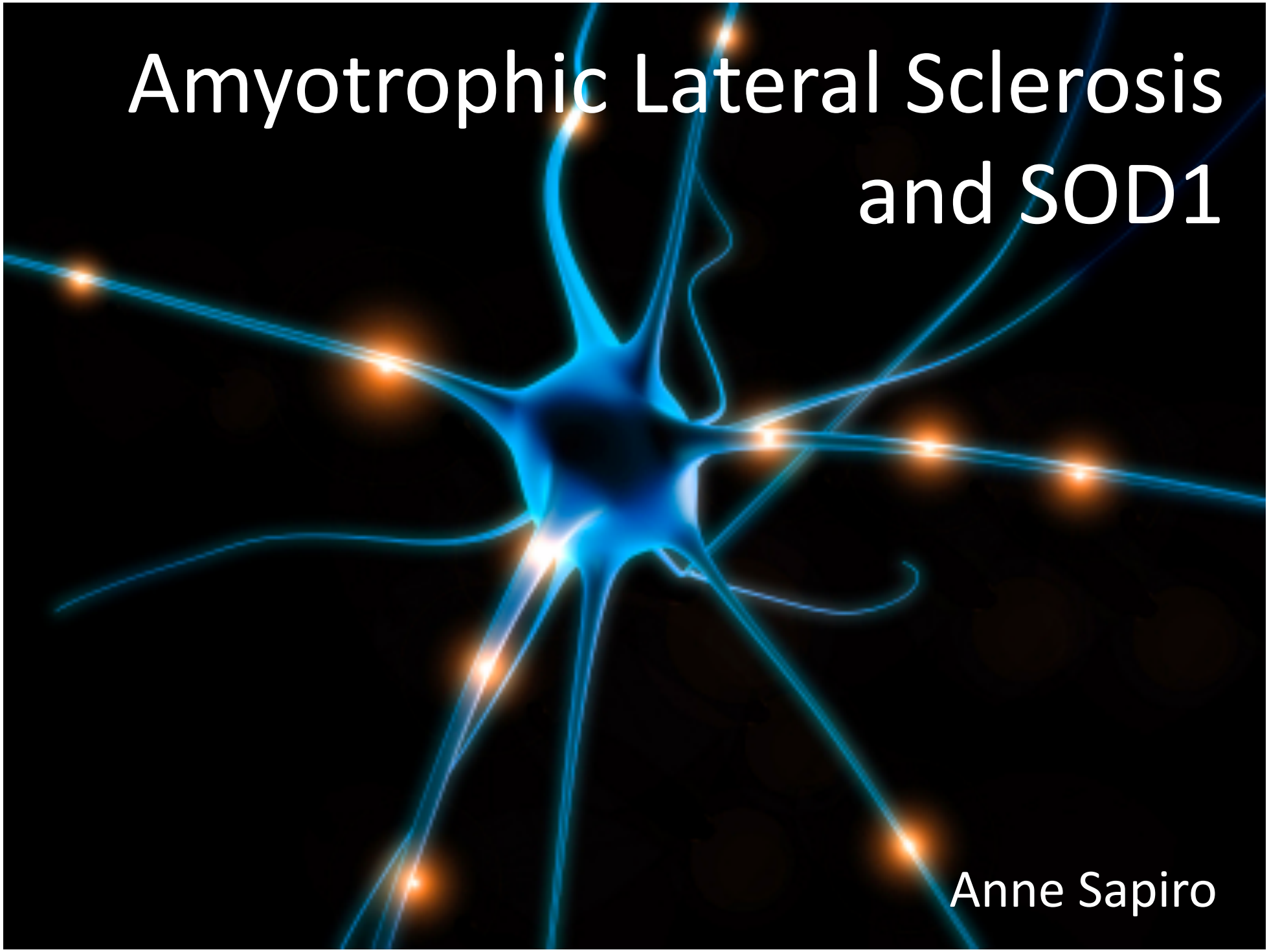
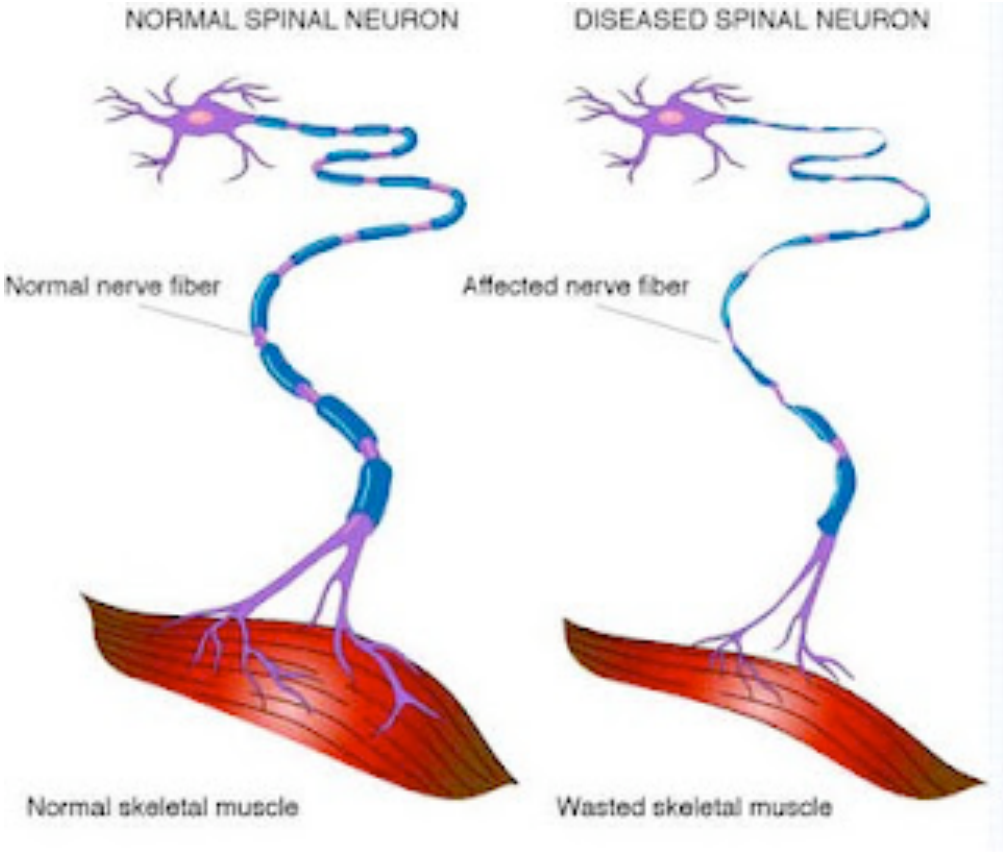
Amyotrophic Lateral Sclerosis and SOD1



Anne Sapiro

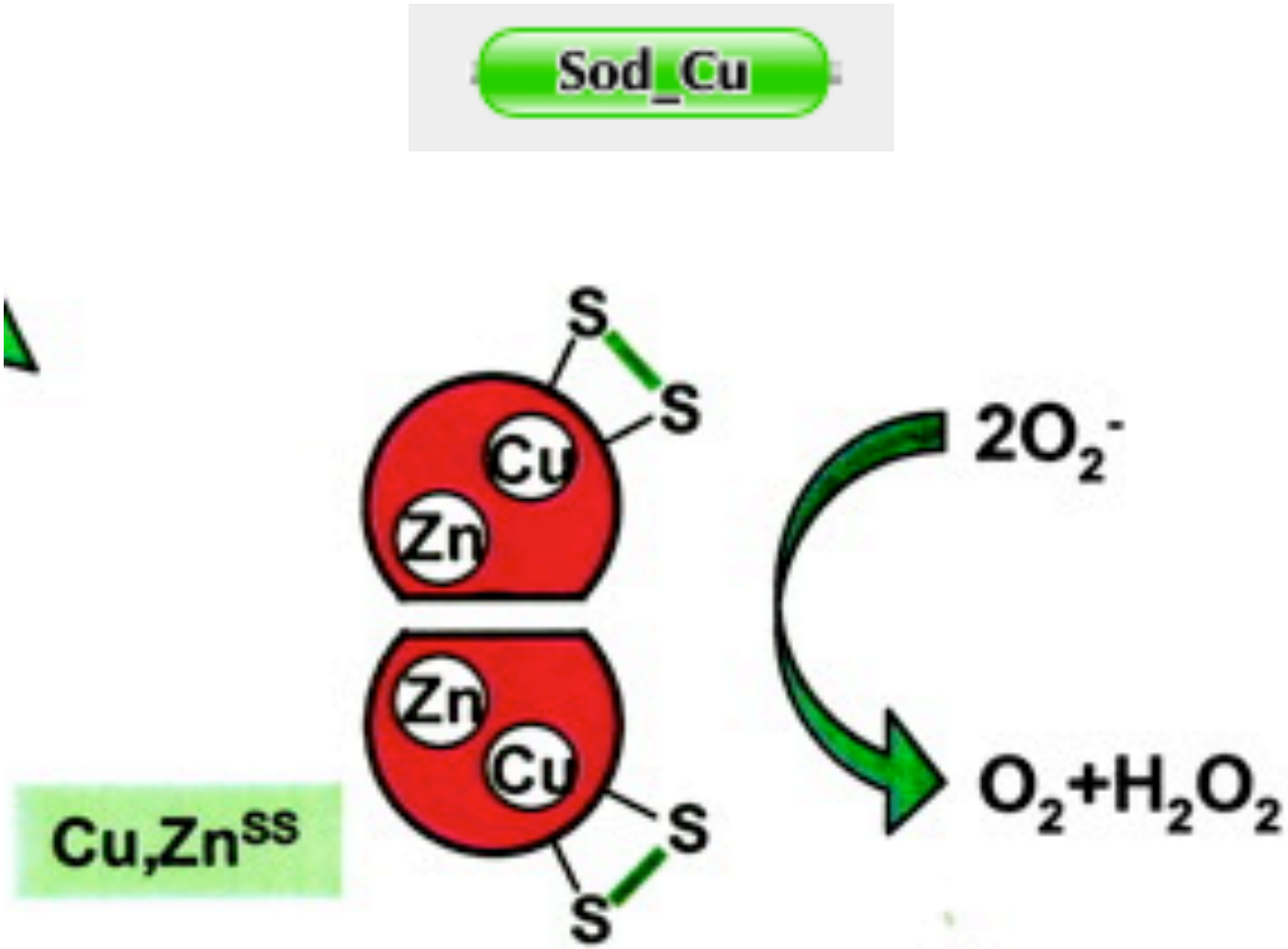
Amyotrophic lateral sclerosis facts

- Neurodegenerative disease
- Loss of motor control
- Fatal within 3-5 years
- 90% sporadic
- 20% of familial ALS caused by mutations in SOD1



