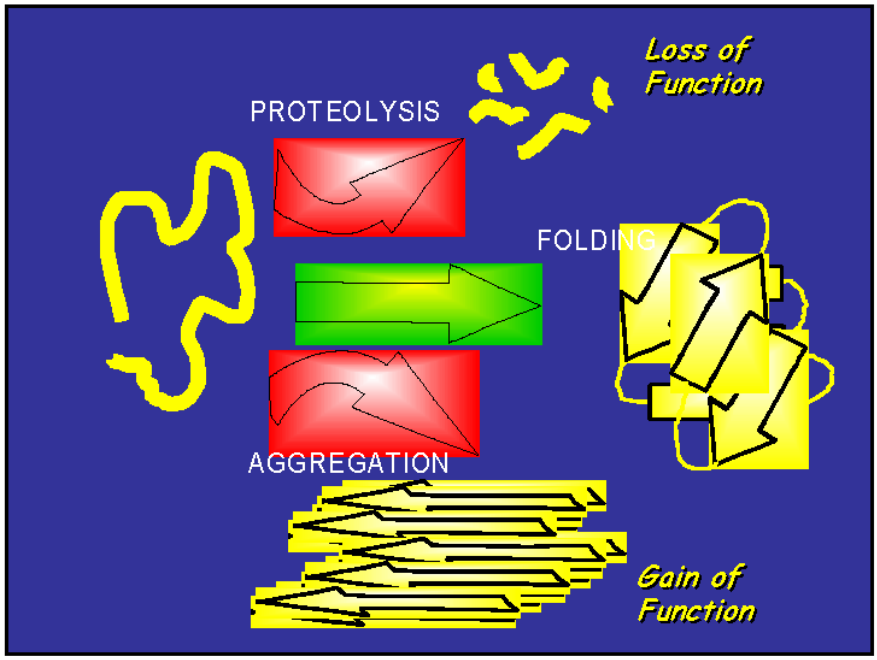
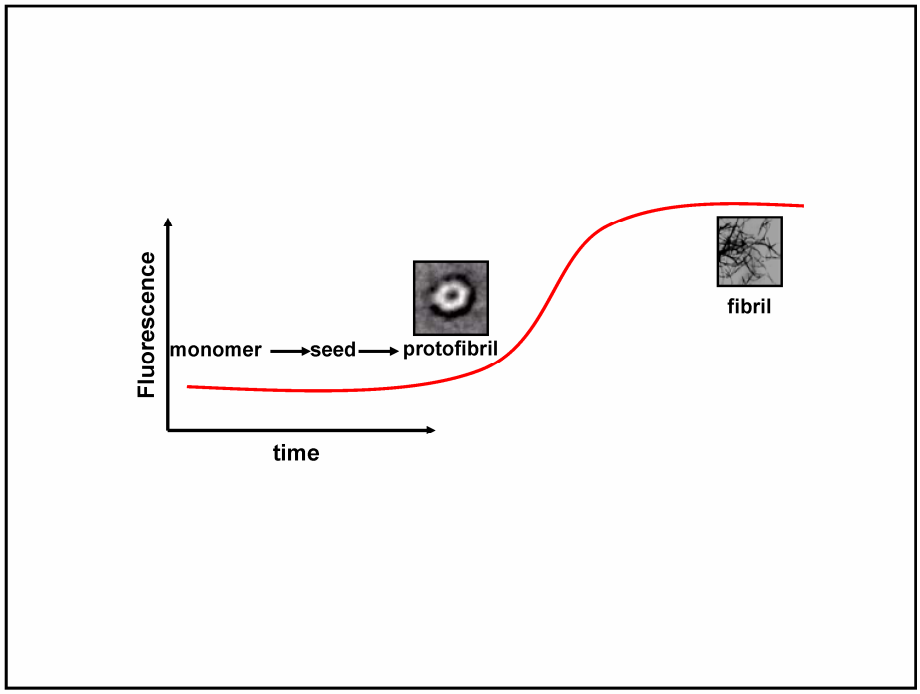
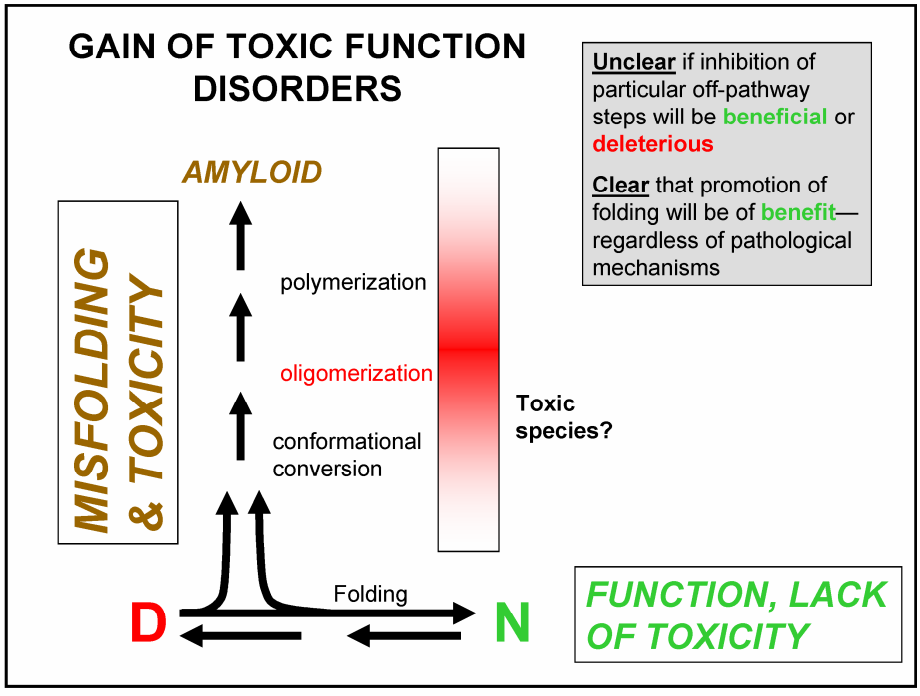
Presentation 7b – Philip Thomas

