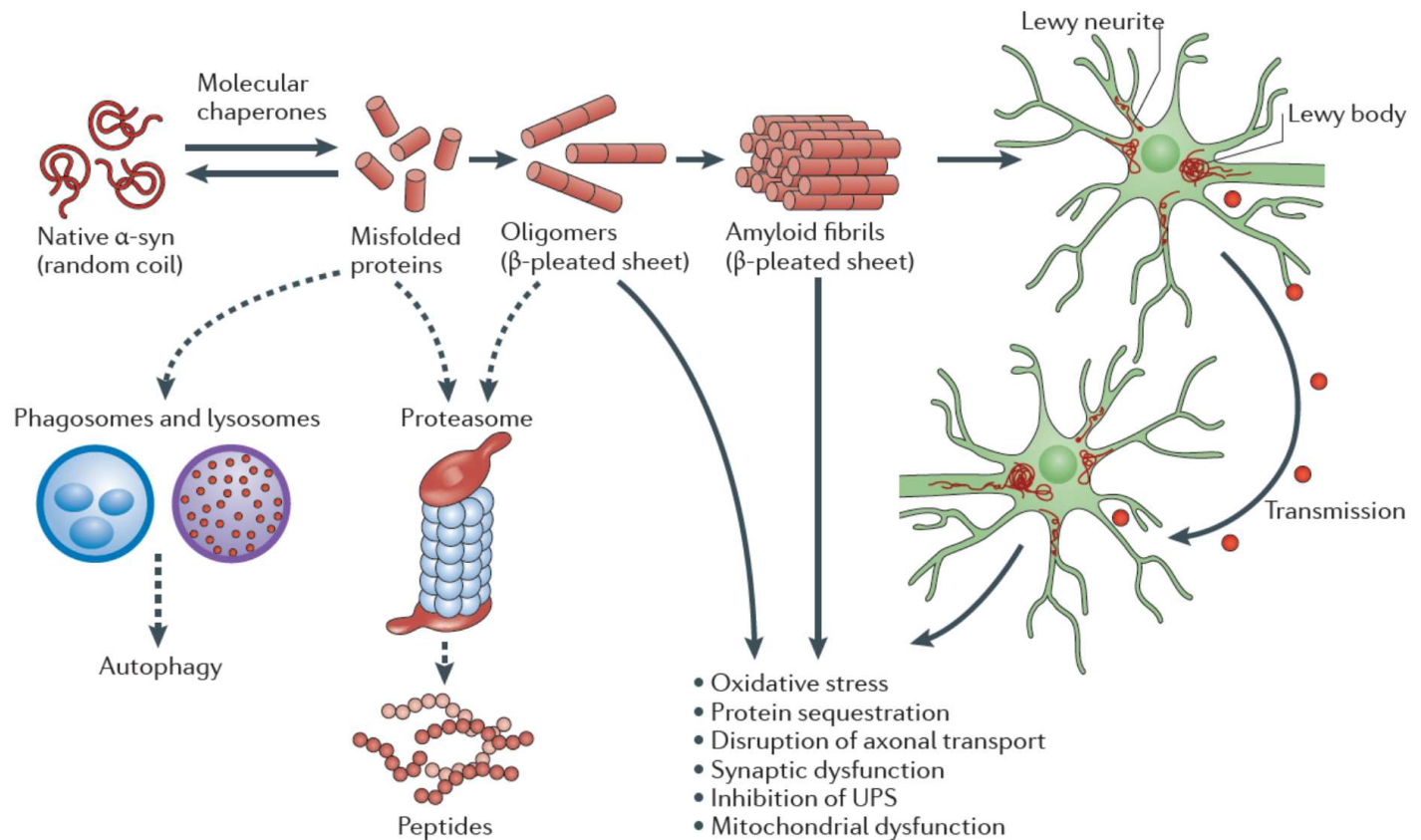
Alpha-synuclein genetics, part 3: non-coding variants

- Genetic changes outside the gene
- Increase risk for PD
- Might alter alpha-synuclein expression



Piper, Sastre & Schüle 2018, Front. Neurosci. 12:199.

Mechanisms of alpha-synuclein pathology in Parkinson's disease

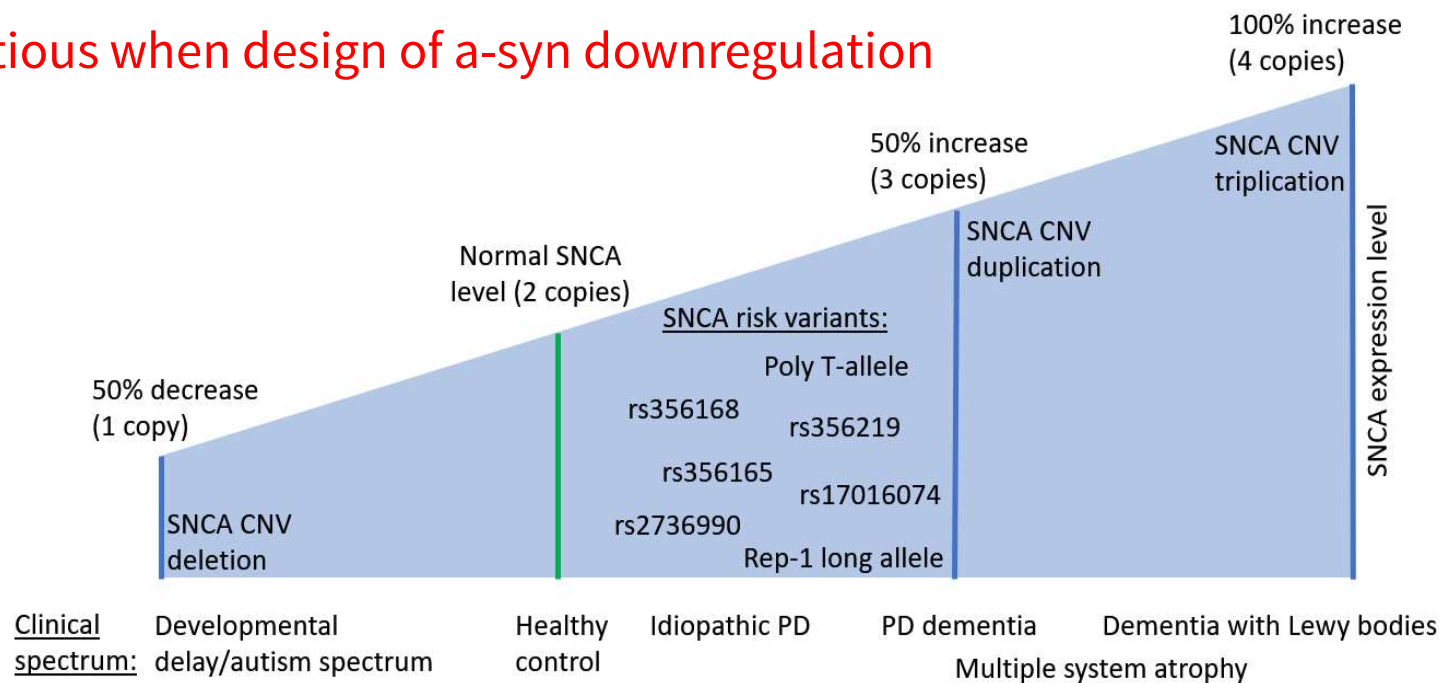


Papadopoulos 2018, Irwin, Lee & Trojanowski 2013

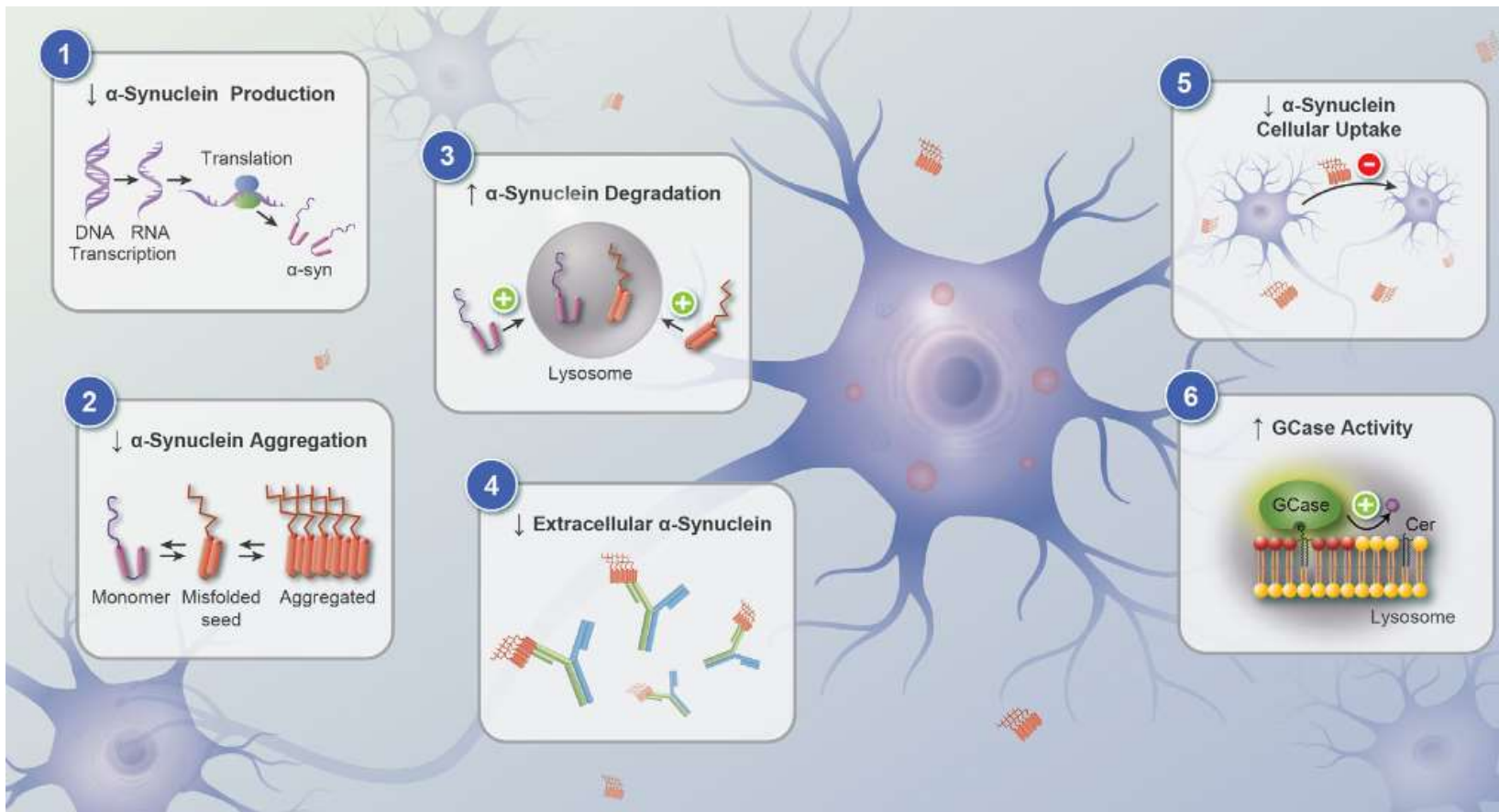
How much reduction of alpha-synuclein is beneficial?