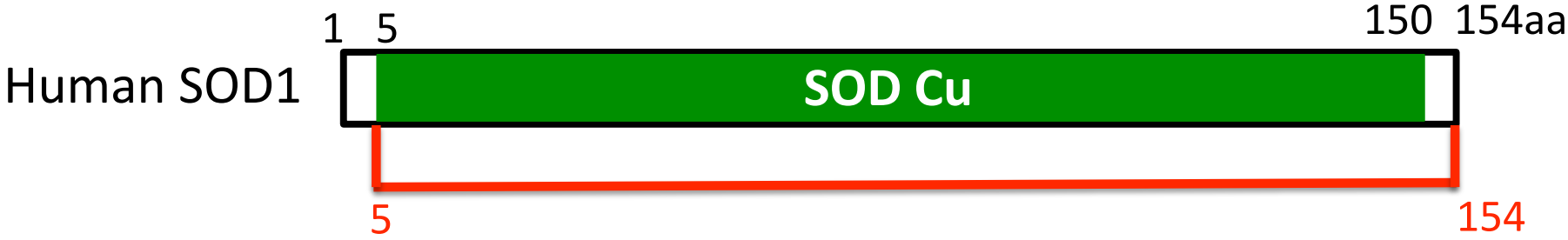
www.thehealthsuccesssite.com

Superoxide Dismutase 1 (SOD1)