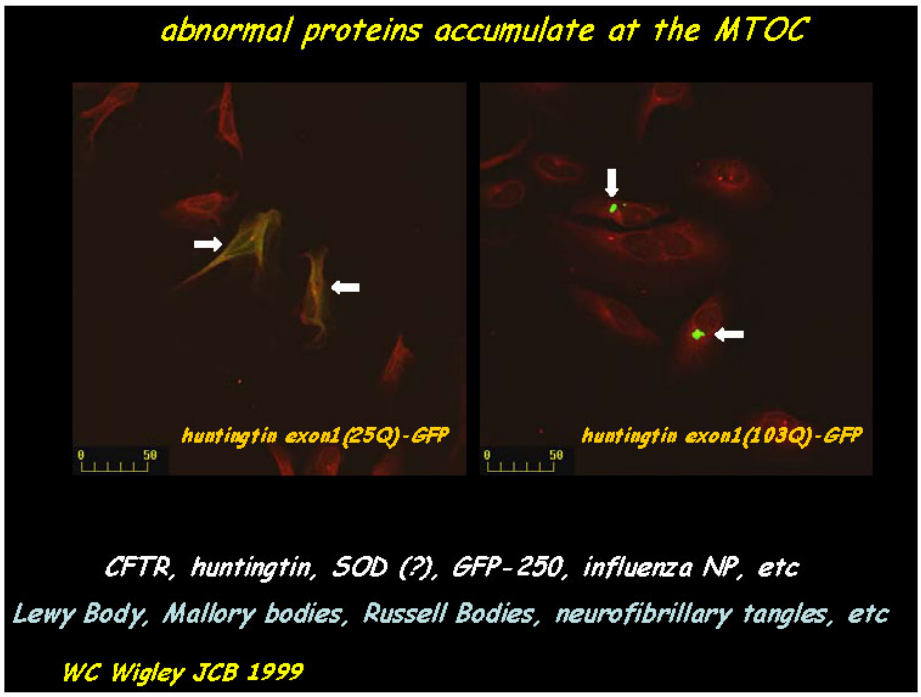


Some Disease States Associated with Protein Misfolding

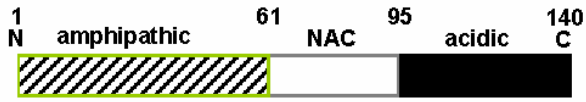
Disease	Protein
Cystic Fibrosis	CFTR
hypercholesterolemia	LDL receptor
maple syrup urine	a-keto acid DH
Scurvy	collagen
Marfan syndrome	fibrillin
cancer	p53
retinitis pigmentosa	opsin
glioblastoma	EGF receptor
ALS	Superoxide dismutase
PD, etc	transthyretin, aβ, PrP, αsyn, etc


Fluorescence
monomer
seed
protofibril
fibril
time


GAIN OF TOXIC FUNCTION DISORDERS
Unclear if inhibition of particular off-pathway steps will be beneficial or deleterious
Clear that promotion of folding will be of benefit—regardless of pathological mechanisms
AMYLOID
MISFOLDING & TOXICITY
polymerization
oligomerization
conformational conversion
Toxic species?
Folding
D
N
FUNCTION, LACK OF TOXICITY