Clinical spectrum of a-syn gene dosage from autism to Lewy body dementia

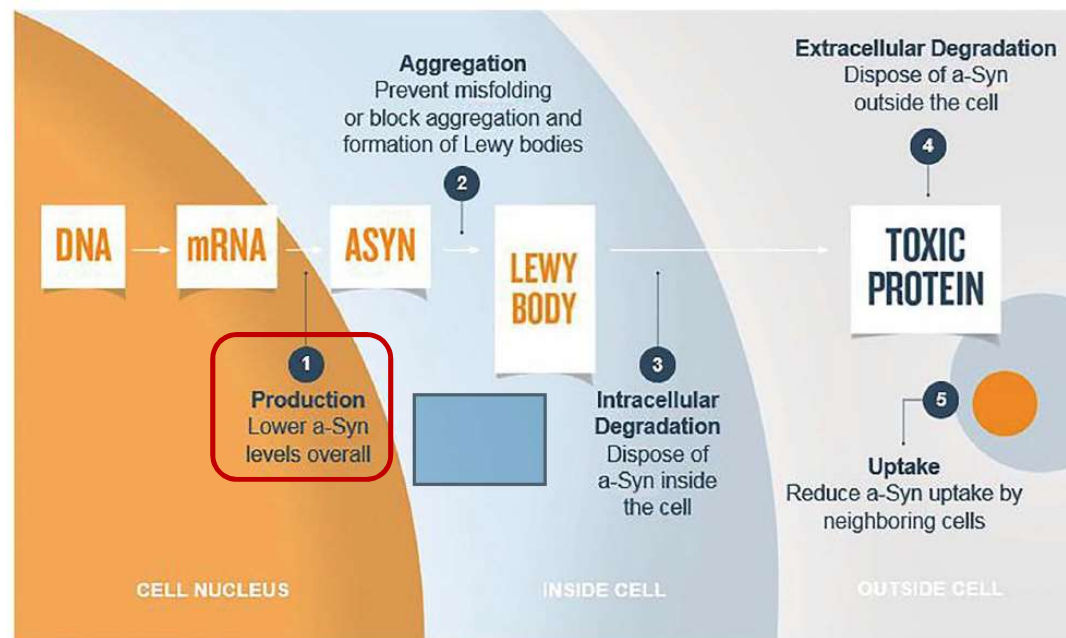
➤ Cautious when design of a-syn downregulation



Therapeutic concepts of lowering alpha-synuclein

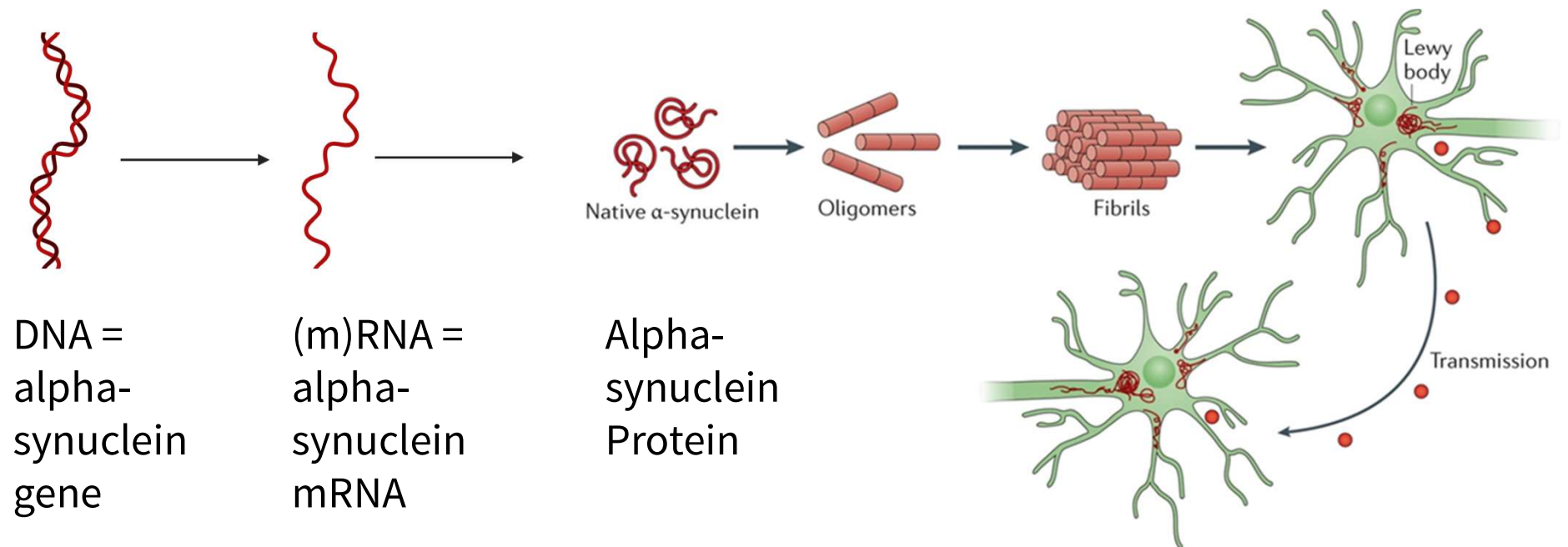


1. Reducing production of alpha-synuclein



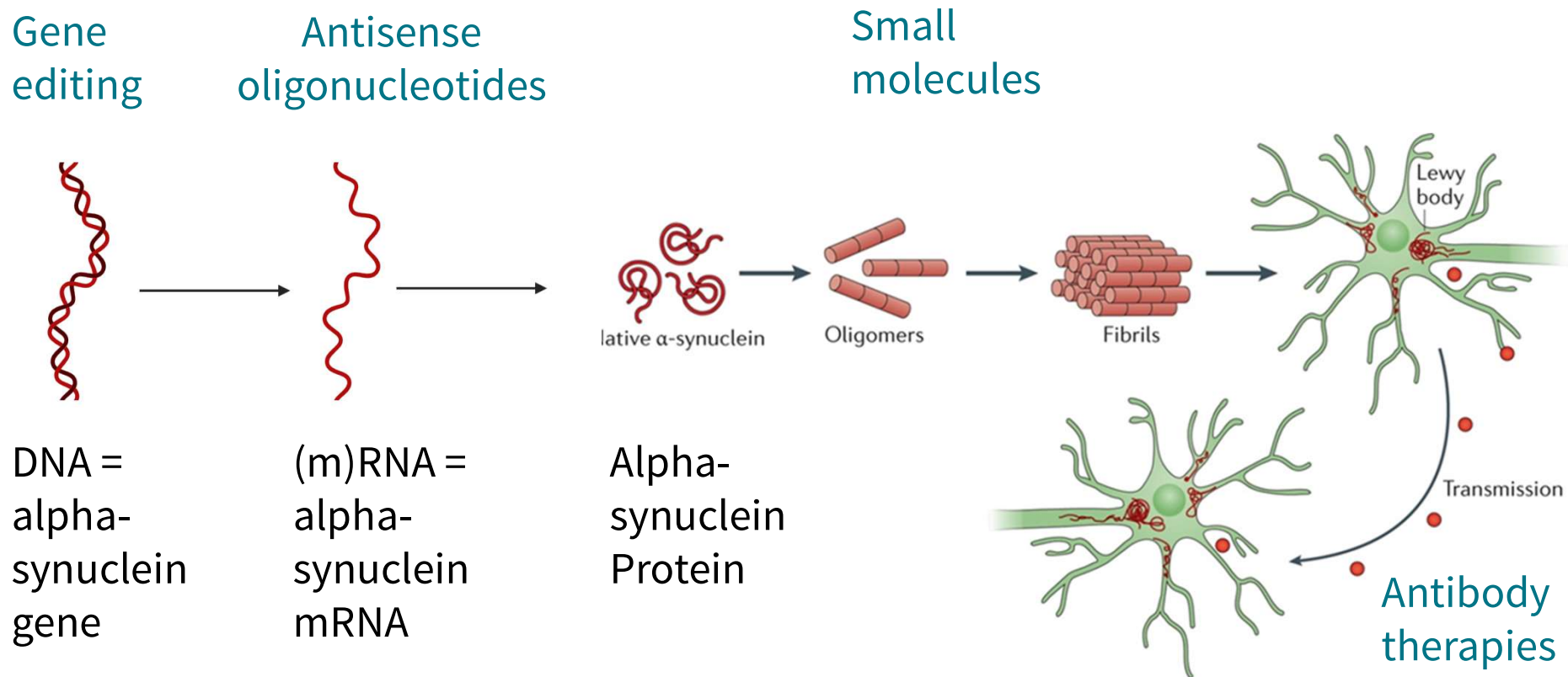
Rationale: if production of a-syn can be prevented then less protein is produced and toxicity of protein misfolding can be avoided.