Furukawa Y , O'Halloran T V J. Biol. Chem. 2005;280:17266-17274

ALS-causing mutations in SOD1

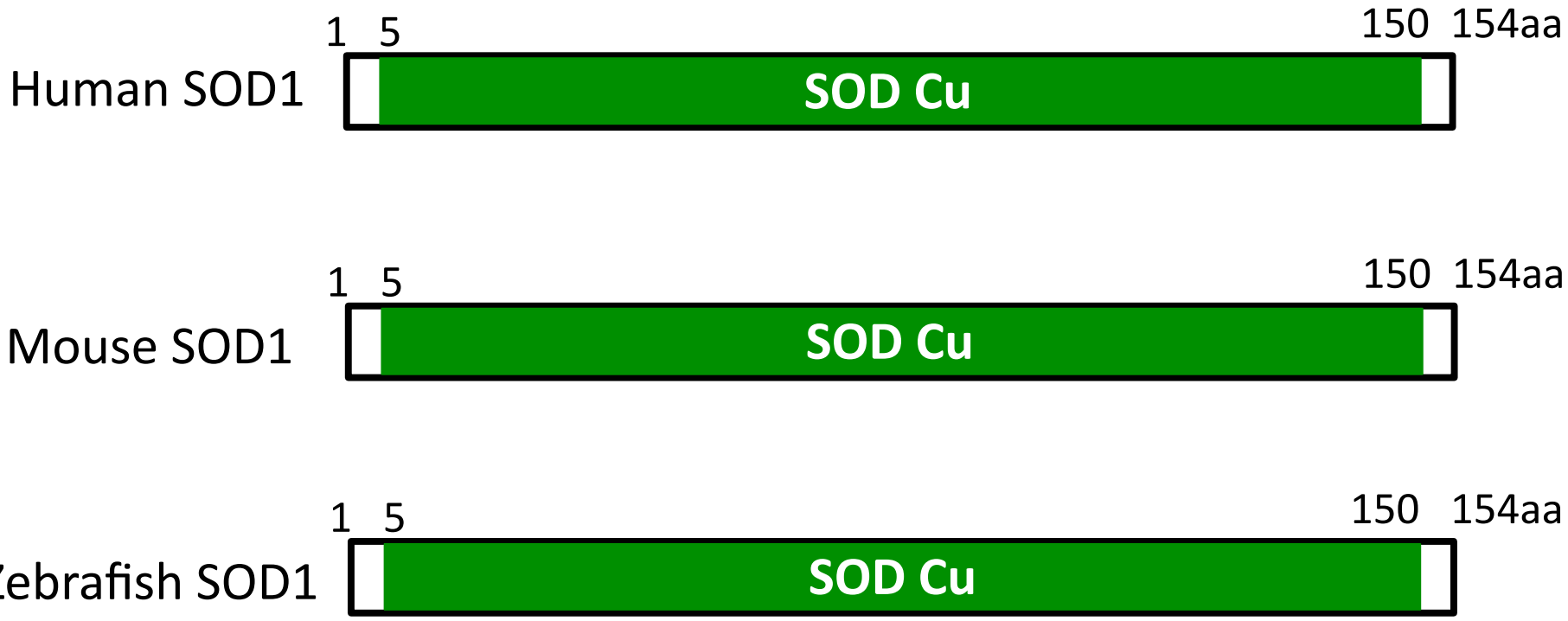


83 amino acids with missense or nonsense mutations

http://alsod.iop.kcl.ac.uk

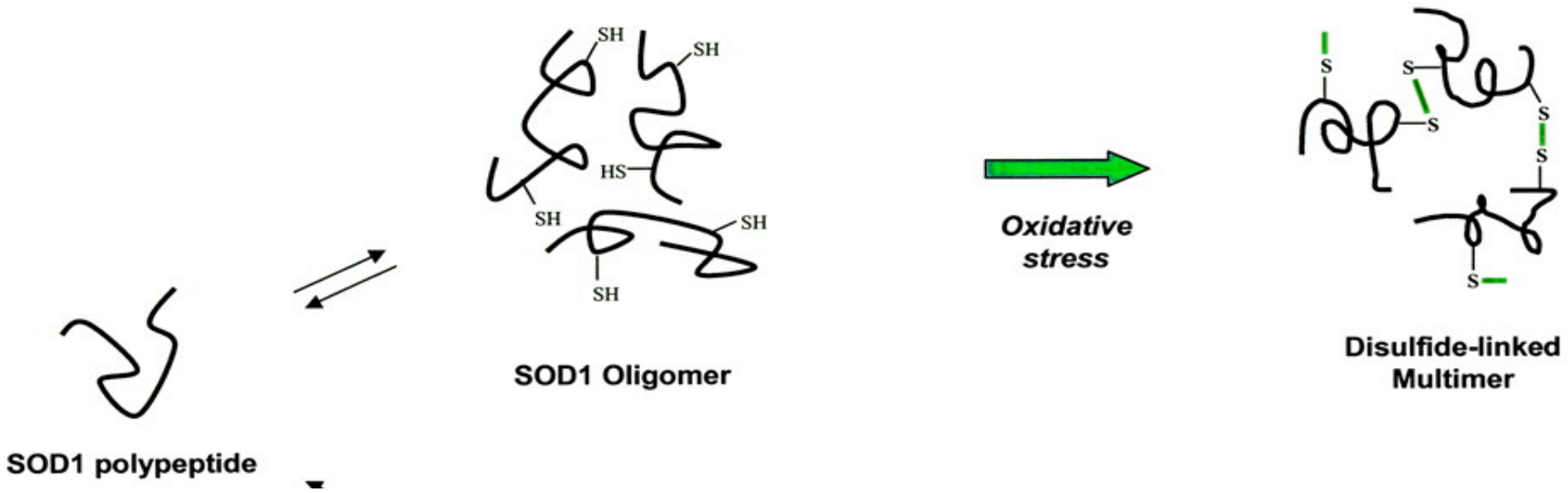
Pfam

SOD1 protein domains across homologs



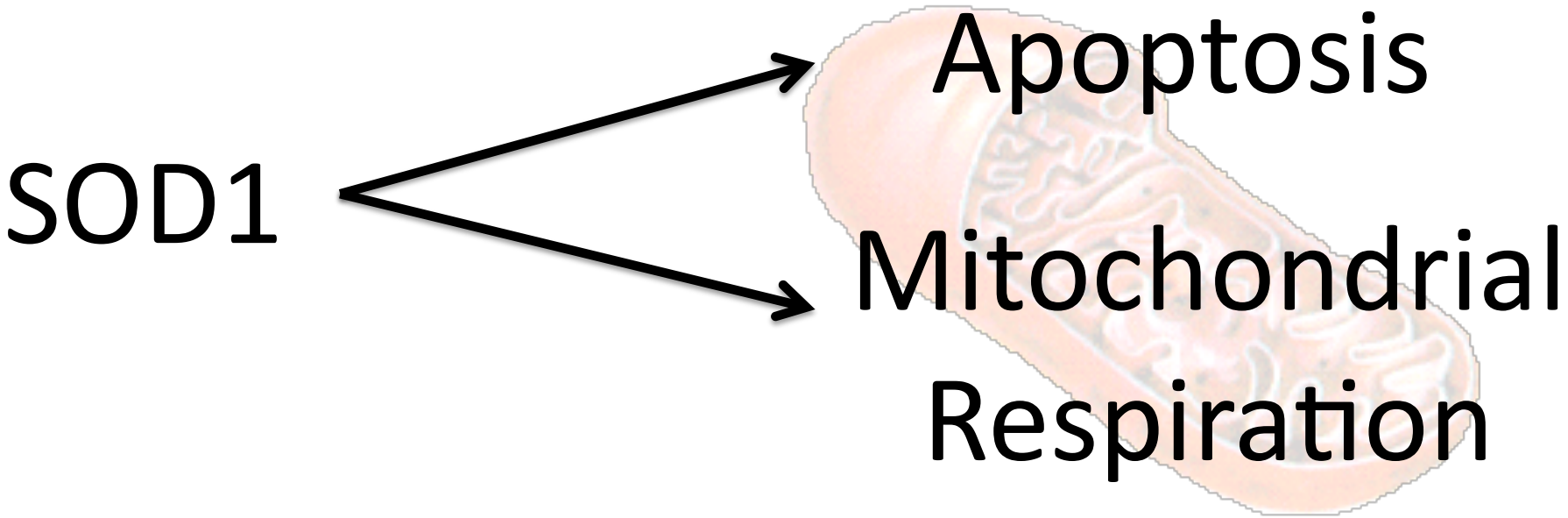
Pfam

Mutant SOD1: Toxic GOF



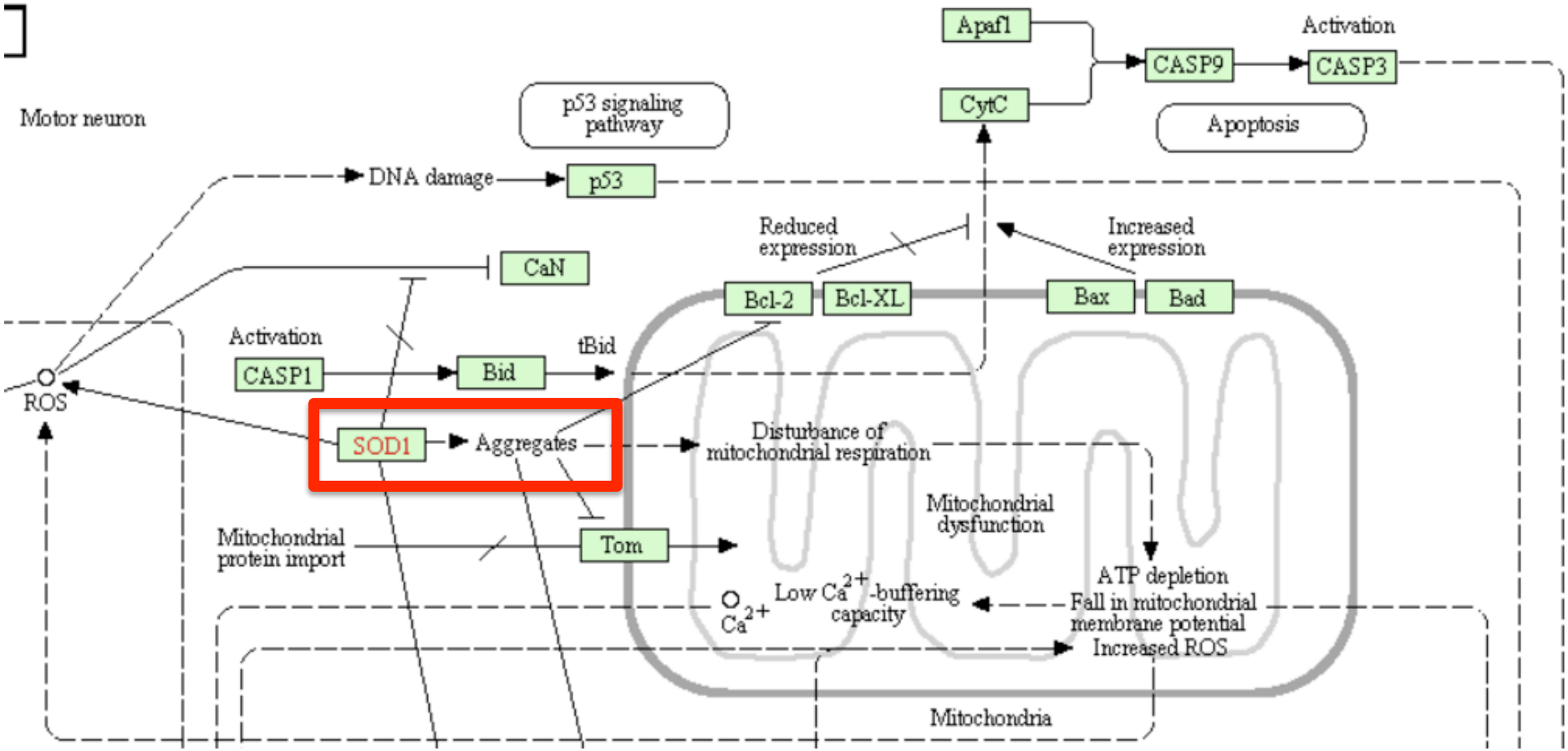
Furukawa Y , O'Halloran T V J. Biol. Chem. 2005;280:17266-17274

Gene Ontology: Biological Processes



AmiGO

SOD1 aggregates lead to mitochondrial defects

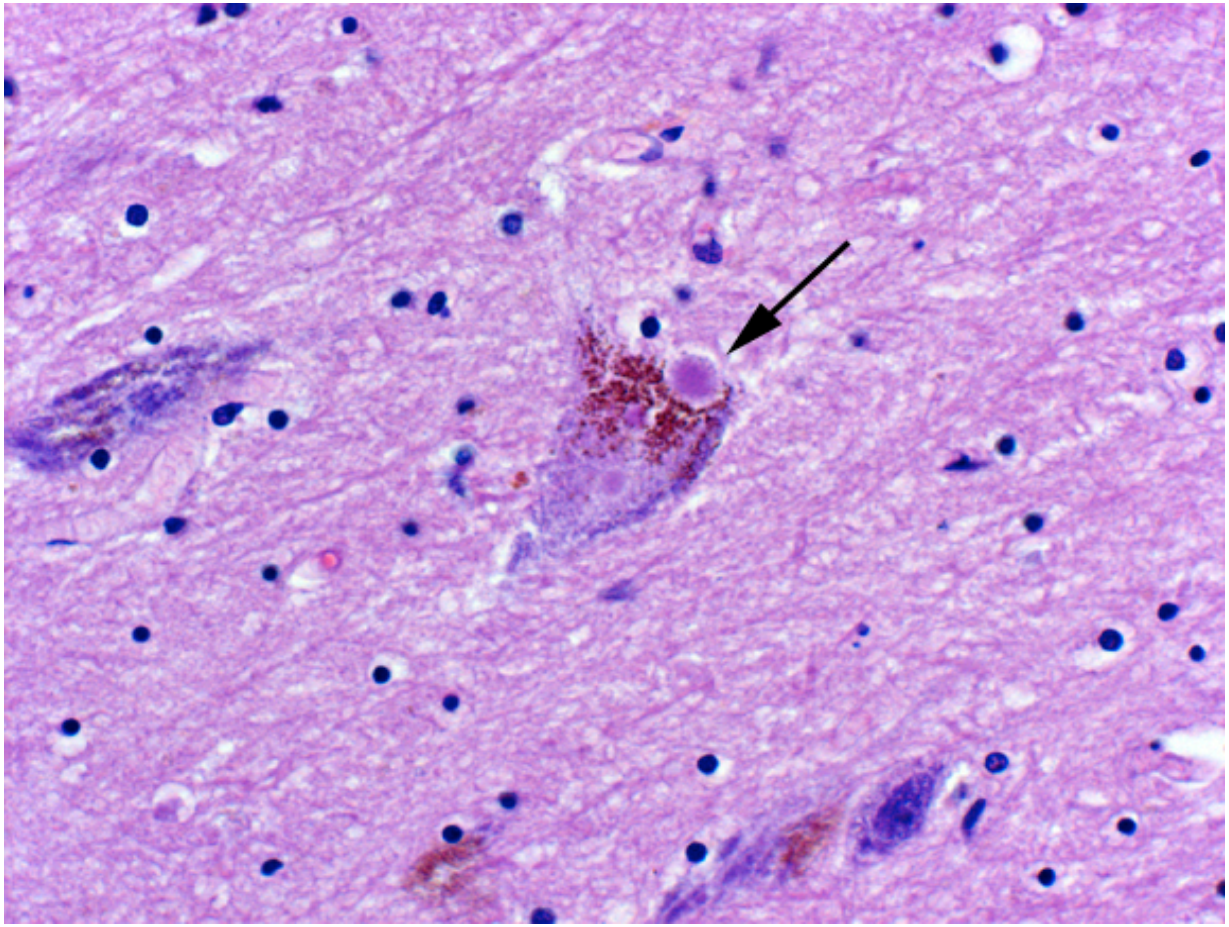


What comprises aggregates?