α-synuclein

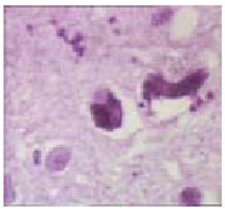


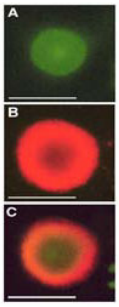
1) Abundantly expressed in brain.
2) Unclear physiological function.
3) Natively unfolded in solution vs. α-helical conformation when binding on vesicle surface.
4) Aggregation associates with several neurodegenerative diseases (PD, DLB). Three missense mutations in αsyn (A30P, E46K, A53T) are involved in rare, earlier-onset familial PD.
5) Degraded by the Proteasome

A conundrum:

If the proteasome is capable of recognizing and degrading α-synuclein, why does it accumulate in several pathological conditions?

Lewy bodies

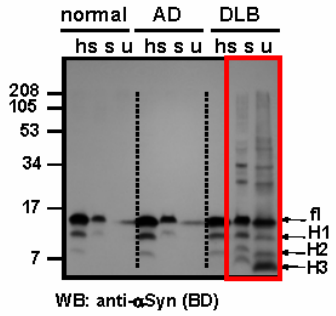




anti-ubiquitin

anti-α-syn

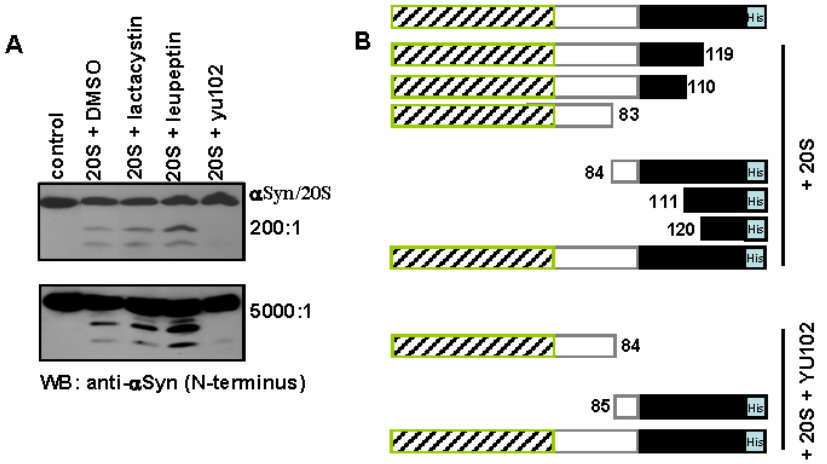
αsyn fragments only aggregate in patients



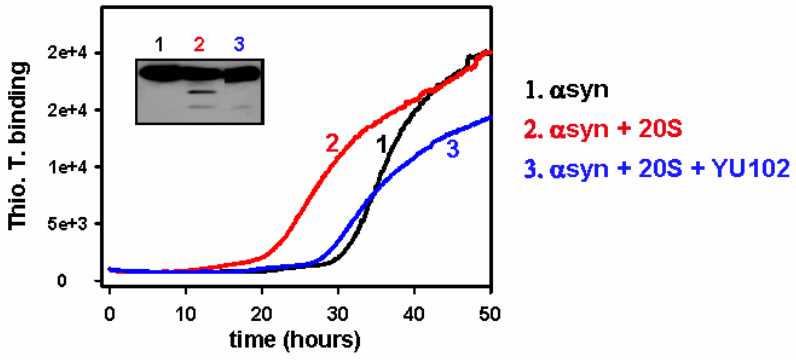
hs: high salt soluble extraction
S: 4% SDS soluble extraction
U: 8M urea soluble extraction

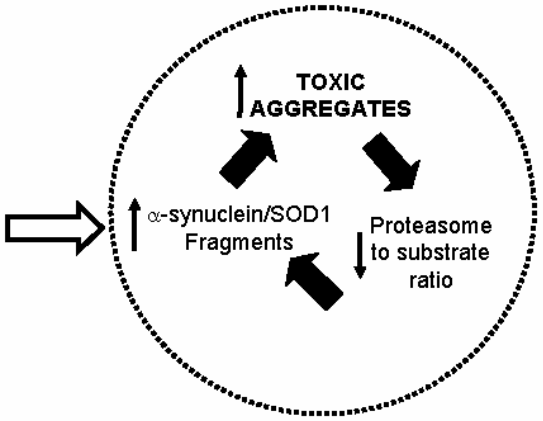
Do aggregation-prone truncated αsyns play a role in inclusion body formation?

the "caspase-like" activity performs endoproteolytic cleavage for the αsyn fragments production



fragments from proteasomal degradation accelerate full-length αsyn aggregation





A VICIOUS CYCLE OF CYTOTOXICITY

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