Therapeutic strategies follow principles of the central dogma of biology

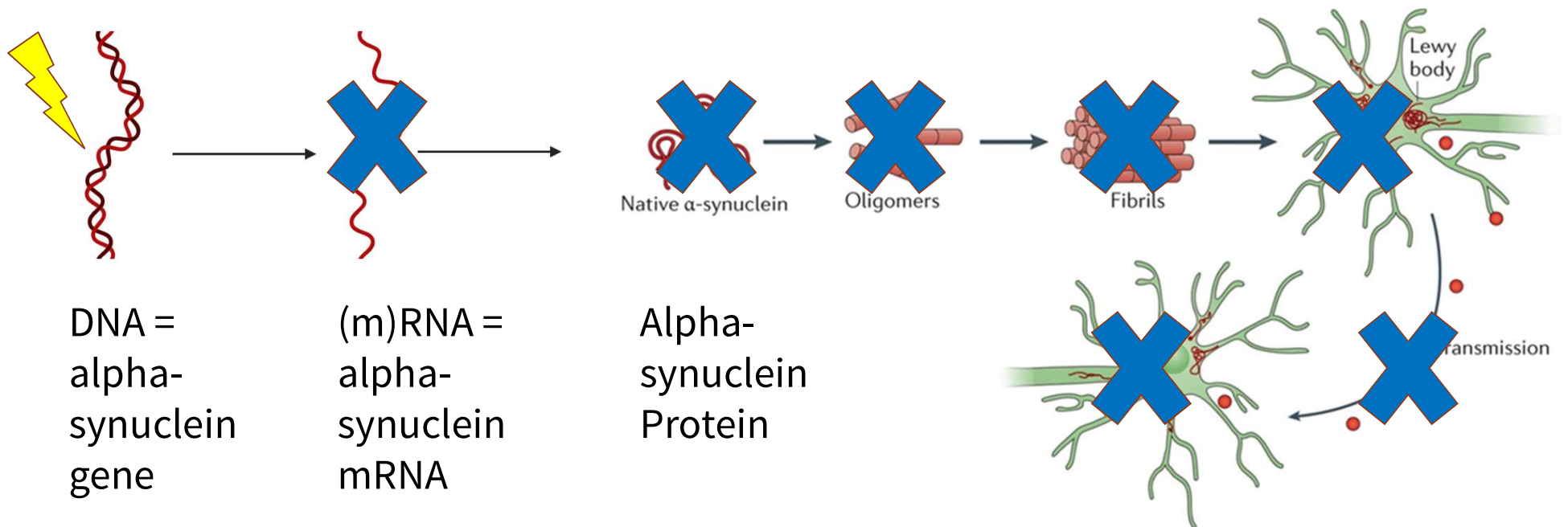


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Therapeutic strategies follow principles of the central dogma of biology



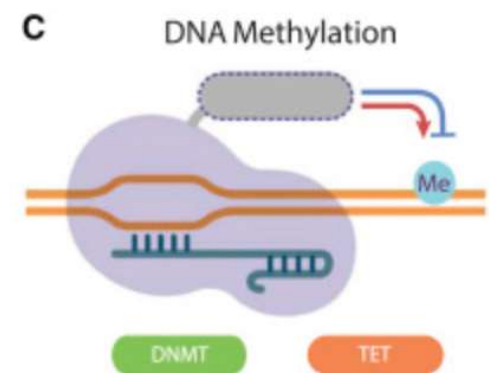
Gene editing targets the DNA



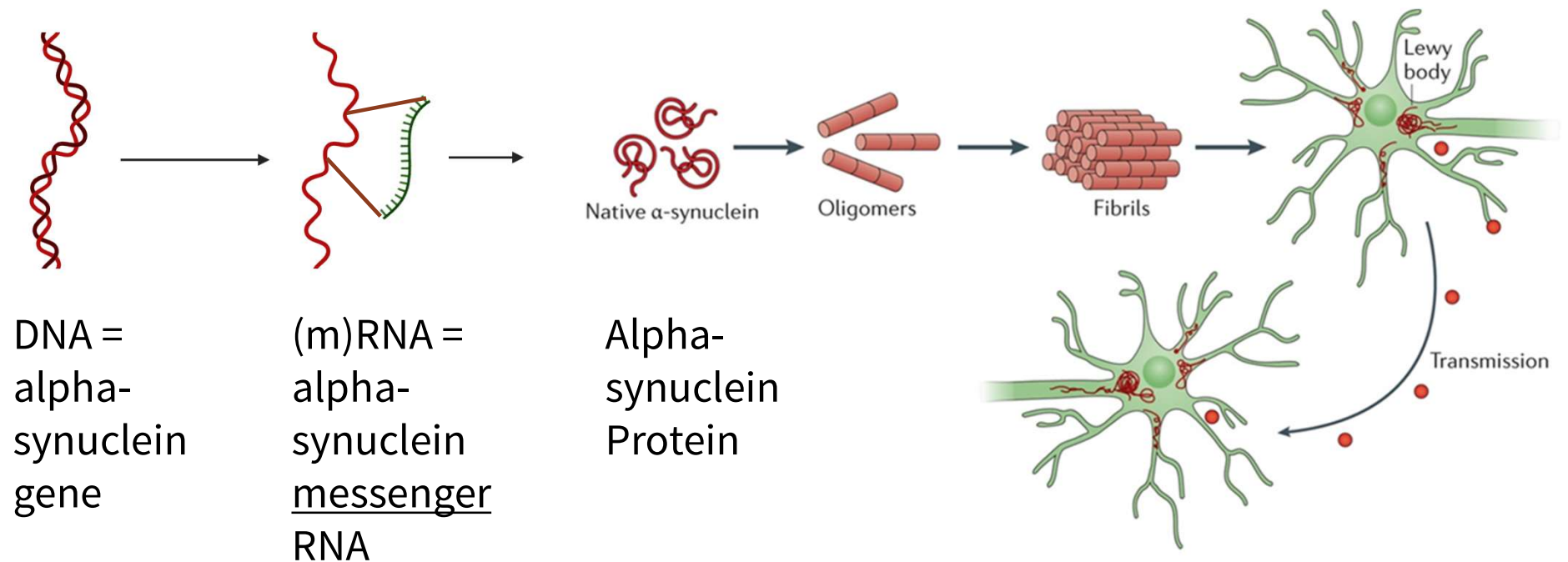
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CRISPR regulation of a-syn gene expression

- “Molecular scissors” for gene engineering
- SLS-004 is lentiviral vector
- Targets epigenome of alpha-synuclein
- *In vitro*: reduces alpha-synuclein expression (by ~30%) & rescued function in dopaminergic neurons
- *In vivo*: single dose leads to 40% alpha-synuclein reduction
- Seelos Therapeutics, Inc. announced the exclusive worldwide licensing of SLS-004 from Dr. Chiba-Falek, Duke University in Summer 2019

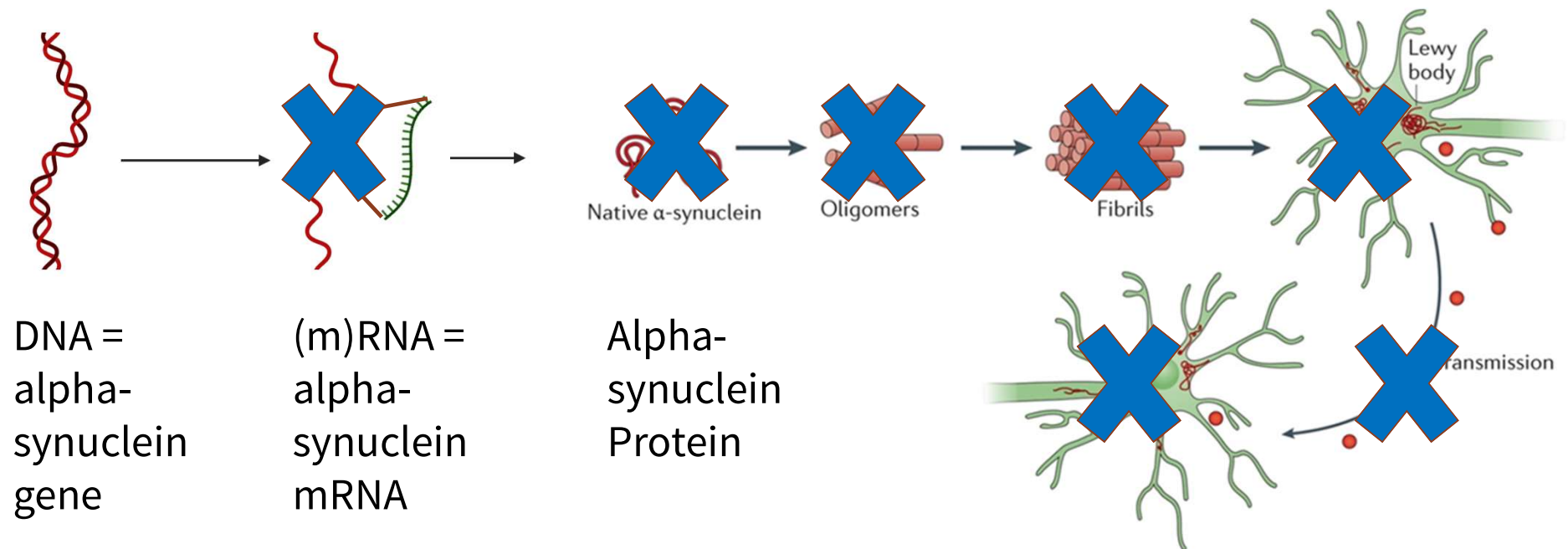


Antisense oligonucleotides = ASO “shooting the messenger”



