

Lewy Body Dementia and the SNCA Gene

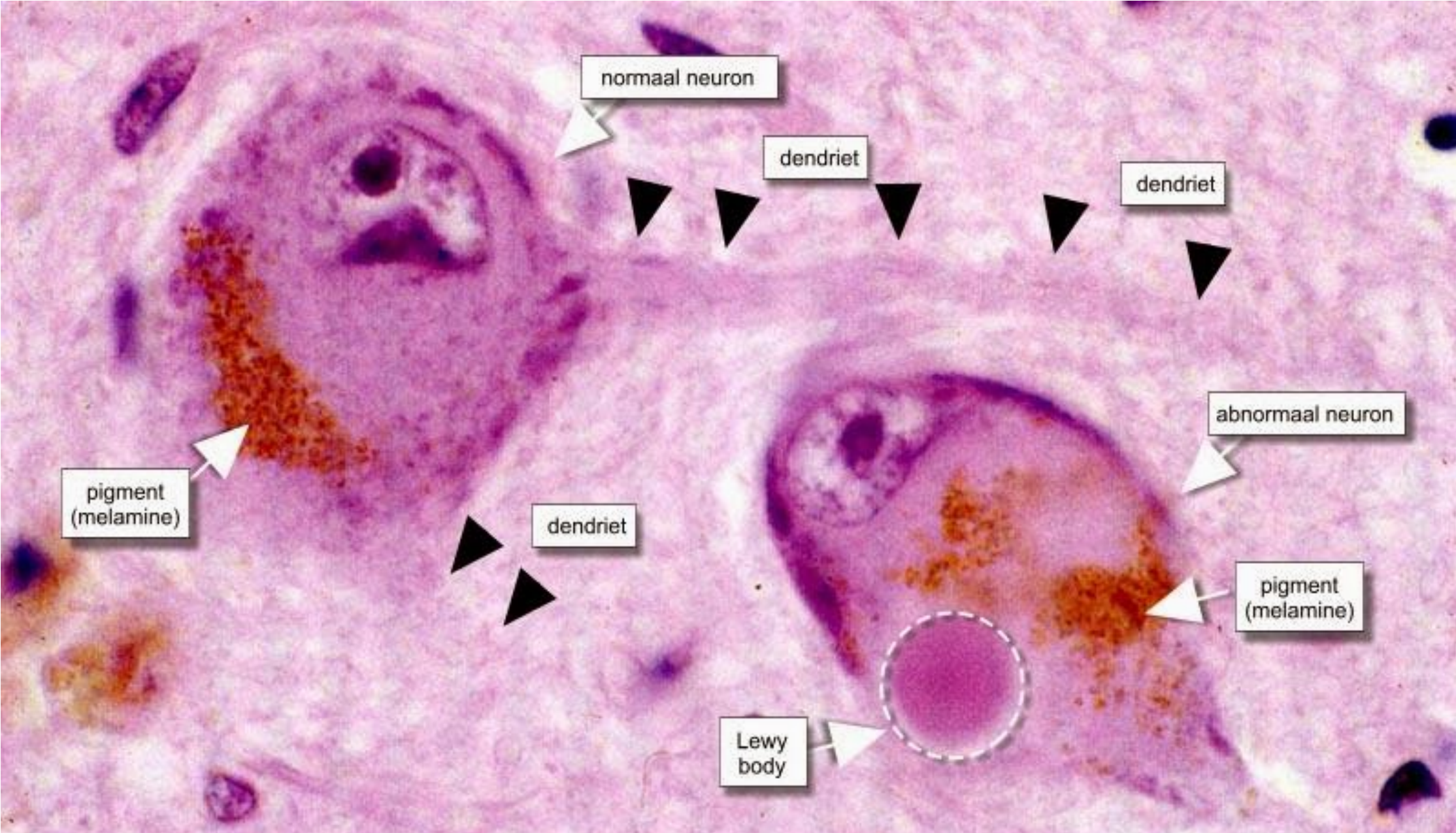


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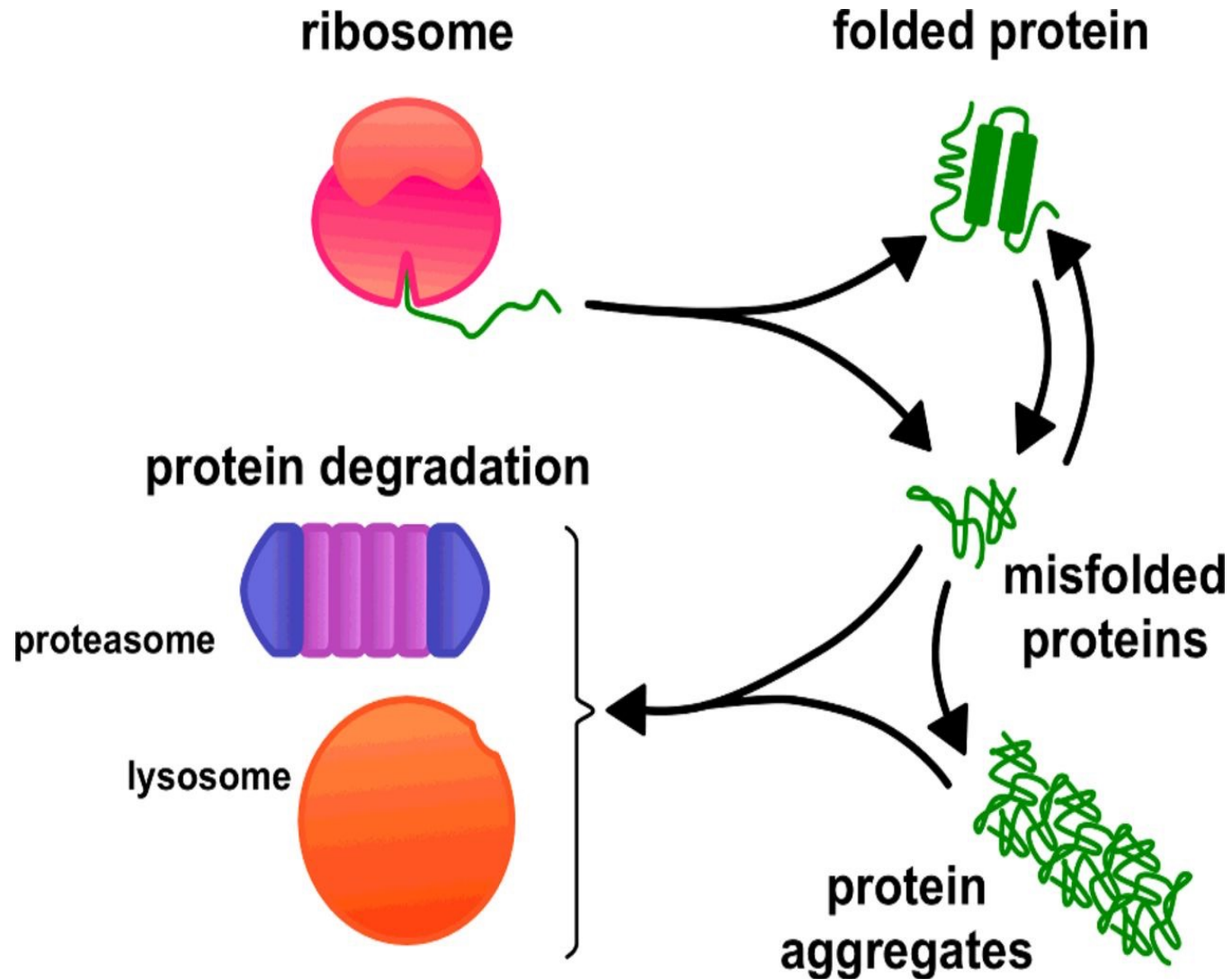
Lewy body dementia—a progressive neurodegenerative disease



