

Presentation 7a – George DeMartino

**Organophosphates and the structure and function
of the ubiquitin-proteasome system**

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Quality control removes damaged cellular proteins

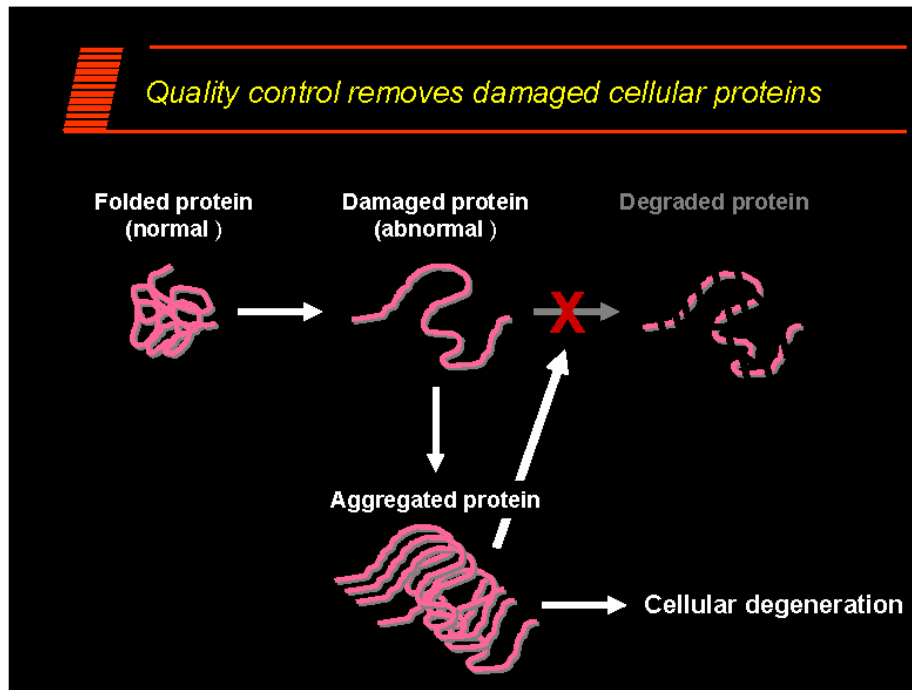
**Folded protein
(normal)**

**Damaged protein
(abnormal)**