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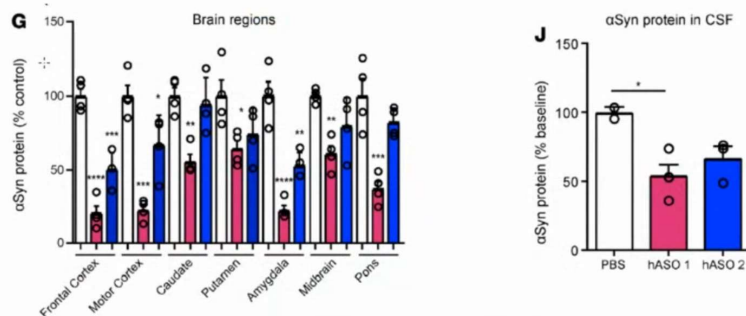
Antisense oligonucleotides = ASO “shooting the messenger”



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Antisense oligonucleotides downregulate alpha-synuclein mRNA

- Synthetic strands of nucleic acid that modulate gene expression
- ASO therapeutics recently FDA-approved for muscular atrophy
- Selective reduction of a-syn production in midbrain monoaminergic regions
- *Clinical trial in MSA via intrathecal injection (HORIZON), NCT04165486*



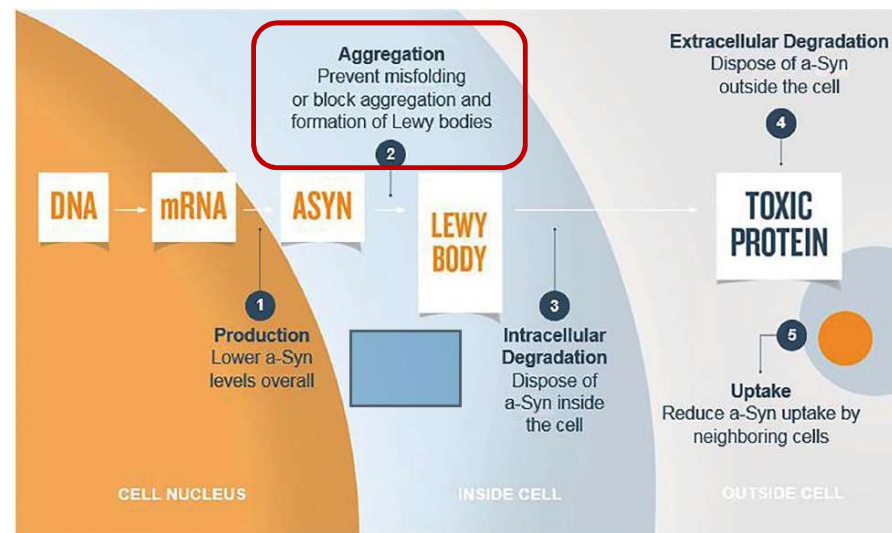
IONIS[®]

Neurological

	Partner	Phase 1	Phase 2	Phase 3
ION464 (SNCA) Multiple System Atrophy & Parkinson's Disease	Biogen			

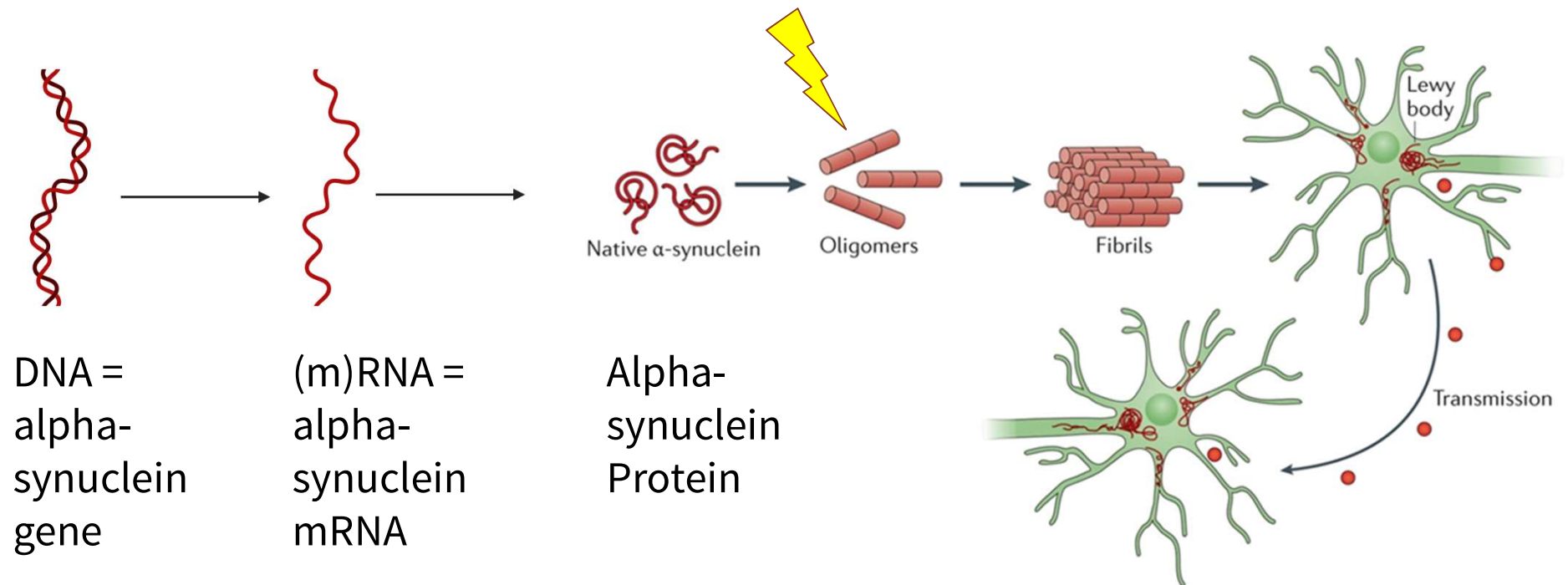
Primate brain and CSF, Cole et al. 2021

2. Reducing aggregation of alpha-synuclein



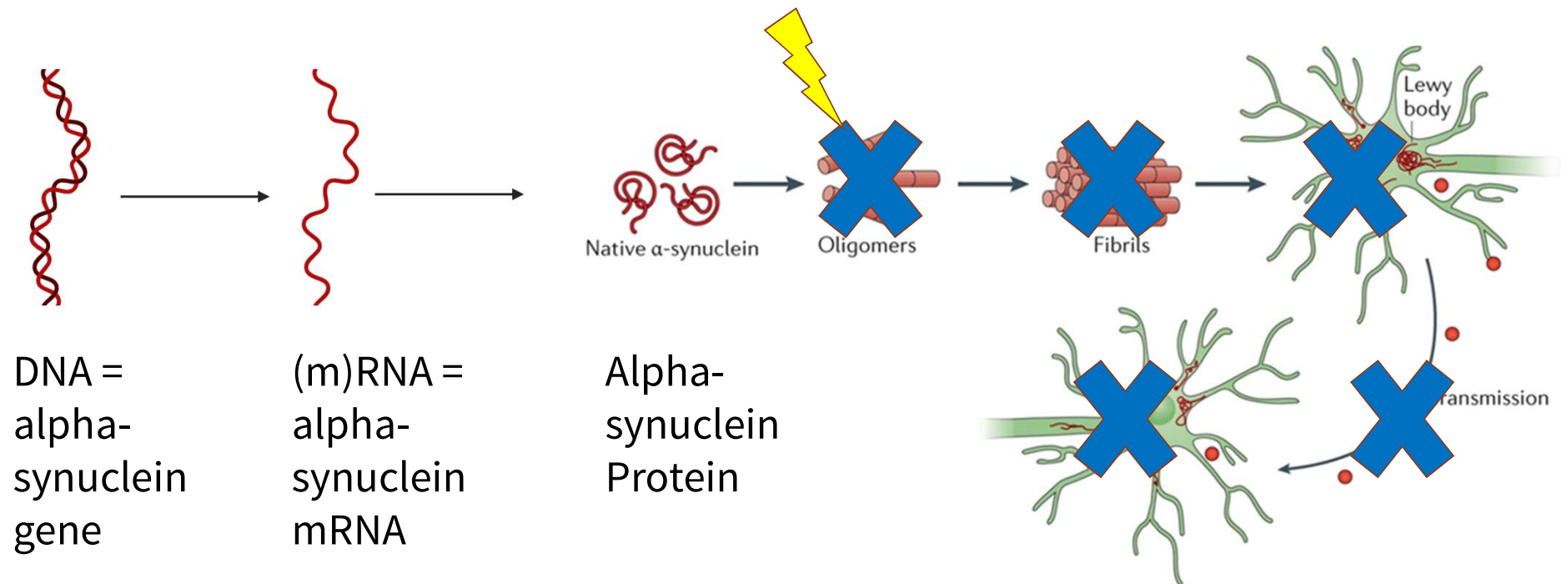
Rationale: if aggregation of a-syn can be prevented then its normal function can be sustained and toxicity of protein misfolding can be avoided.