Lewy body dementia symptoms differ from Parkinson's and Alzheimer's disease symptoms

	PD	DLB	AD
Dementia	Later onset, usually 1 year after parkinsonism onset. Less prominent than DLB & AD	Earlier compared to PD, less than a year after parkinsonism. Compared to AD, visuospatial and visual memory more severe.	Prominent features
Fluctuation of cognitive impairment	Absent	Present	Absent
Visual Hallucination	Not common	Common, usually non-threatening and insight remain.	Not common
Parkinsonism	Prominent features	Relatively mild, rarely asymmetry, tremor not prominent	Rarely present

Lewy bodies result from misfolded alpha synuclein proteins

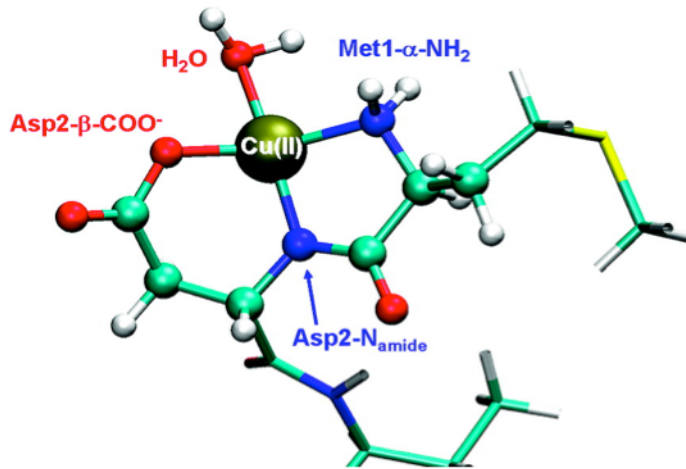


Formed through improper protein degradation

SNCA is associated with Lewy Body Dementia

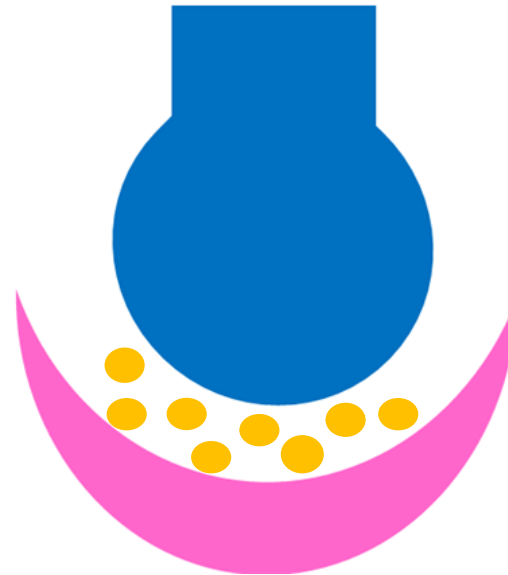
Synuclein

Molecular function



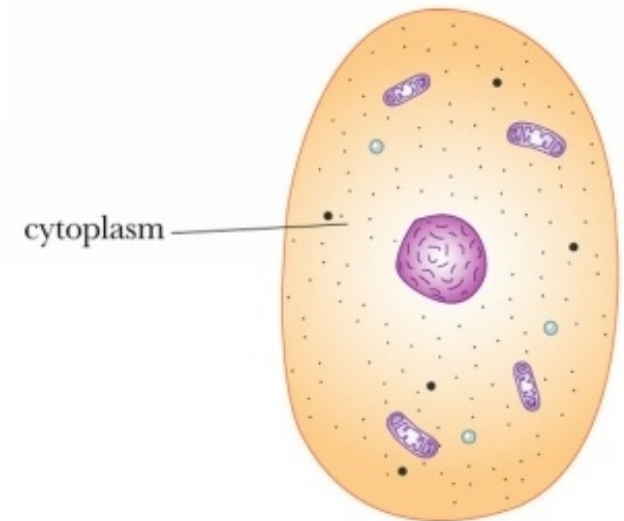
Copper binding

Biological process



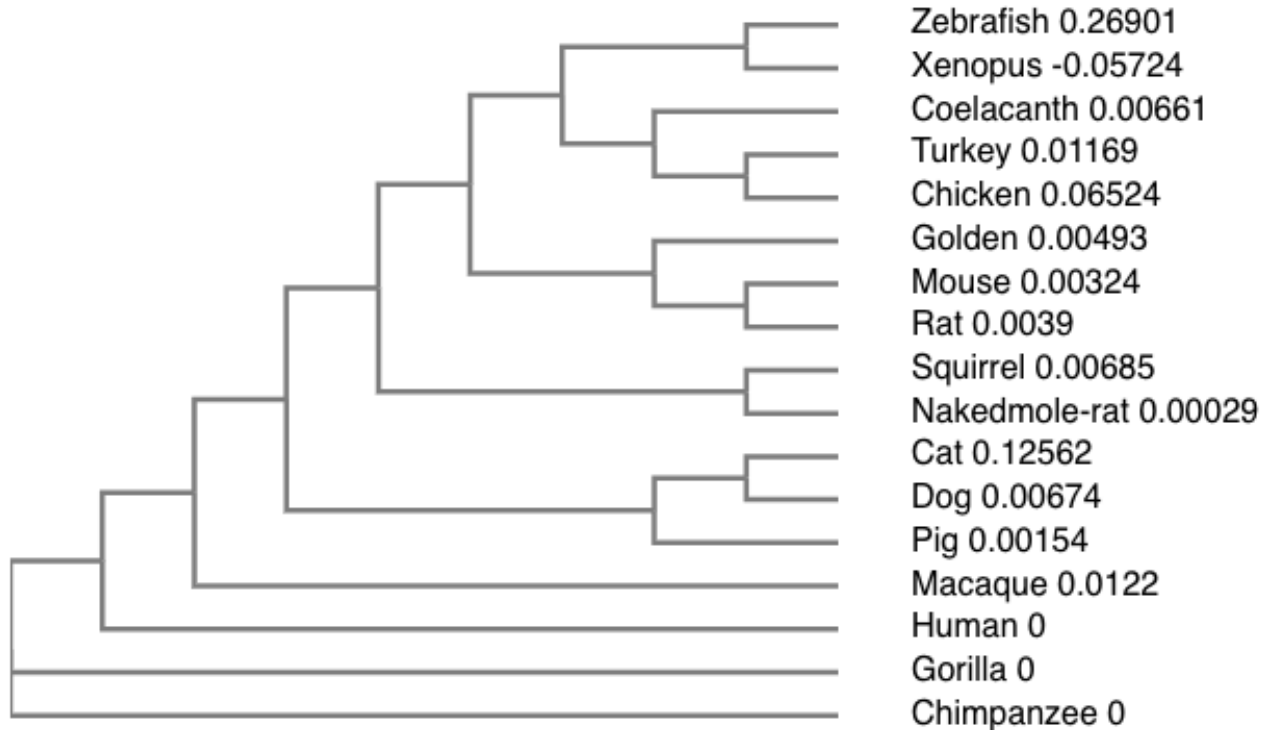
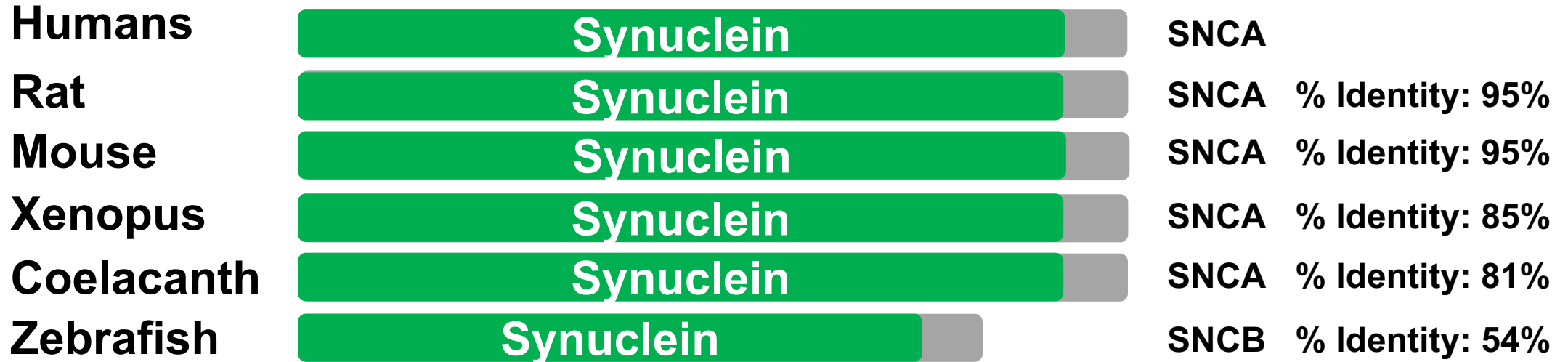
Neurotransmission