Human SOD1 Interaction Network

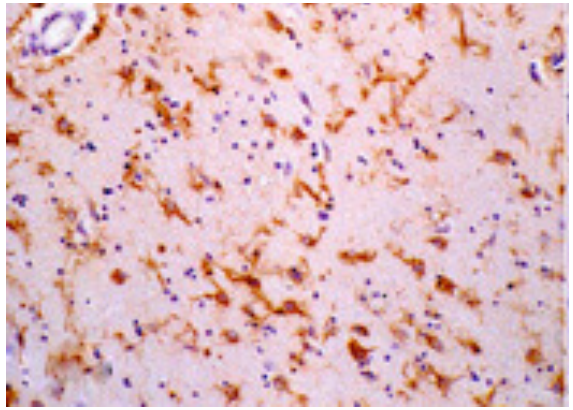
Aggregates and neurodegeneration

Parkinson's Lewy bodies



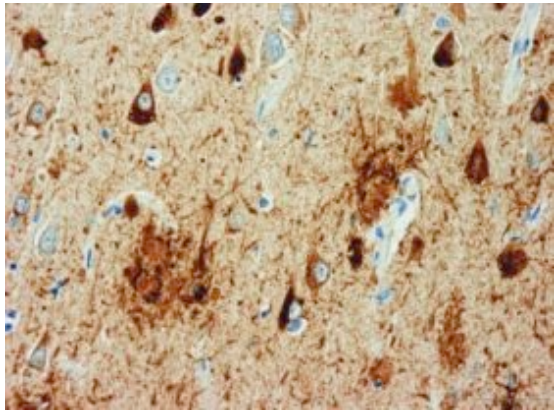
http://missinglink.ucsf.edu/lm/ids_104_neurodegenerative/Case2/Case2Micro.htm

Huntington's inclusions



http://neuropathology-web.org/

Alzheimer's plaques



http://cdn.physorg.com

Parkinson's Lewy bodies

α-synuclein

Neurofilaments

Ubiquitin

Adapted from Branco et al. 2010

Hypothesis:

ALS aggregates contain components of Parkinson's Lewy bodies.

Approach:

Look at 

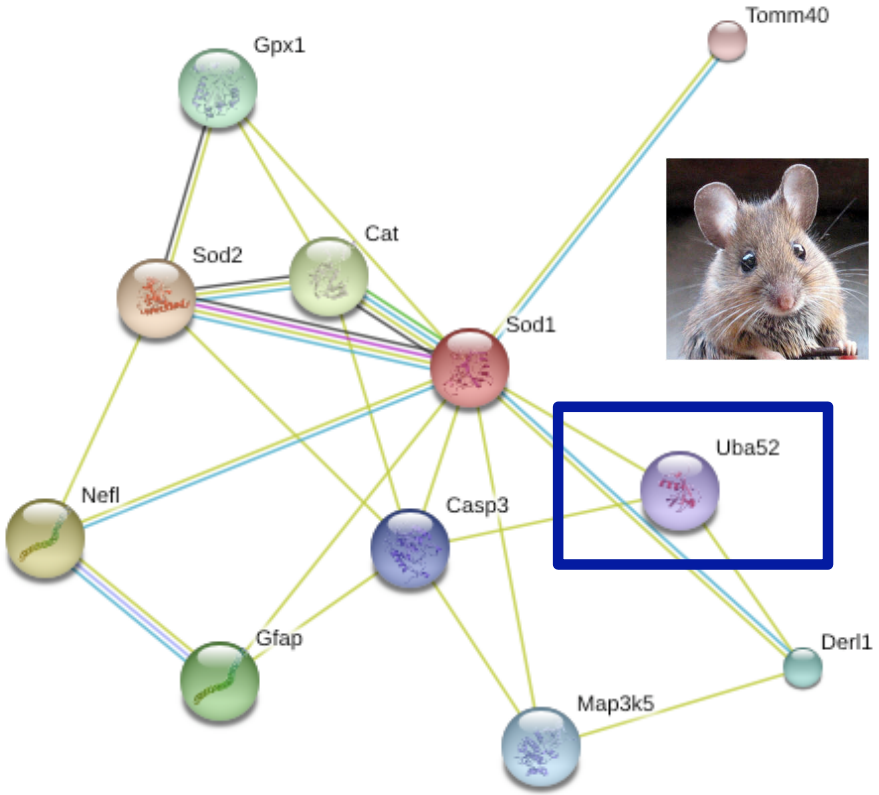
interaction networks in humans and homologs