Small molecule binds to alpha-synuclein oligomers



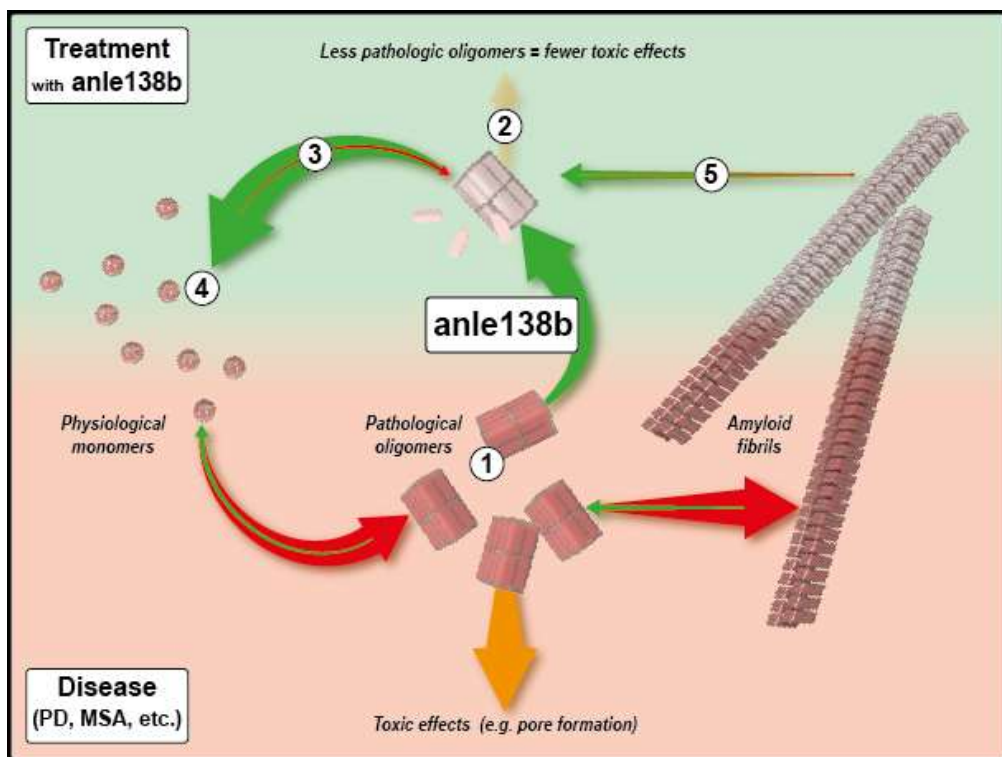
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Prevention of alpha-synuclein fibril formation



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Anle138b modulates alpha-synuclein oligomers



- Binding to oligomers alters structure & inhibits neurotoxic properties
- Modulation towards non-toxic oligomers and monomers
- normal alpha-synuclein function regained
- depletes pre-amyloid oligomers and impairs fibril growth, but not a “fibril breaker”
- *First-in-Human Study of Single and Multiple Doses of anle138b in Healthy Subjects shows good safety profile (ClinicalTrials.gov Identifier: NCT04208152)*

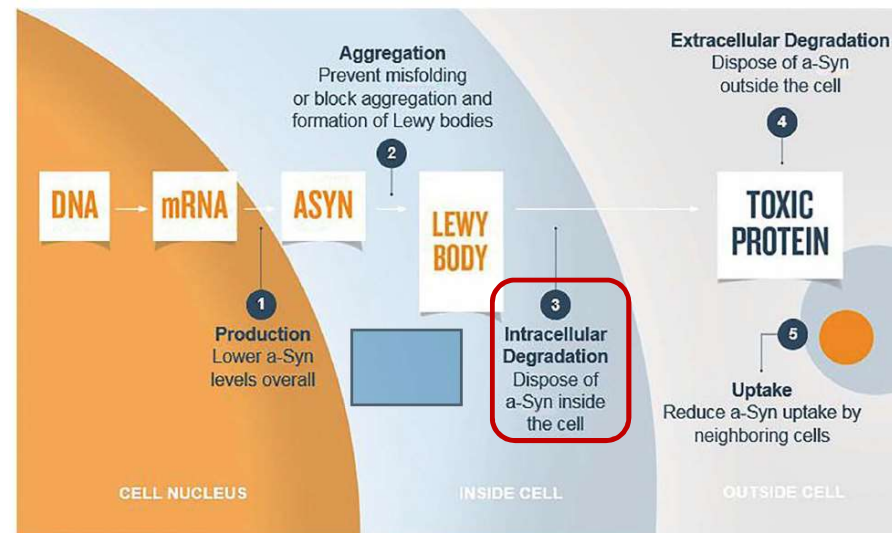
Teva and MODAG Announce Licensing Collaboration for Neurodegenerative Disease Drug Candidate

Small molecule candidate Anle138b targets disease modification for multiple system atrophy and other neurological disorders

October 26, 2021 04:45 PM Eastern Daylight Time

TEL AVIV & WENDELSHEIM, Germany--(BUSINESS WIRE)--Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) and MODAG GmbH today announced a strategic collaboration on the exclusive worldwide licensing and development of MODAG's lead compound anle138b and a related compound, sery433.

3. Increasing degradation of alpha-synuclein



Rationale: Autophagy plays major role in degradation of a-syn aggregates

Enhancing autophagy/lysosomal function

- Enhancement of autophagic processes leads to increased degradation of pathological α -syn
- Examples:
 - Rapamycin (natural anti-fungal antibiotic)
 - Trehalose (natural sugar)
 - Modulator of the mitochondrial pyruvate carrier (MSDC-160)

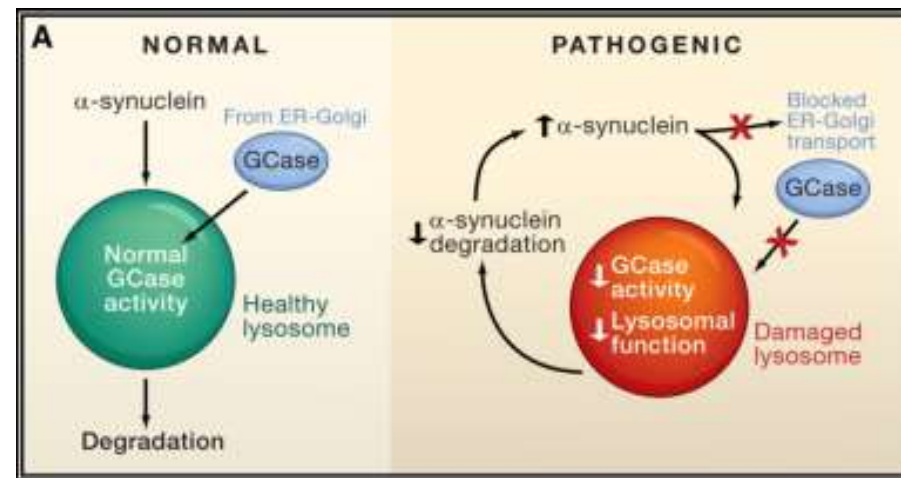


Challenges:

- Lack of specificity for α -syn (effects on other essential pathways)
- Side-effects (e.g. immunosuppression)