Cellular component

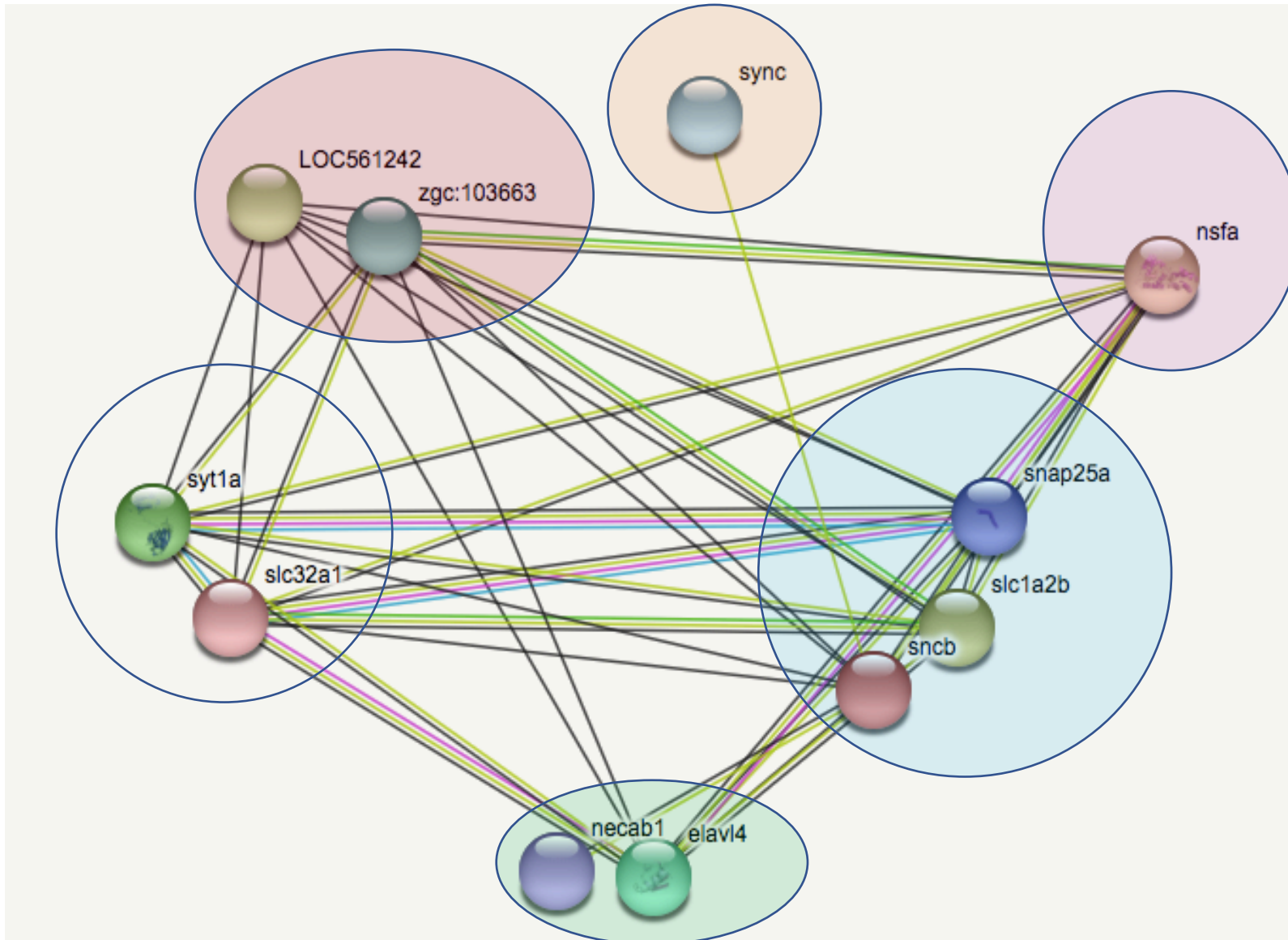


Localizes in the cytoplasm

SNCA is highly conserved across species



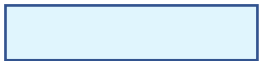
Alpha synuclein interacting proteins in Zebrafish are important for **brain function**