Ubiquitin-related proteins in SOD1 interaction networks

RNF19A

E3 Ubiquitin-protein ligase

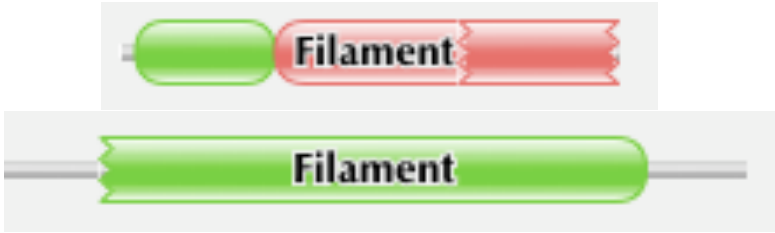
Uba52

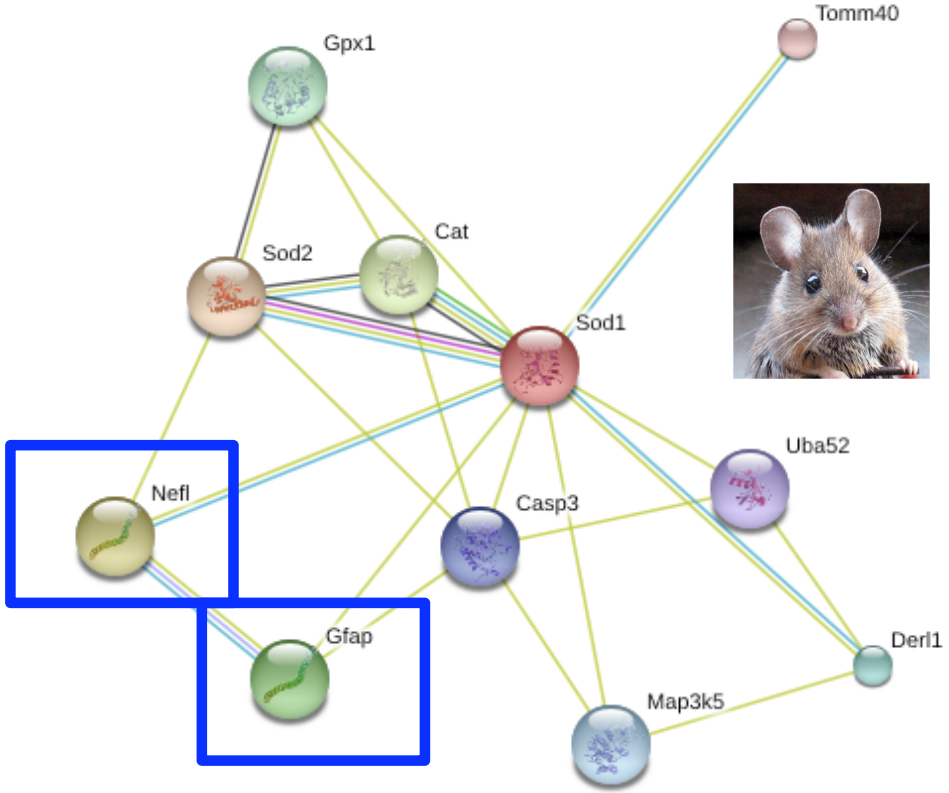


STRING 9.0

SMART

Neurofilaments in SOD1 interaction networks





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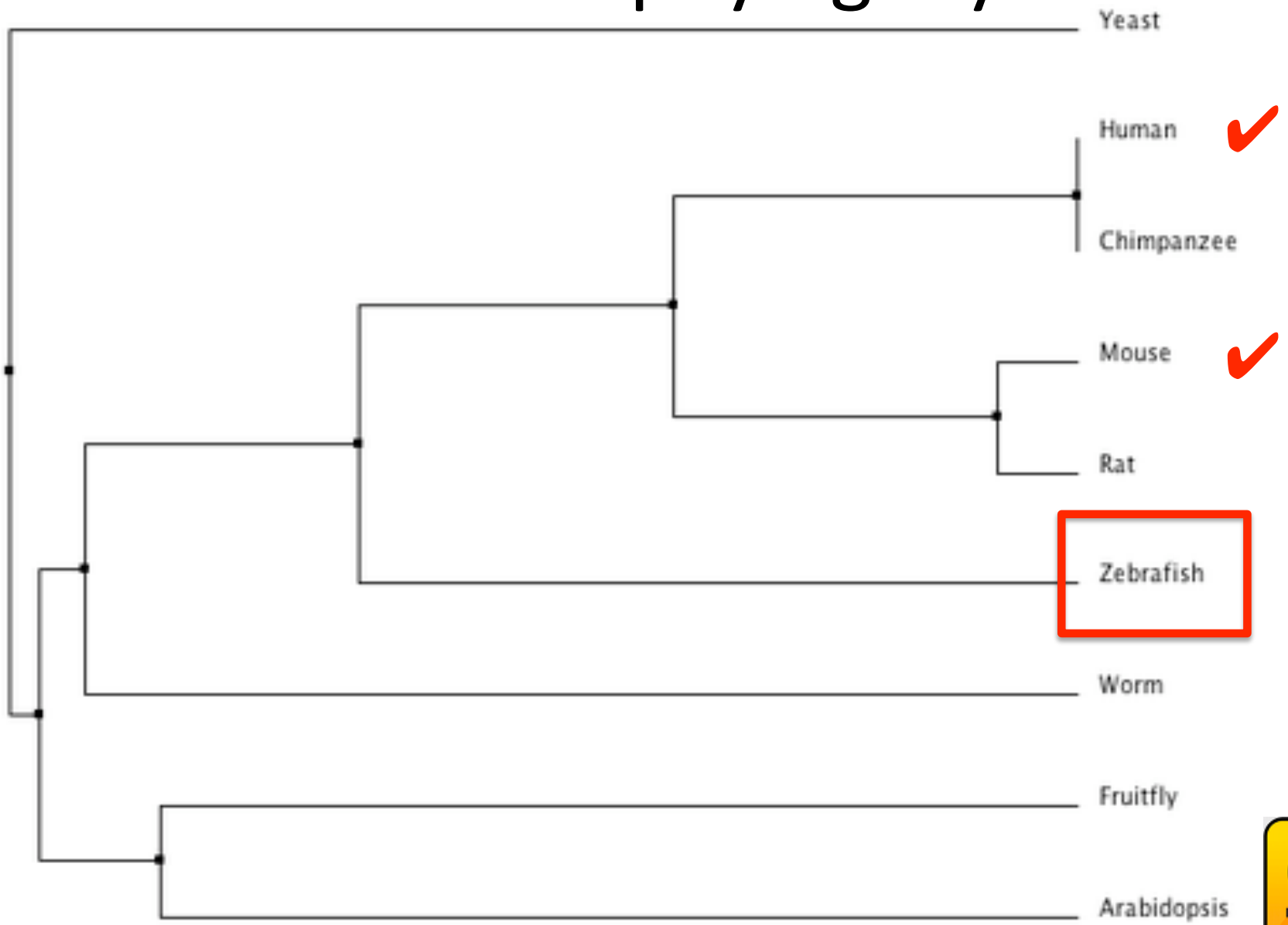
Pfam

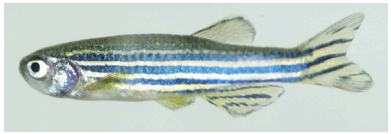
Question:
What else is in ALS aggregates?

Approach:
Proteomics in model organism

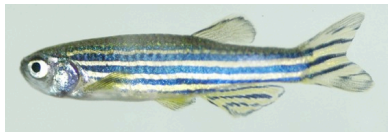
SOD1 phylogeny



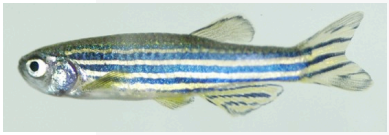
Zebrafish SOD1 interaction network



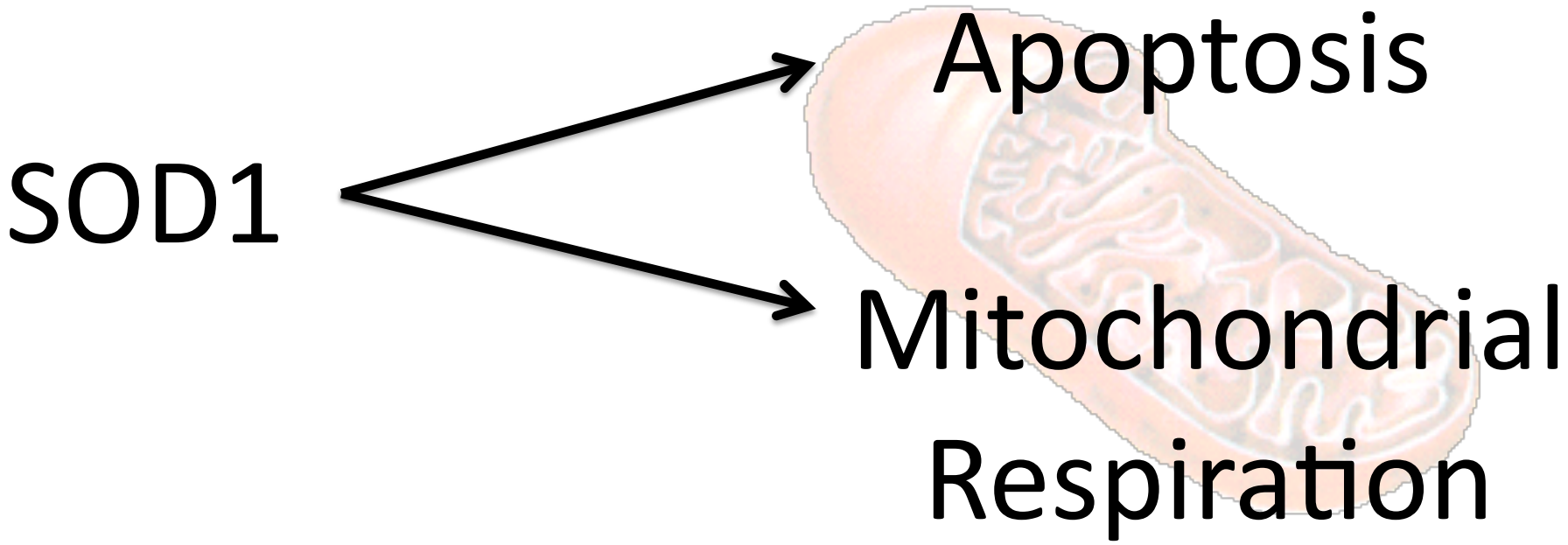
Zebrafish SOD1 and PARK7 interaction network