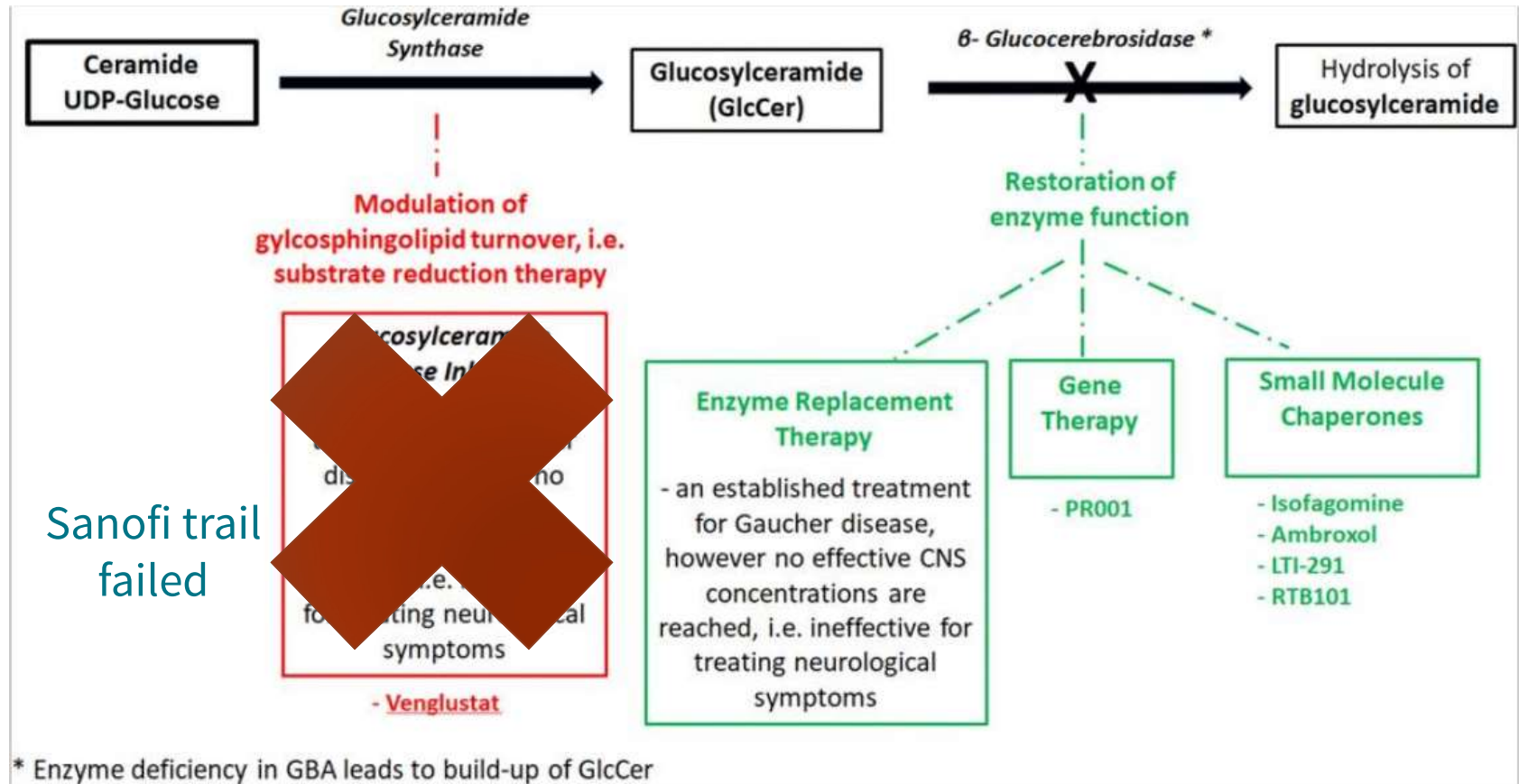
GBA encodes the GCase enzyme & mutations increase risk for PD

- *GBA* mutations account for 7-10% of PD
- *GBA* carriers have 20-fold increased risk of developing PD
- *GBA* encodes lysosomal enzyme, beta-glucocerebrosidase (GCase),
- Required for degradation & recycling of glycolipids
- *GBA* mutation affects:
 - severity
 - age of onset
 - rate of progression
 - likelihood of dementia



GBA = gene, GCase = gene product/enzyme

Restauration of GCase enzyme function



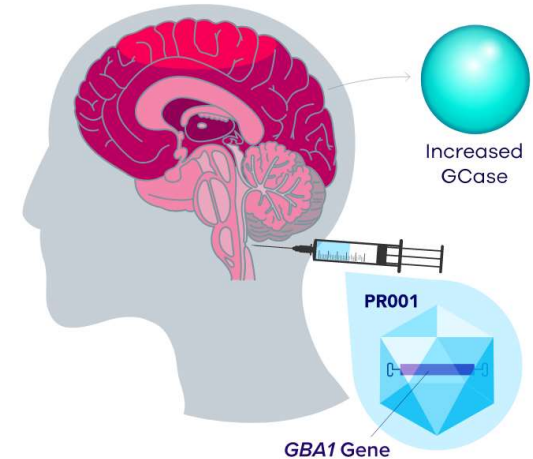
GBA gene therapy

- Study PRV-PD101 is a Phase 1/2a first in-human study
- Evaluate safety of intracisternal PR001A administration
- Patients with at least 1 pathogenic *GBA1* mutation
- PR001 utilizes an AAV9 viral vector to deliver the *GBA1* gene
- Goal: correct lysosomal enzyme deficiency
- Open-label, 12 participants, multi-center



A Wholly Owned Subsidiary
of Eli Lilly and Company

ClinicalTrials: Phase 1/2a Clinical Trial of PR001 in Patients With Parkinson's Disease With at Least One GBA1 Mutation (PROPEL)
NCT04127578



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Ambroxol “shuttles” GCase through the cell

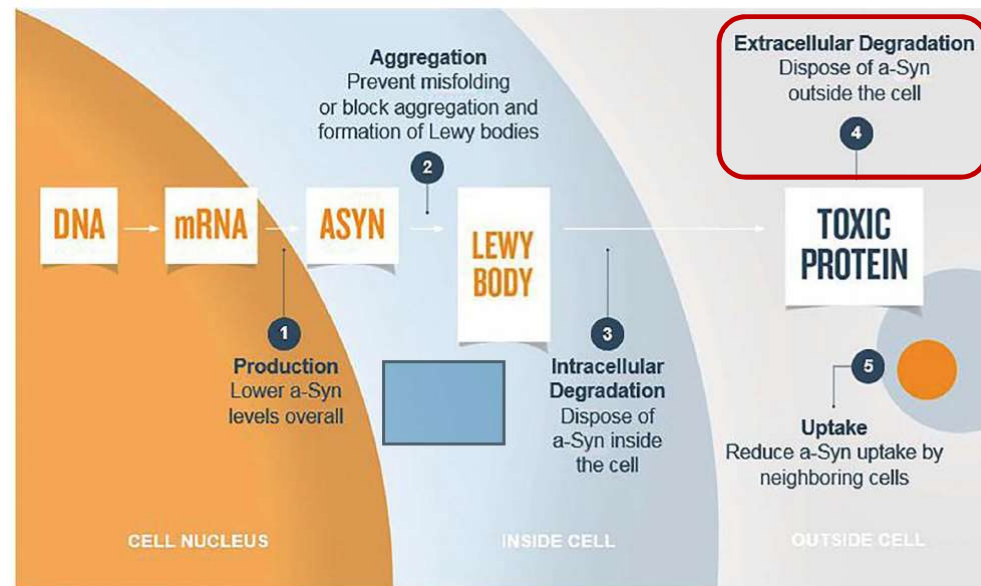
- Small-molecule chaperones drive correct folding of mutant GCase molecules in the cell
- Efficient transport to lysosomes & increased GCase activity, rescue neurodegeneration
- Ambroxol, an FDA-approved over-the-counter cough medication
- *Four clinical trials ongoing or completed testing efficacy of Ambroxol in PD and Dementia with Lewy bodies*



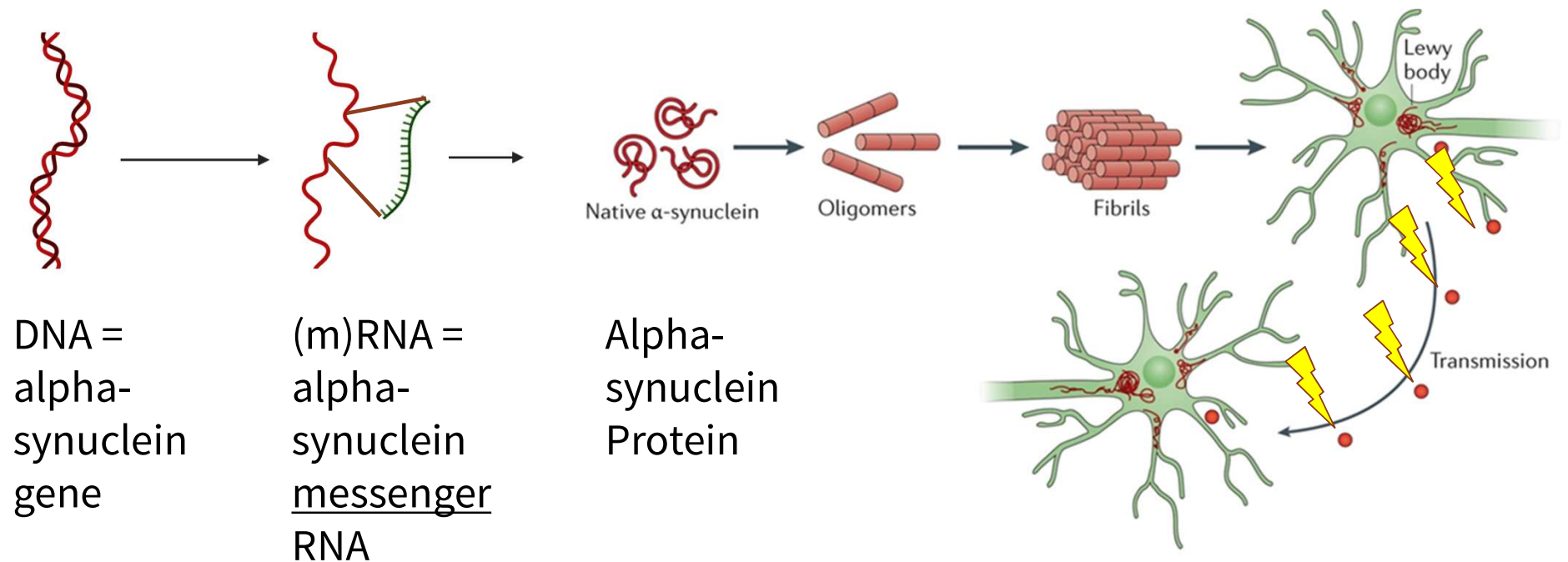
Ambroxol “Shuttles
GCase through cell”