Neuron development



Locomotor development



RNA/protein binding



Secretion/transport



Unknown

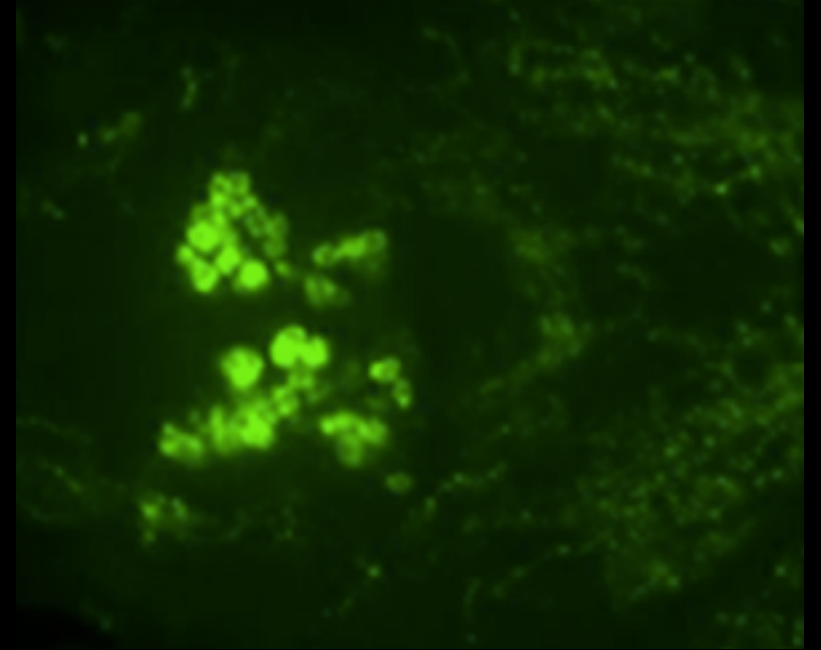
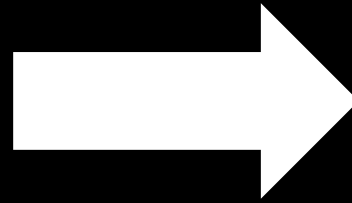


Filament protein



What is the primary goal?

Synuclein



Determine how SNCA regulates dopamine expression in neurons

Zebrafish as a model organism for Lewy Body Dementia



locomotor activity
Wildtype

Easily observed neurons and mutant phenotype, similar brain structure

AIMS



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graph TD; AIMS[AIMS] --> Aim1[Aim 1: Identify conserved amino acids in alpha synuclein important for dopamine release]; AIMS --> Aim2[Aim 2: Identify small molecules that rescue SNCA mutant behavioral phenotypes]; AIMS --> Aim3[Aim 3: Identify proteins that interact with alpha synuclein that are important for dopamine release];
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Aim 1: Identify conserved amino acids in alpha synuclein important for dopamine release

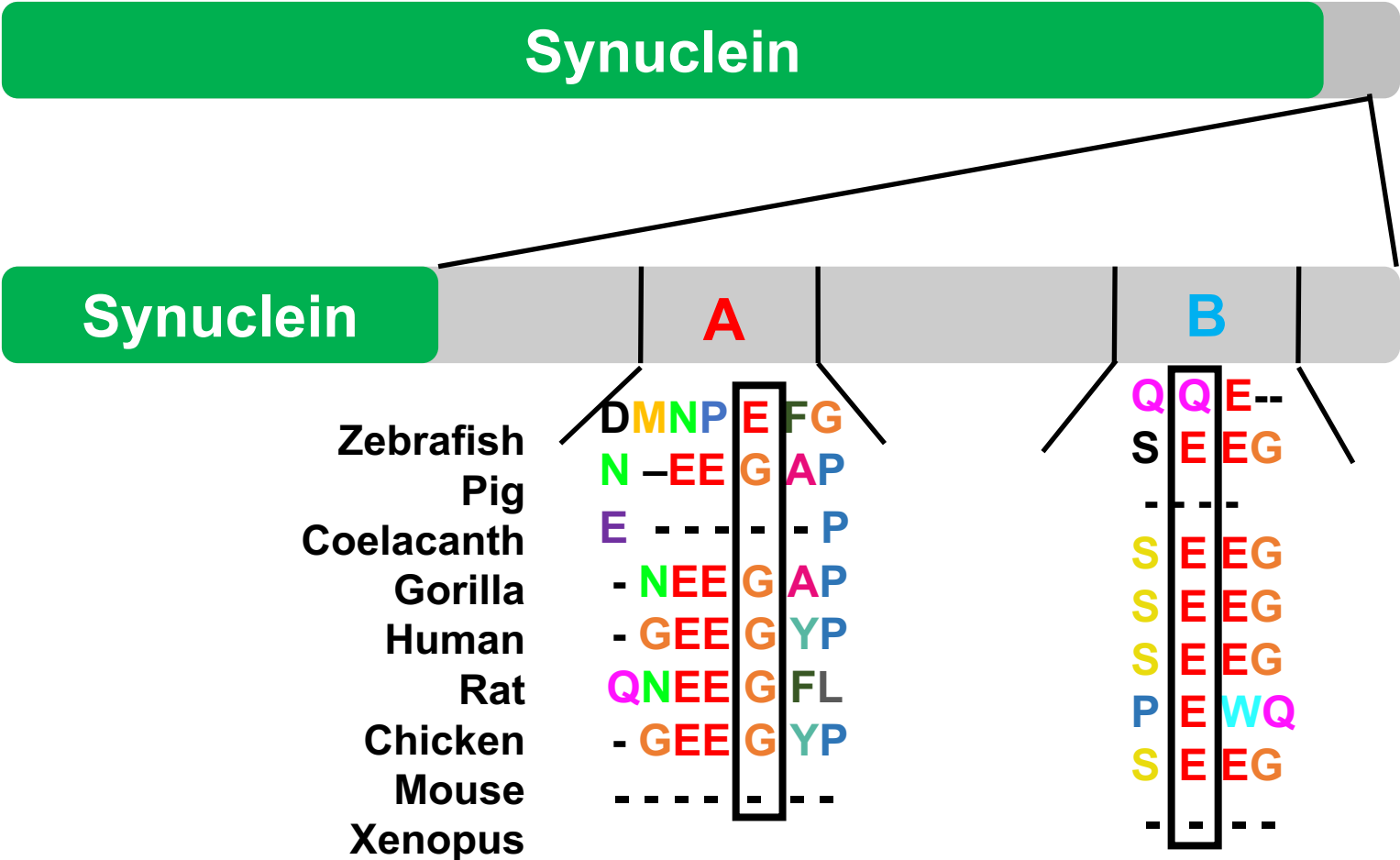
Aim 2: Identify small molecules that rescue SNCA mutant behavioral phenotypes

Aim 3: Identify proteins that interact with alpha synuclein that are important for dopamine release

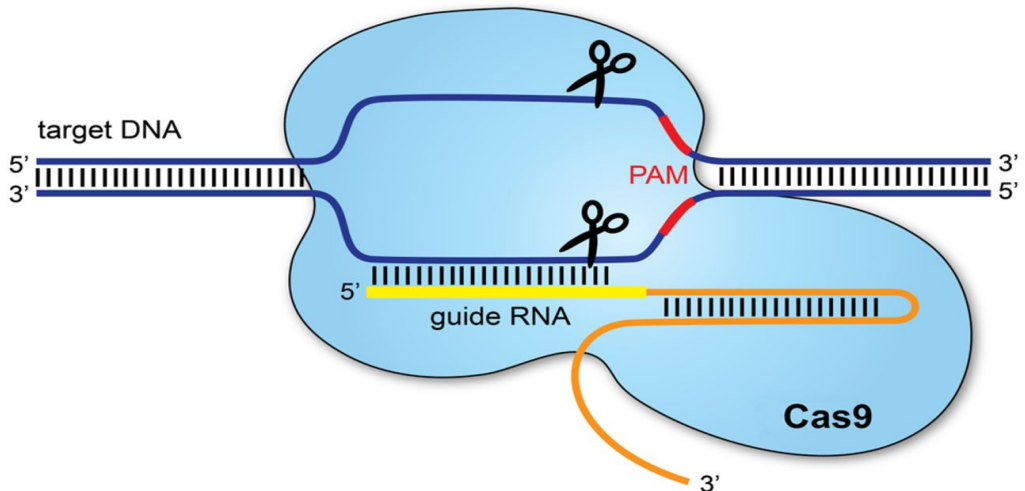
Hypothesis: SNCA is used to regulate dopamine release machinery