SOD1 and PARK7 in mitochondria

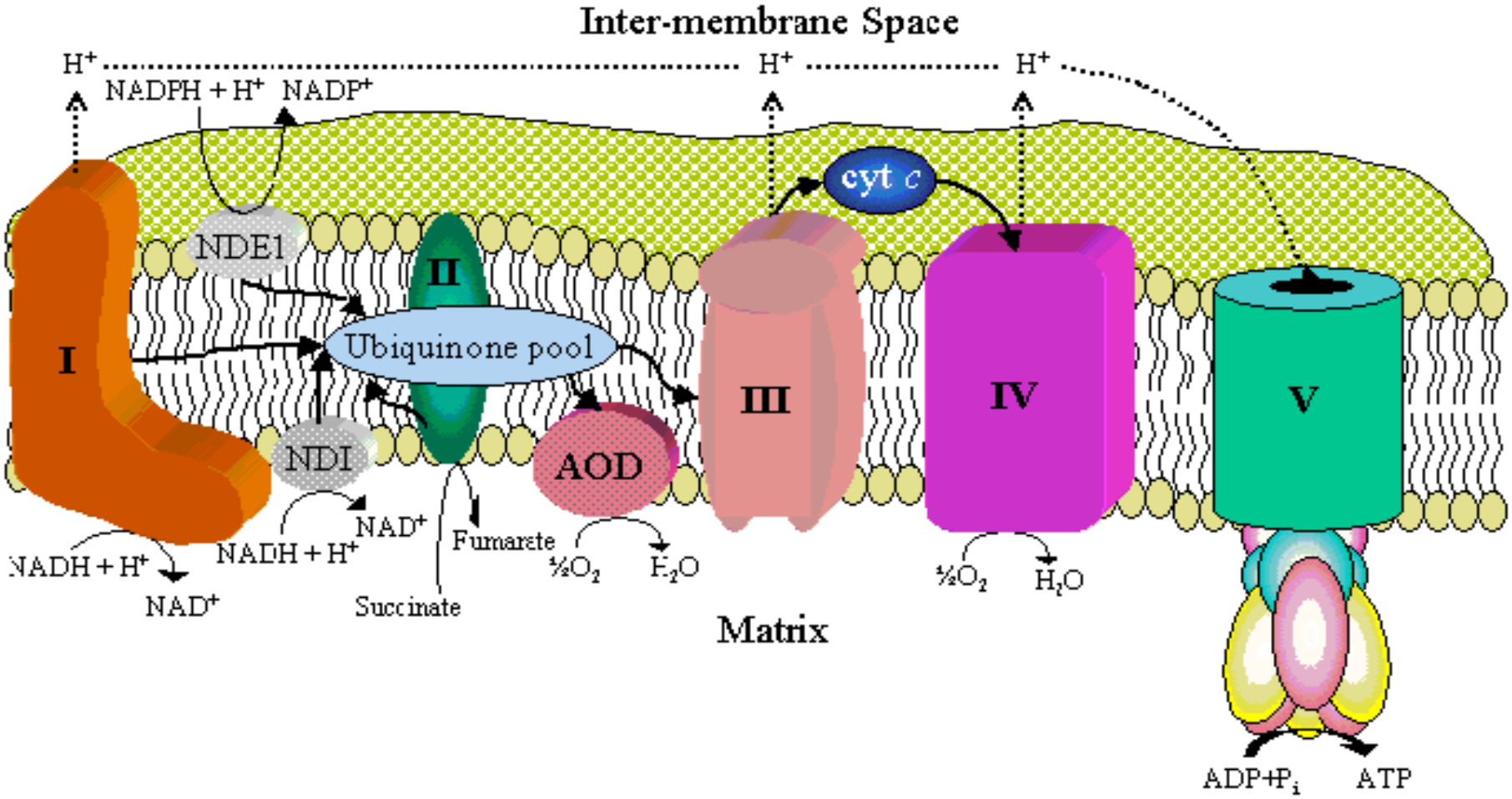


Gene Ontology: Biological Processes



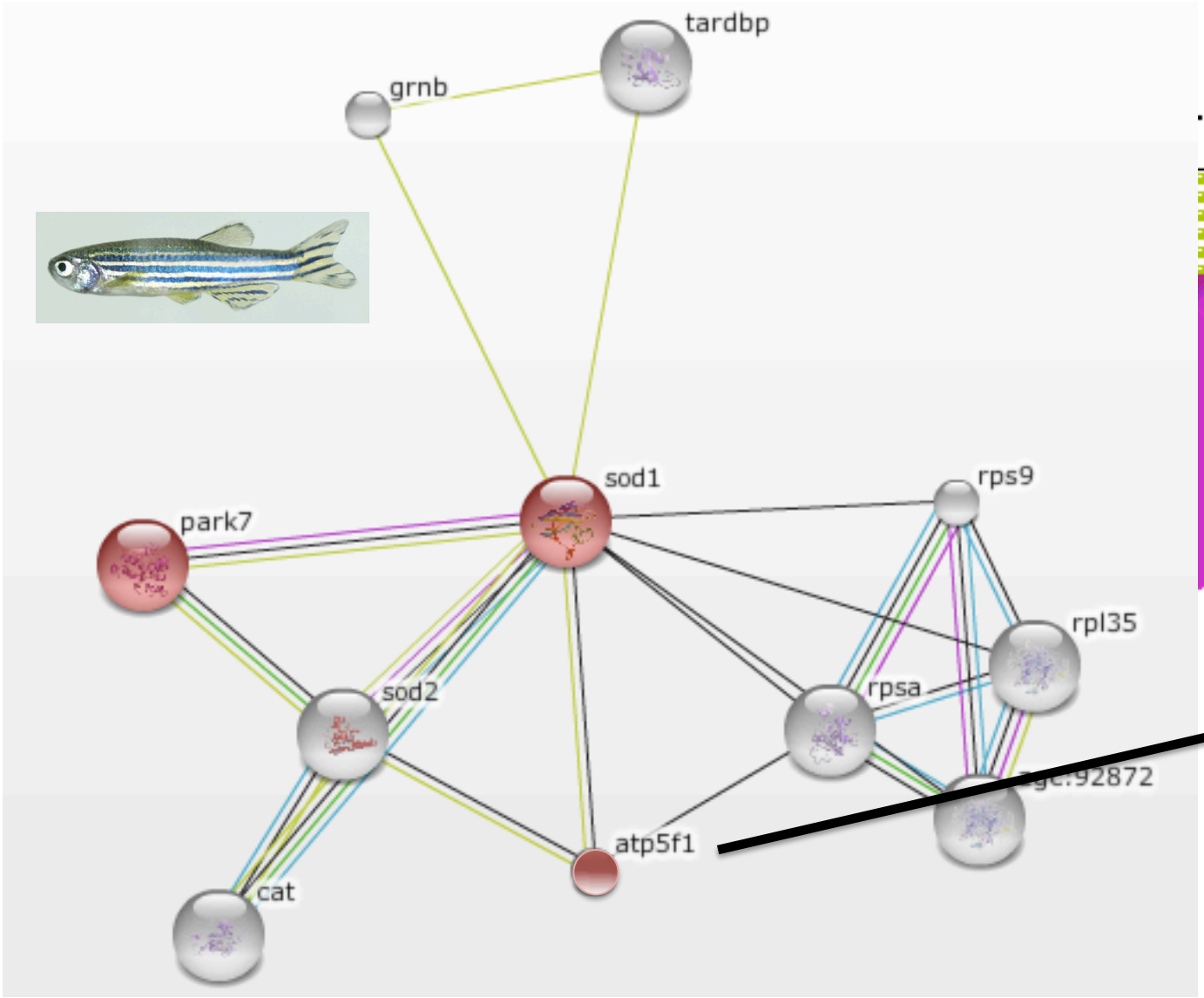
AmiGO

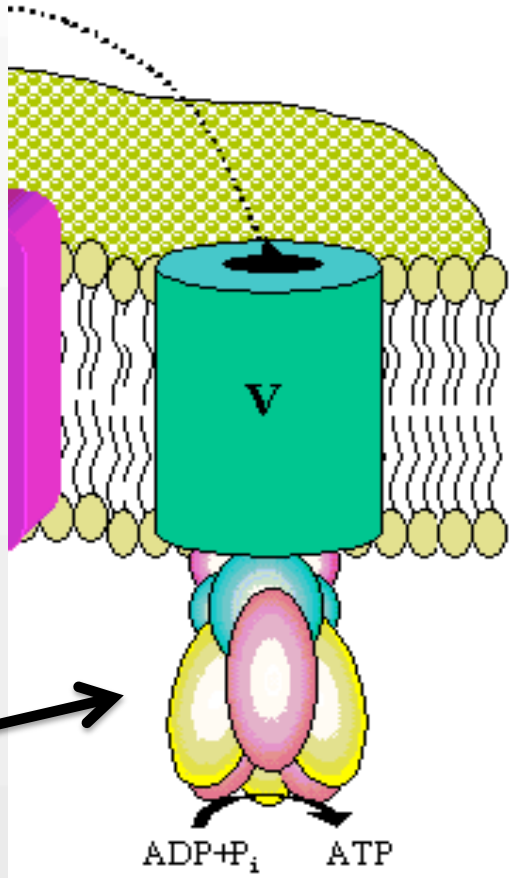
Mitochondrial respiration



http://pages.slu.edu/faculty/kennellj/images/respchain2.gif

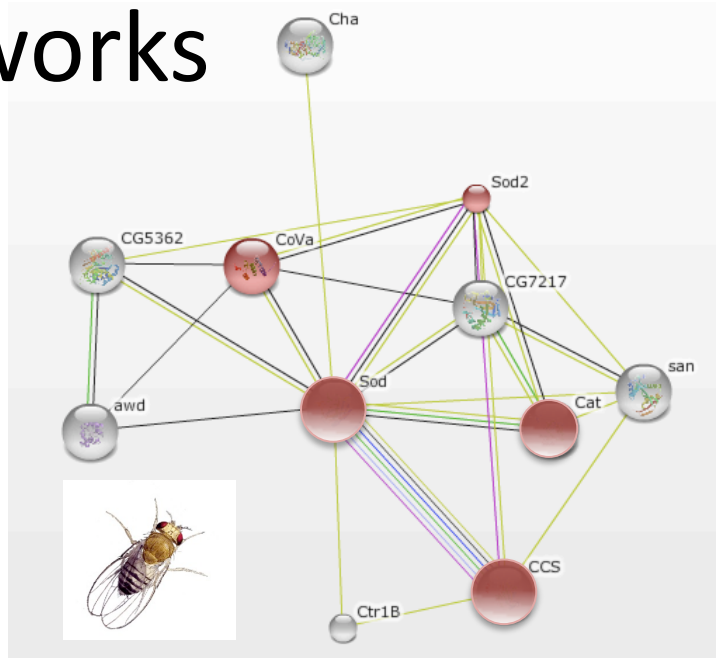
Mitochondrial respiration

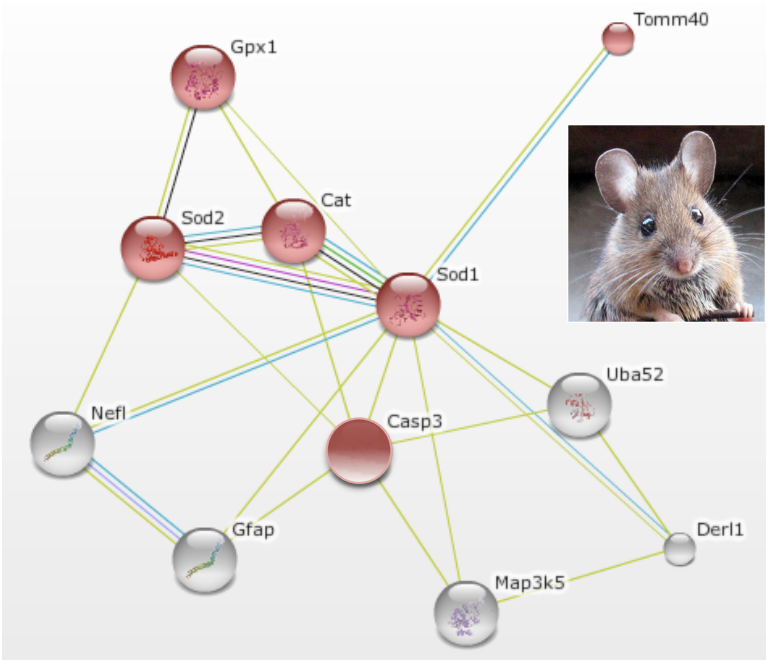


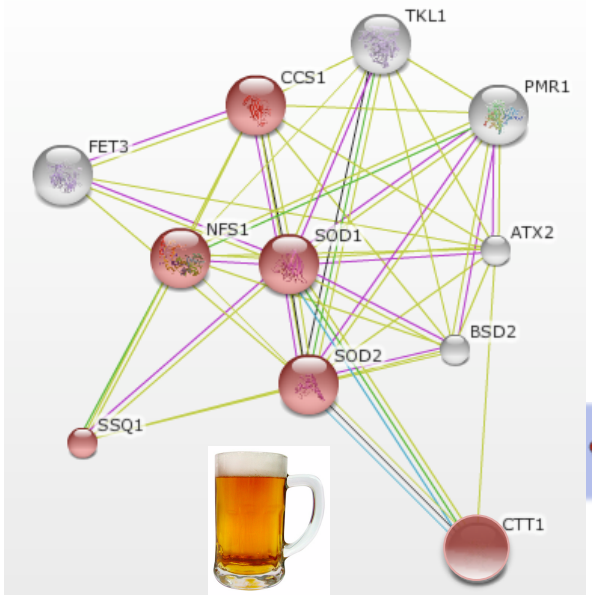


http://pages.slu.edu/faculty/kennellj/images/respchain2.gif

High incidence of mitochondrial proteins in interaction networks







STRING 9.0

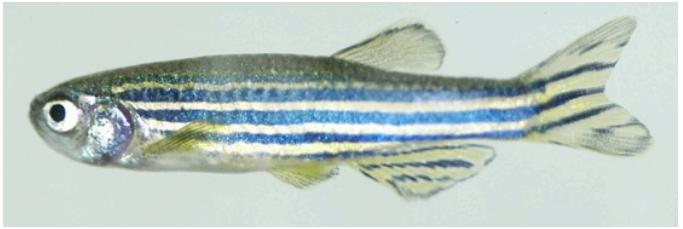
AmiGO

Question:
What else is in ALS aggregates?

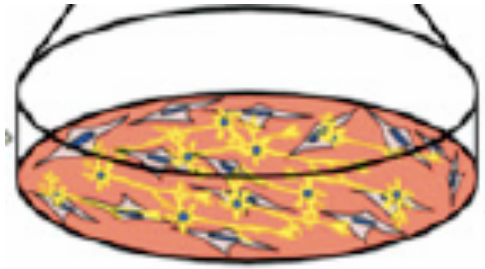
Hypothesis:
ALS aggregates will include SOD1, Ubiquitin, Neurofilaments, mitochondrial proteins.

Approach:
Proteomic analysis of aggregates in SOD1 mutant zebrafish

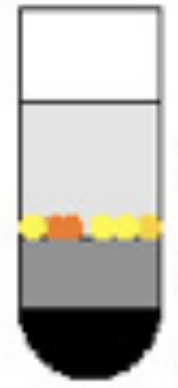
Experimental Design



G93R-SOD1
overexpression mutant



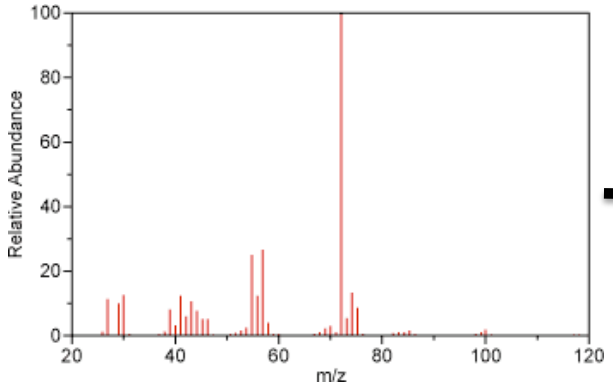
Culture motor neurons

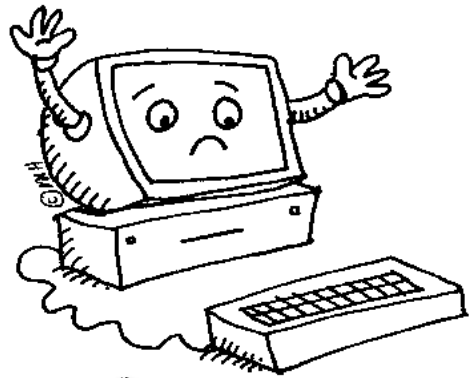


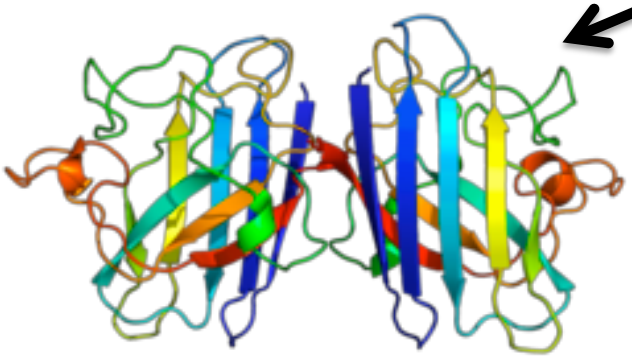
Subcellular fractionation

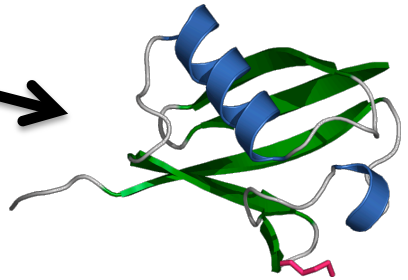
MudPIT on aggregates to identify components

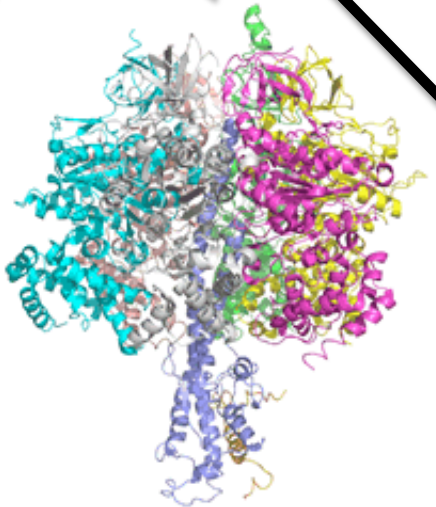
Hypothetical results

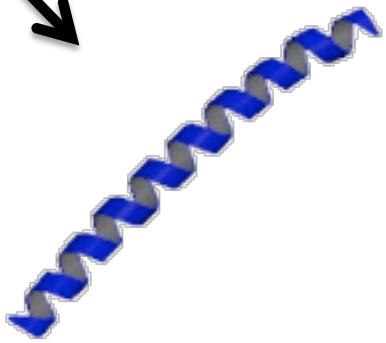




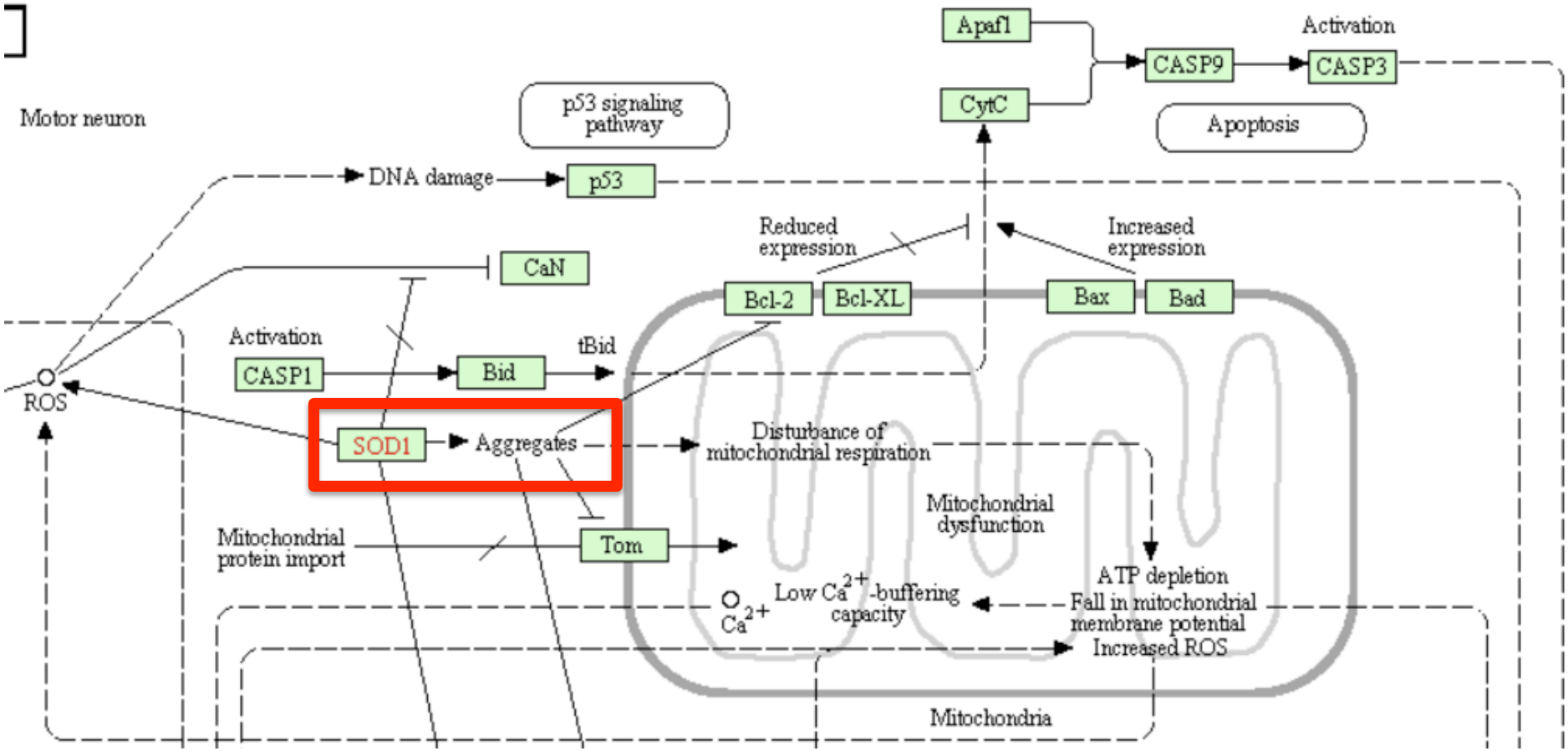








SOD1 aggregates lead to mitochondrial defects



Hypothesis:
Mutations in genes encoding mitochondrial proteins in aggregates cause ALS.