4. Reducing extracellular alpha-synuclein

Immunotherapies

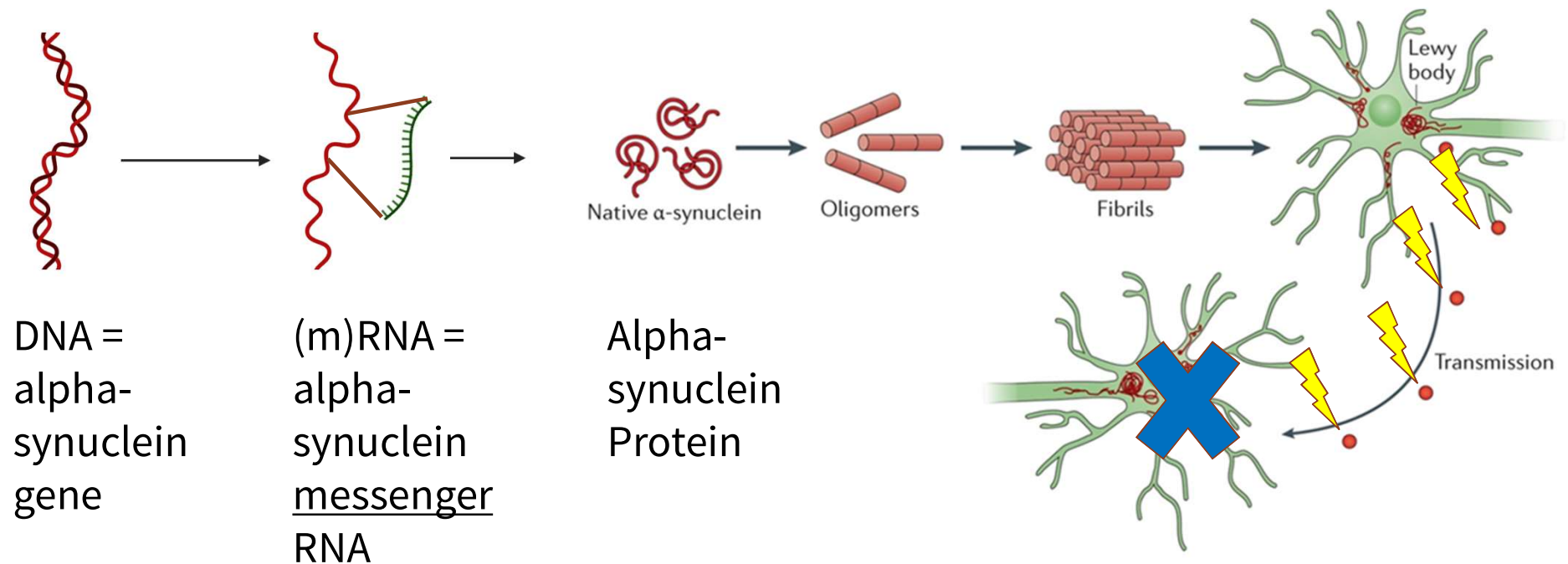


Antibodies target extracellular alpha-synuclein



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Antibodies target extracellular alpha-synuclein



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Immunotherapies target extra-cellular a-syn

- Antibodies are unable to enter cells
- Immunotherapy reduce a-syn aggregation in transgenic mice overexpressing a-syn and prevent rescue phenotypes
- Anti-inflammatory effect in neurodegenerative models

Challenges:

- potential to trigger off-target responses
- non-specific inflammatory reactions
- need for repetitive administration
- limited penetration of antibodies into the CNS (0.1-1%)

Completed phase I trials – low BBB penetration

Table 1. Completed phase I trials of α -synuclein-targeted immunotherapy

Name	Type	Target of the antibody	Affinity (oligomeric/monomeric)	Trials	Dose	Half-life (d)	Change in serum α -syn level	Change in CSF α -syn level	BBB penetration rate	Safety
PRX002	Passive	C-terminus	> 400 fold	Phase Ia	Single ascending dose	18.2	-	-	-	No severe or serious TEAEs
				Phase Ib*	Multiple ascending doses	10.2	Up to 97% reduction	No	0.3%	No severe or serious TEAEs
BIIB054	Passive	N-terminus	> 800 fold	Phase I [†]	Single ascending dose	28–35	-	-	0.3–0.5%	No severe or serious TEAEs
PD01A	Active	C-terminus	-	Phase I	Single dose	-	-	-	-	No serious adverse events

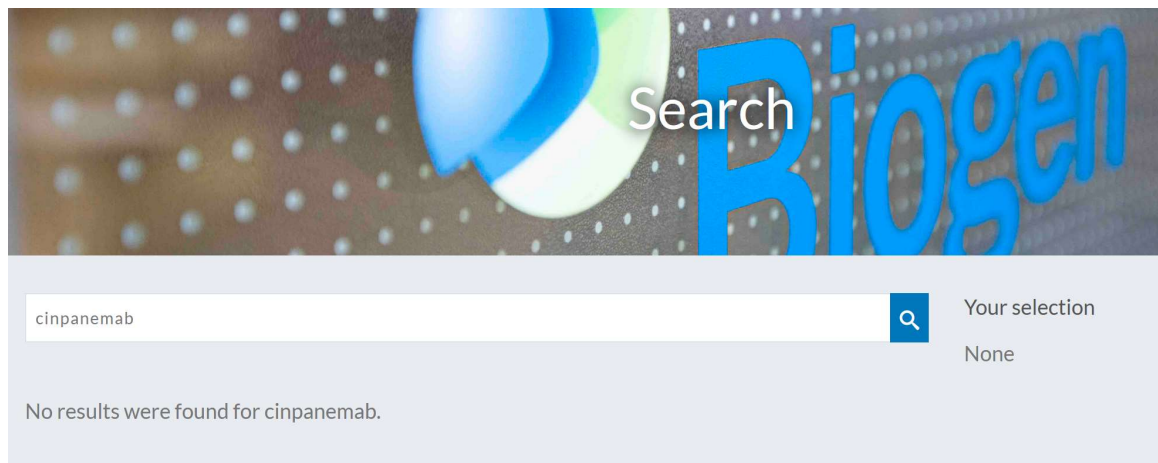
*adapted from Jankovic et al.⁶⁴; [†]adapted from Brys et al.⁶⁵ d: day, syn: synuclein, CSF: cerebrospinal fluid, BBB: blood-brain barrier, TEAEs: treatment-emergent adverse events.

Shin et al. 2020, J. Mov. Disorders

Biogen alpha-synuclein antibody therapy failed

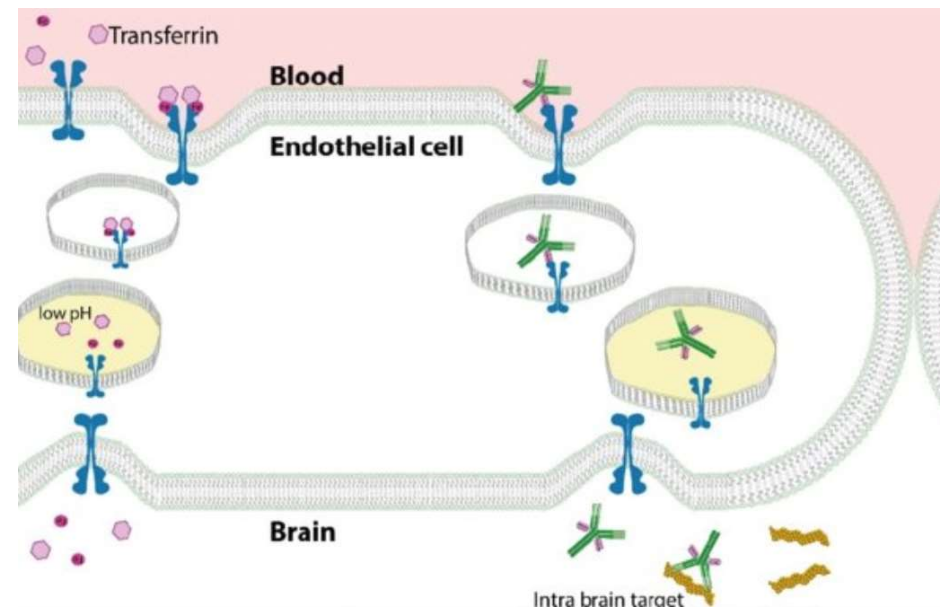
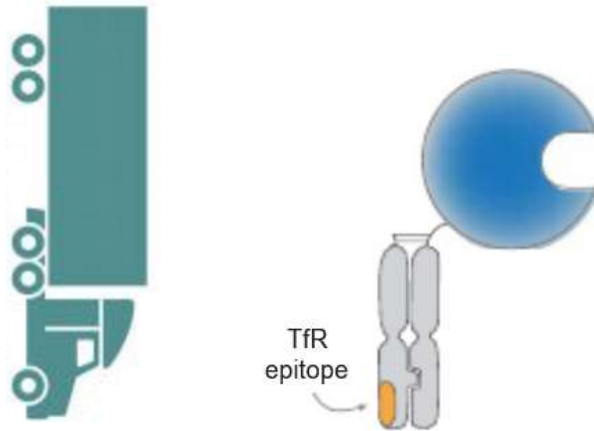
Biogen tosses out Parkinson's hopeful cinpanemab, pays \$75M for its syn