Aim 1: Identify conserved amino acids in alpha synuclein important for dopamine release

SNCA



Aim 1: CRISPR highly conserved amino acids to determine their influence on dopamine expression



Mutant A



Zebrafish	E
Pig	G
Coelacanth	-
Gorilla	G
Human	G
Rat	G
Chicken	G
Mouse	G
Xenopus	-

➔ **E to G**

Mutant B



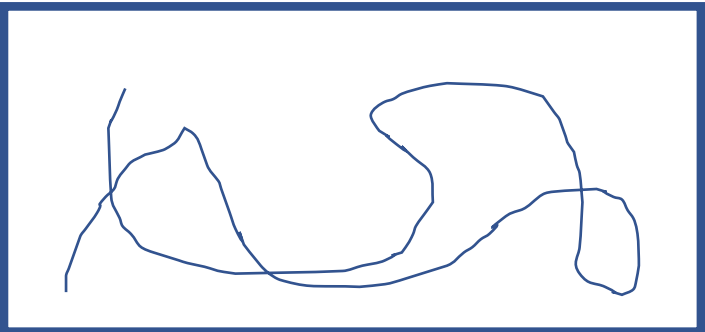
Zebrafish	Q
Pig	E
Coelacanth	-
Gorilla	E
Human	E
Rat	E
Chicken	E
Mouse	E
Xenopus	-

➔ **Q to E**

Aim 1: Assay zebrafish locomotor behavior and dopamine expression

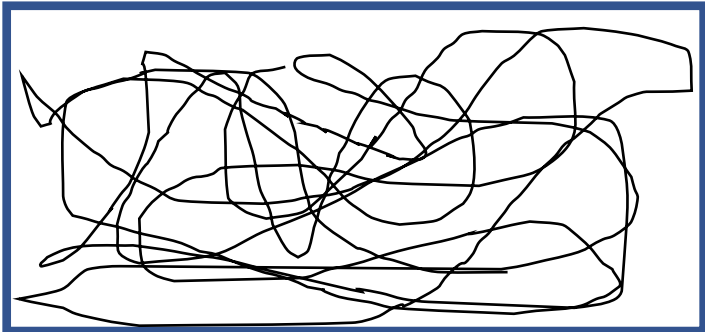
Mutant A

Locomotor behavior

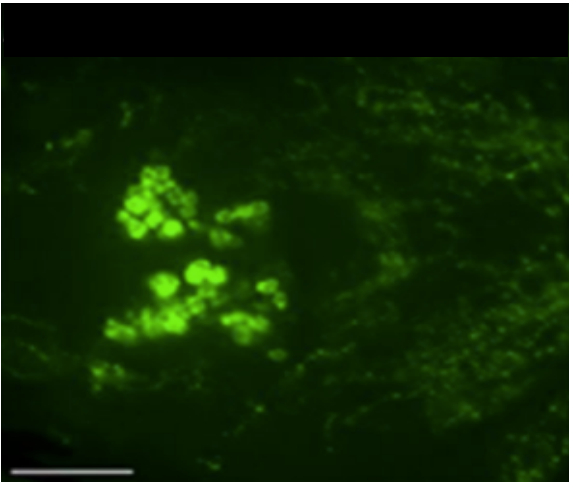
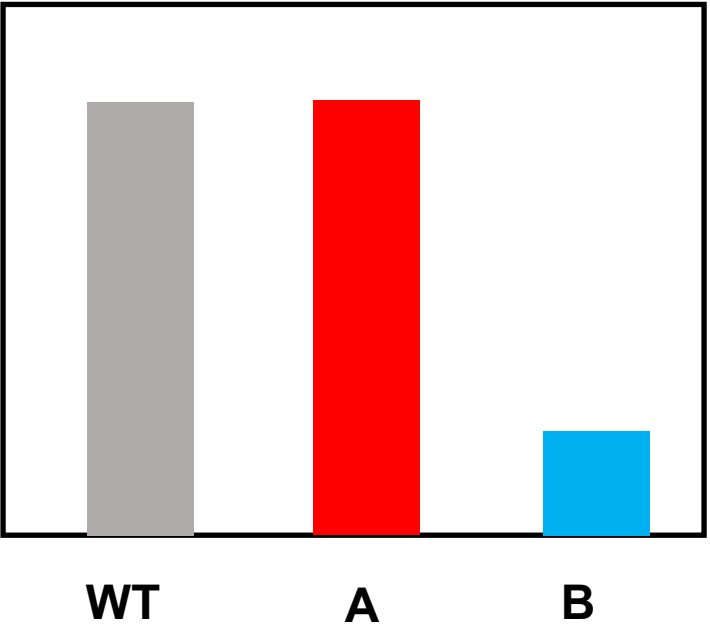


Mutant B

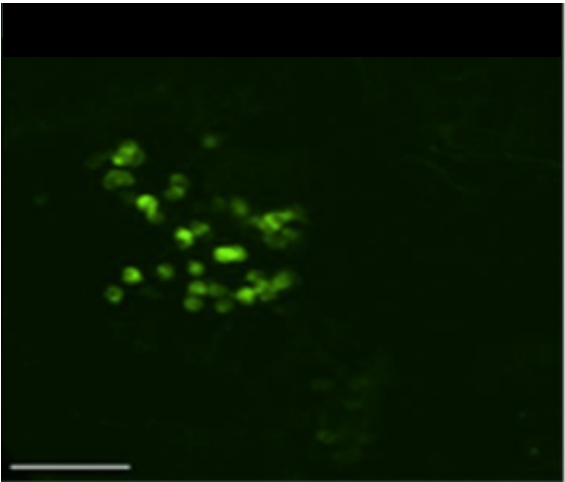
Locomotor behavior



Dopamine expression



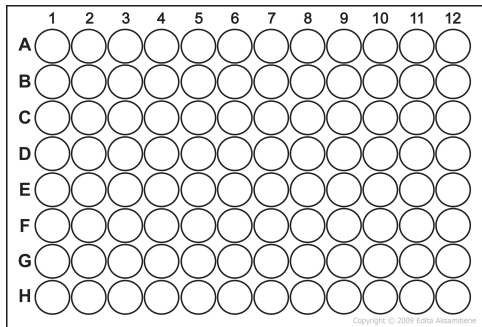
Dopaminergic neurons



Dopaminergic neurons

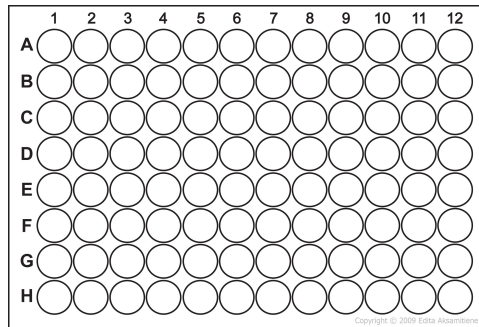
Aim 2: Identify small molecules that rescue SNCA mutant behavioral phenotypes