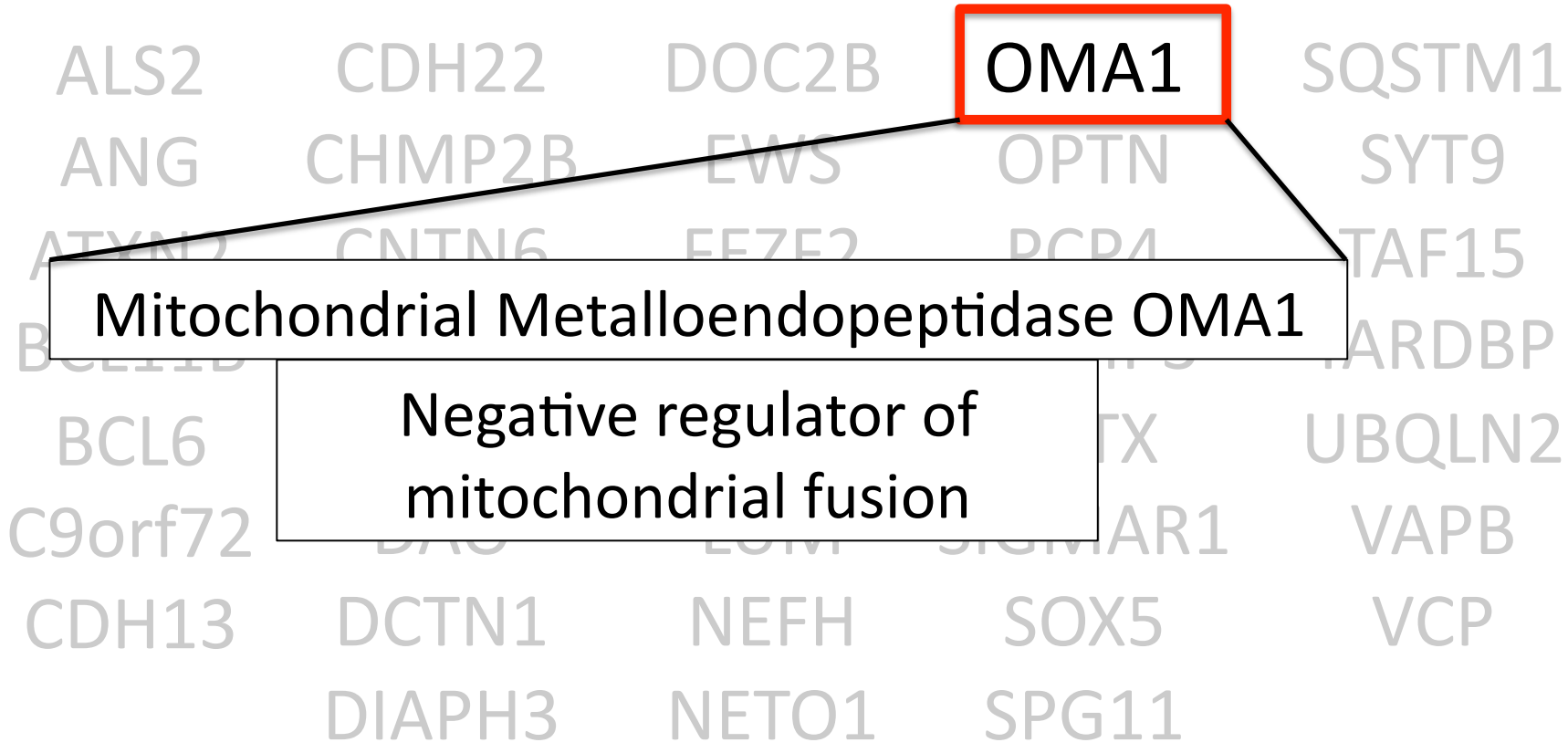
Genes known to cause ALS

ALS2	CDH22	DOC2B	OMA1	SQSTM1
ANG	CHMP2B	EWS	OPTN	SYT9
ATXN2	CNTN6	FEZF2	PCP4	TAF15
BCL11B	CRIM1	FIG4	RAMP3	TARDBP
BCL6	CRYM	GRB14	SETX	UBQLN2
C9orf72	DAO	LUM	SIGMAR1	VAPB
CDH13	DCTN1	NEFH	SOX5	VCP
	DIAPH3	NETO1	SPG11	

http://alsod.iop.kcl.ac.uk/misc/dataDownload.aspx#C1

AmiGO

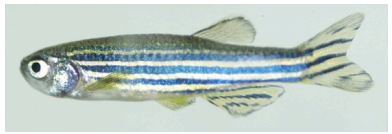
Genes known to cause ALS



http://alsod.iop.kcl.ac.uk/misc/dataDownload.aspx#C1

Pfam AmiGO

Zebrafish SOD1 and PARK7 interaction network



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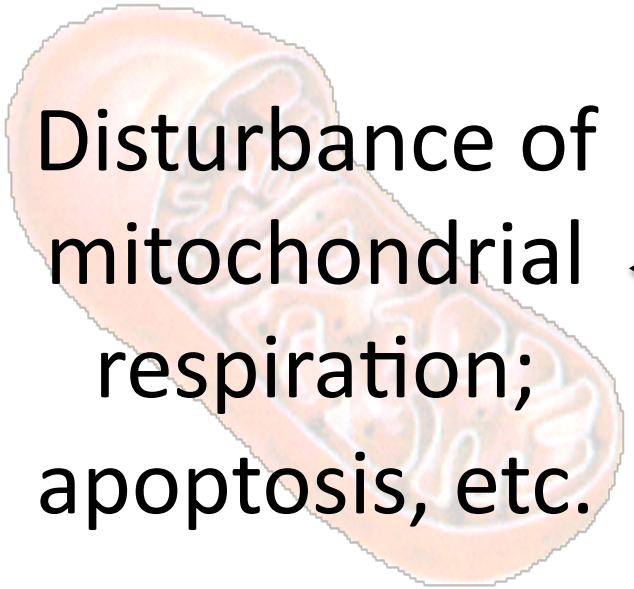
Proposed model

mSOD1 →

↓

Abnormal mitochondrial dynamics

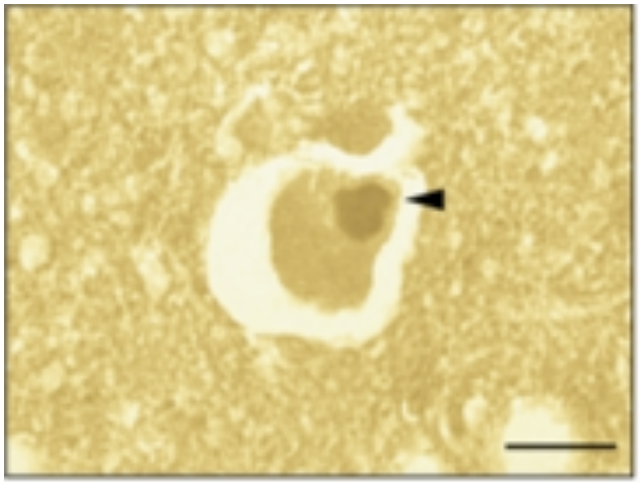
←



Disturbance of mitochondrial respiration; apoptosis, etc.

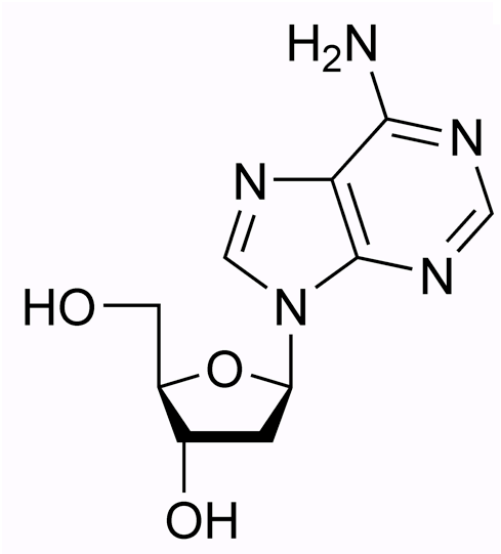
Future experiments

Further characterization of OMA1



(Tateno et al. 2009)

Chemical genetics: mitochondrial proteins in fusion and fission




Questions?