by Ben Adams | Feb 3, 2021 7:55am



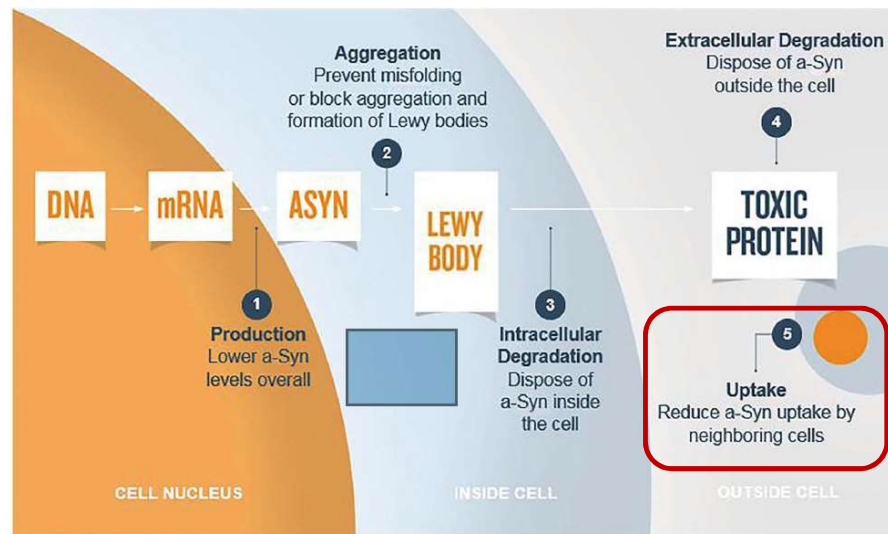
Getting through ---- the blood brain barrier

using TVs = transport vehicles



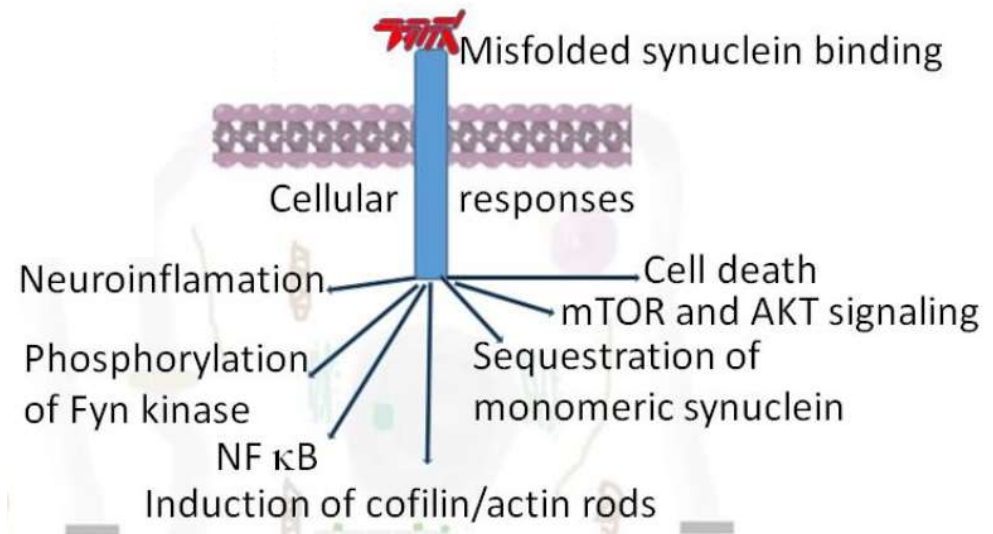
carrying a drug across the blood-brain barrier = receptor-mediated transcytosis

5. Reducing cellular uptake of a-syn



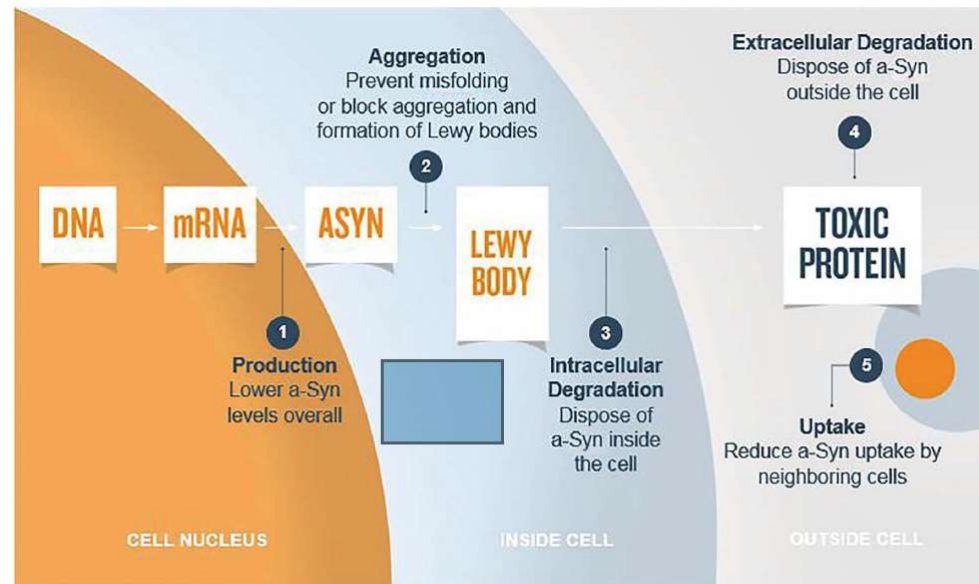
Cell surface receptors bind misfolded alpha-synuclein

- Extracellular alpha-synuclein propagates between cells
- Oligomeric alpha-synuclein binds to cell surface receptors
- induces transmission of signals into cells



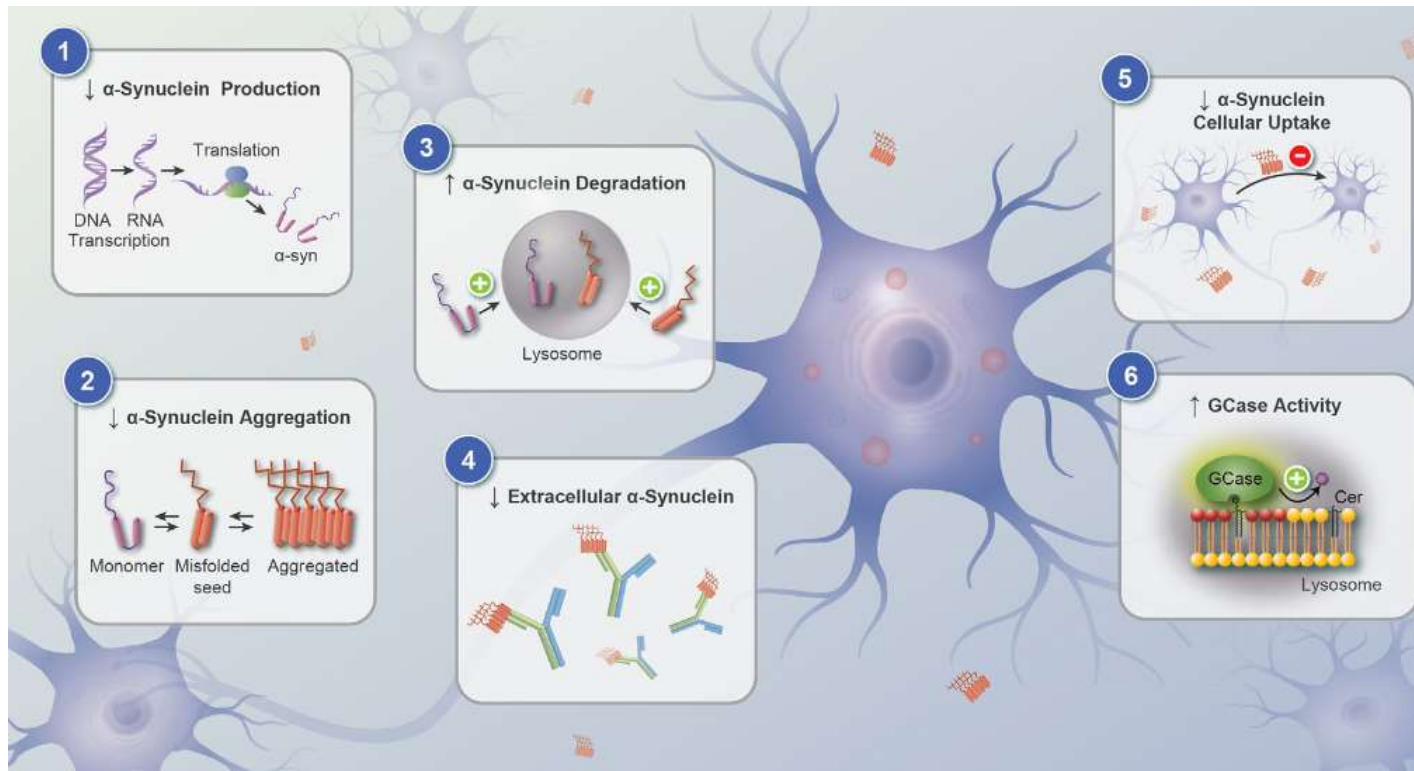
New therapeutic avenues: modulate receptors to inhibit alpha-synuclein update

Summary



- Alpha-synuclein is well-established therapeutic target for alpha-synucleinopathies
- Different strategies of alpha-synuclein lowering strategies
- Some are already in clinical trials
- Challenges: route of administration, passing BBB, frequency of treatment

Thanks so much for your attention!



Any questions? Contact: bschuele@stanford.edu

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