Wild type



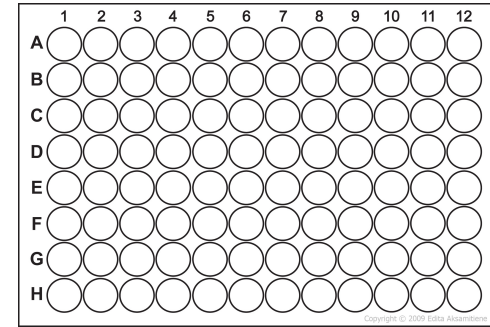
Chemical library

Mutant A



Chemical library

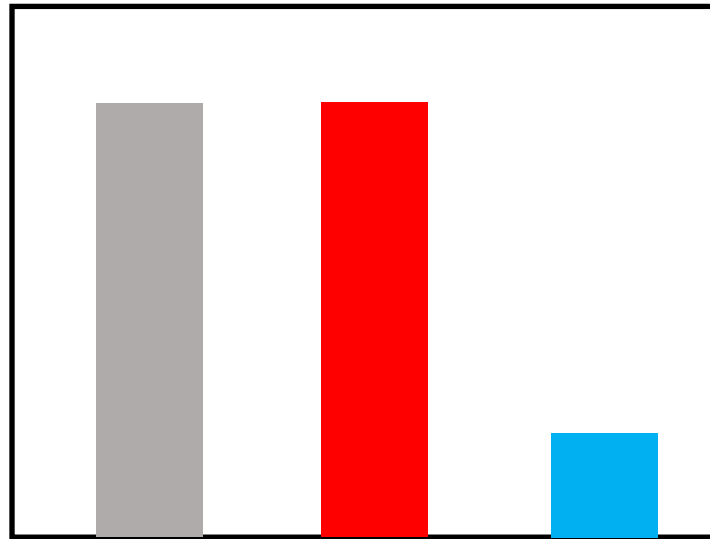
Mutant B



Chemical library

Aim 2: Assay zebrafish to determine if molecule interactions affect dopamine expression

Dopamine expression



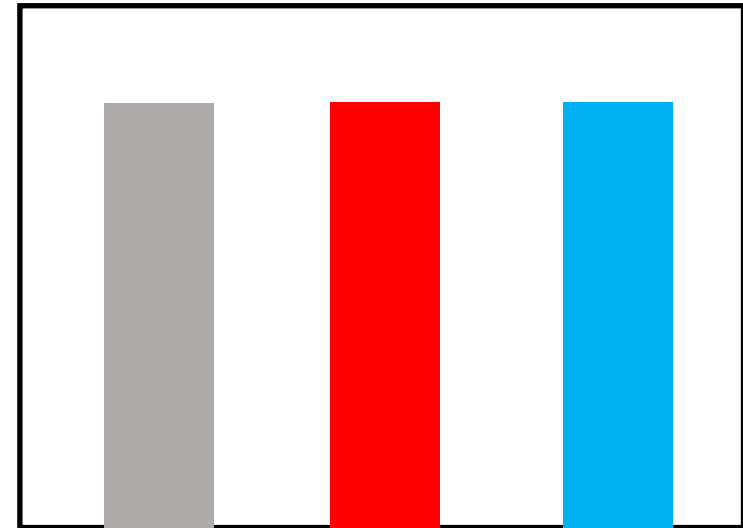
WT

A

B

No small molecule interaction

Dopamine expression



WT

A

B

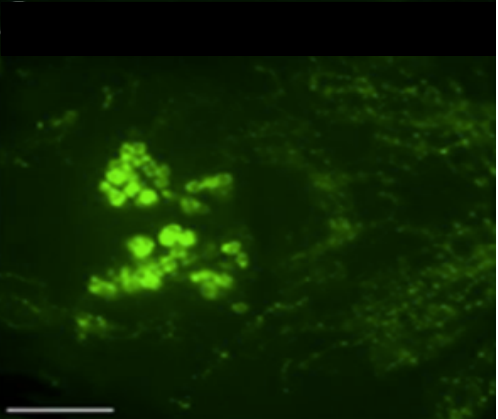
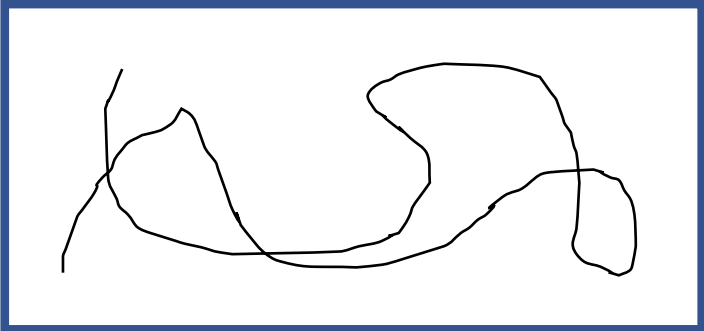
Small molecule interaction,
dopamine rescue

Aim 2: Assay zebrafish behavior to determine if molecule interactions rescue dopamine expression

No small molecule interaction

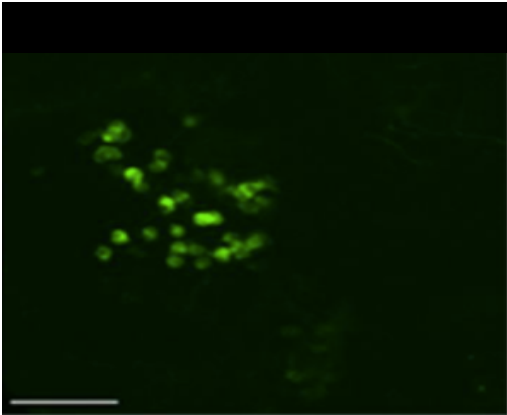
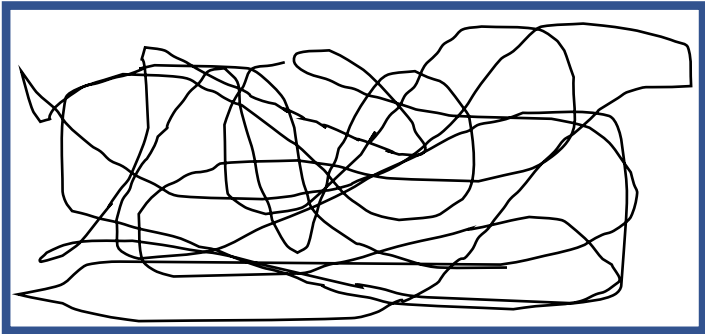
Interaction, dopamine rescue

Wild type locomotor behavior



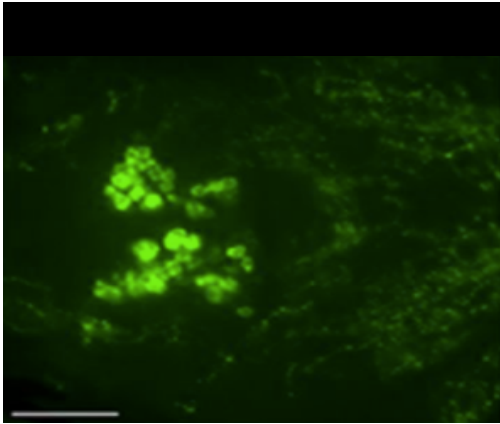
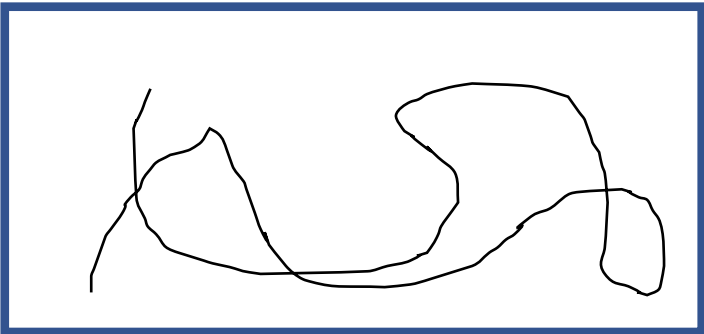
Dopaminergic neurons

Mutant B locomotor behavior



Dopaminergic neurons

Mutant B locomotor behavior



Dopaminergic neurons

Aim 3: Use Co-IP to identify proteins that interact with alpha synuclein

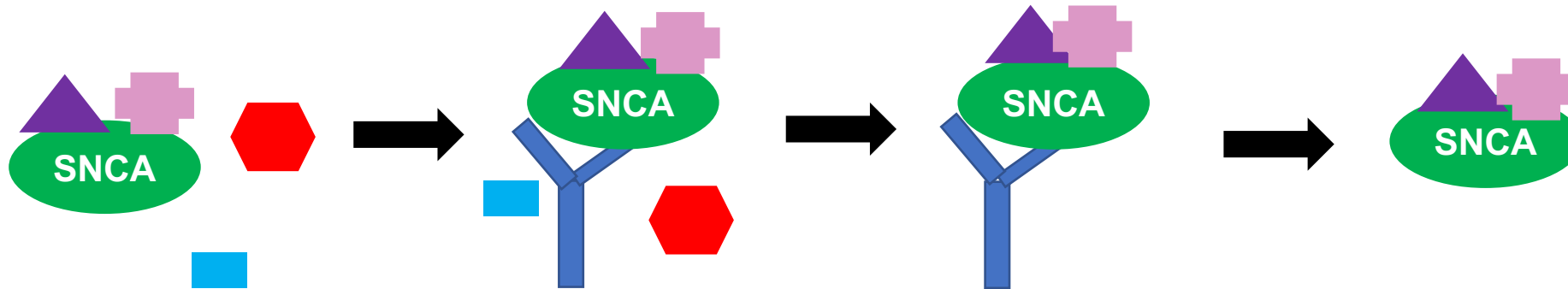
Wild type



Mutant A



Mutant B



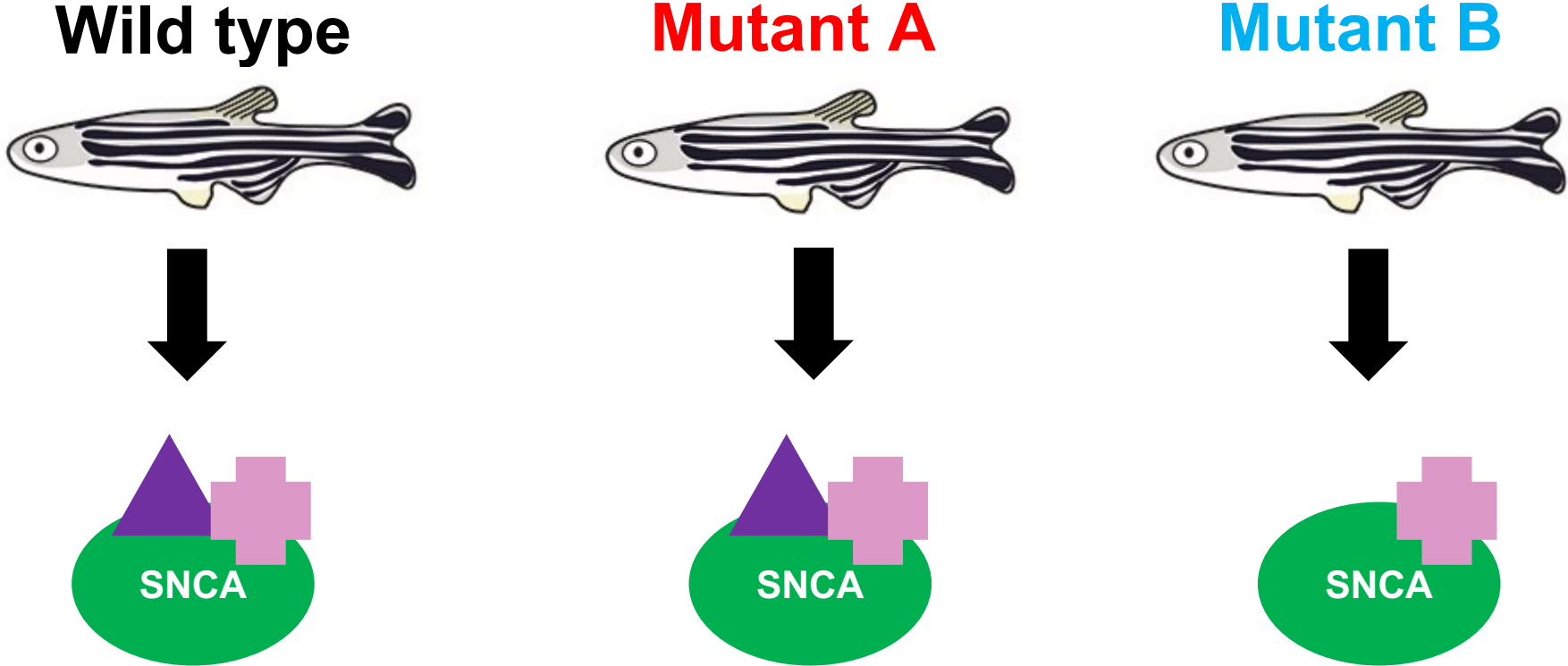
Cell lysis

**Incubation
with antibody**

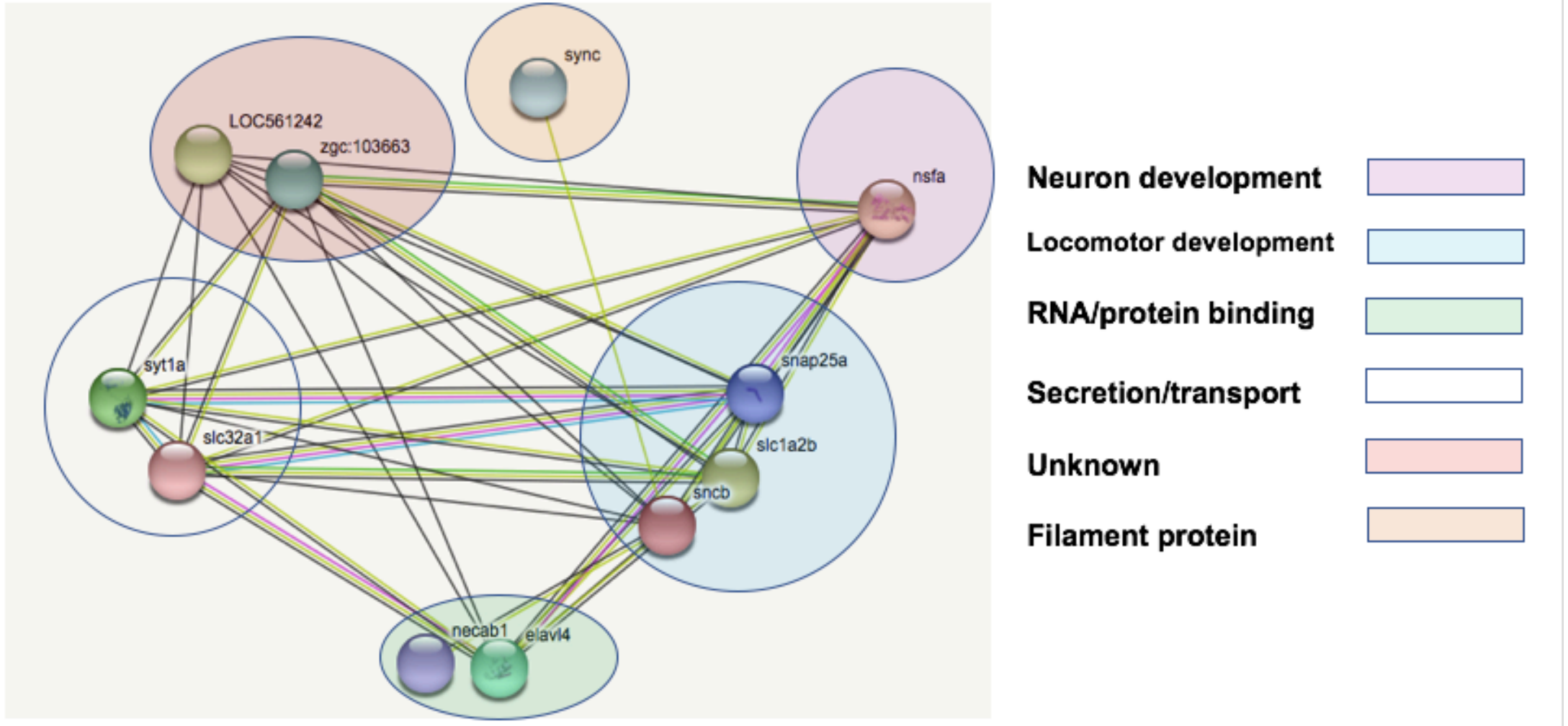
**Removal of
unbound proteins**

**Identify interacting
proteins with mass
spectrometry**

Aim 3: Differences in protein interactions could identify proteins that are important for dopamine release



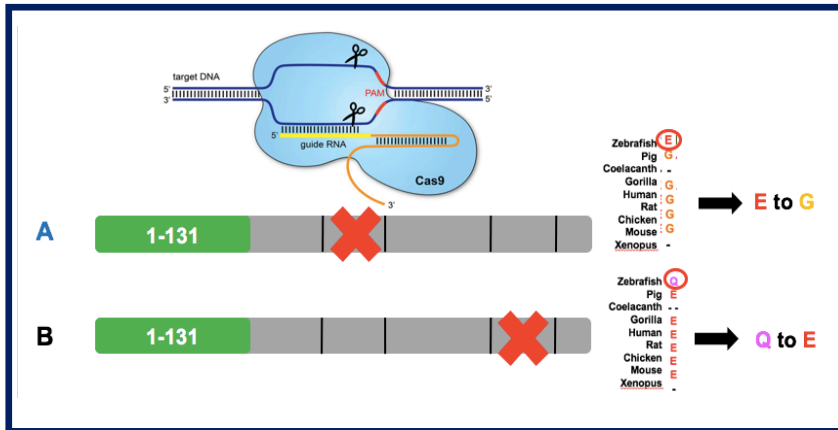
Future directions



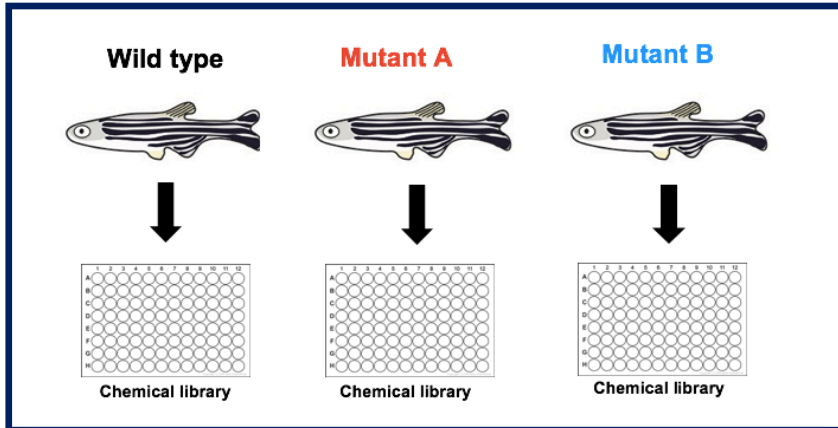
Identify the function of the **unknown proteins** in the SNCA protein interaction network

Conclusions

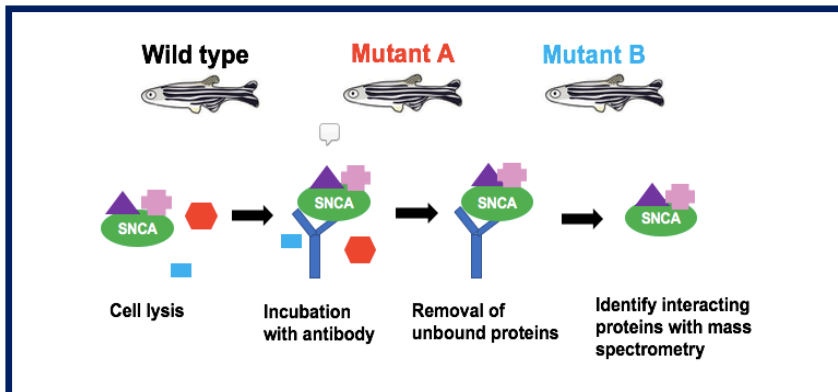
Highly conserved amino acids are likely important in dopamine expression



Small molecules that rescue mutant behavioral phenotypes may aid in dopamine release



Protein interactions that differ from wild type are likely involved in dopamine expression



Questions?



References

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