Degraded protein



Mutations
Errors in synthesis
Metabolic damage
Environmental toxins



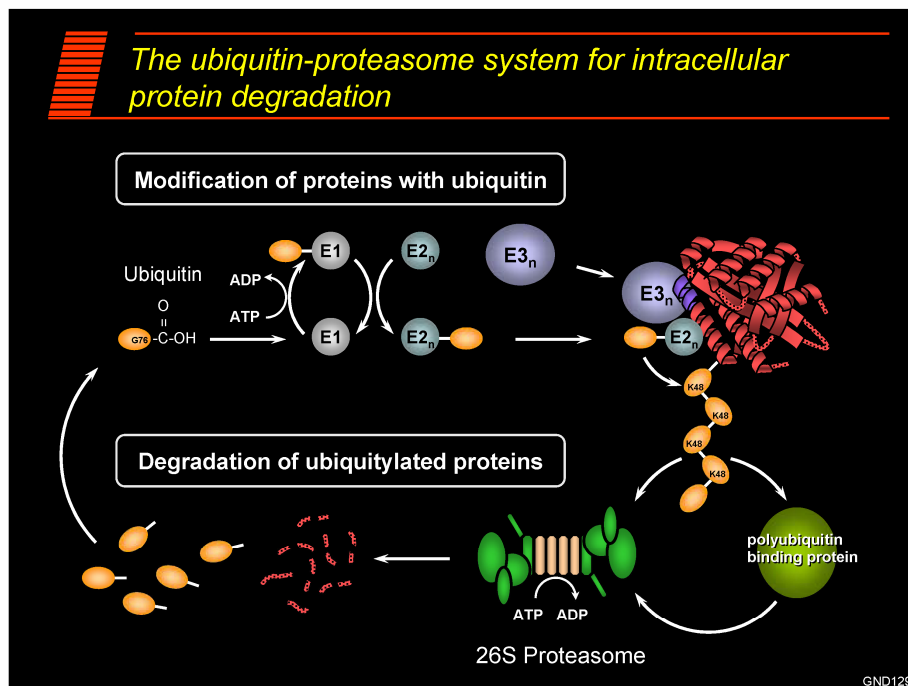
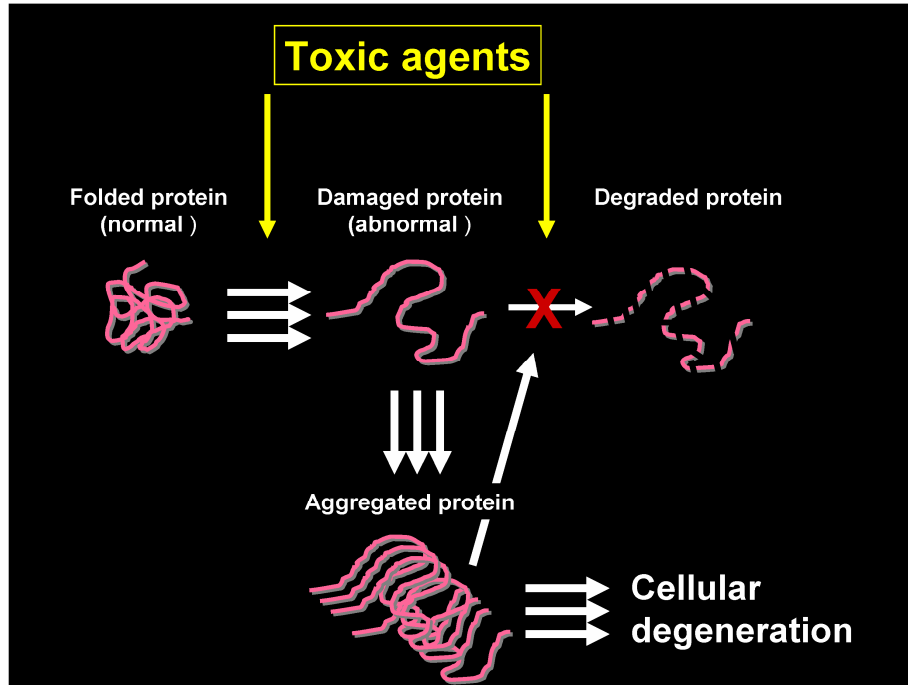
Many neurological diseases may be caused by aggregation rather than degradation of proteins with abnormal structures.

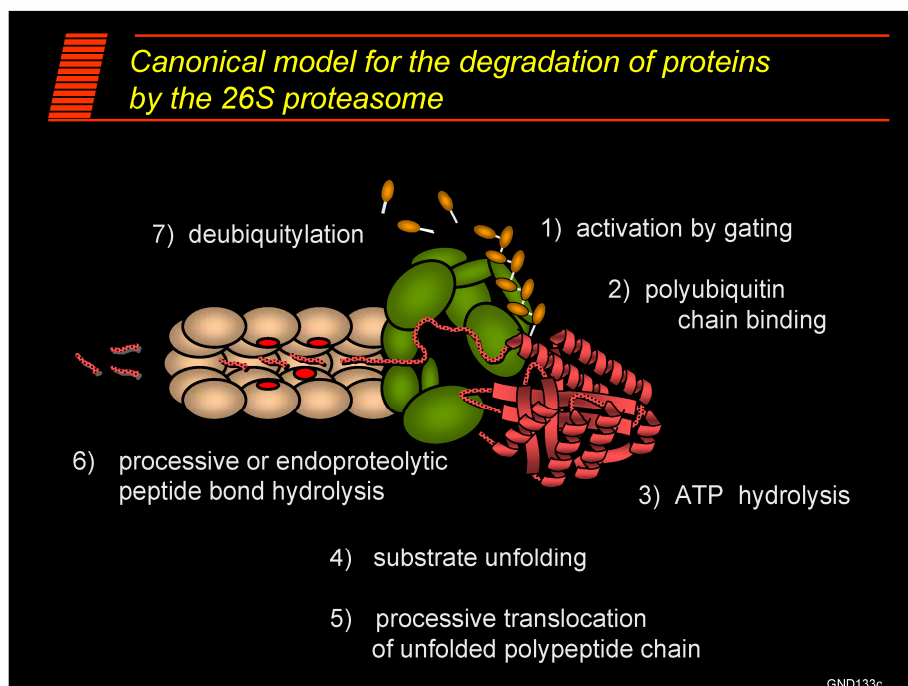
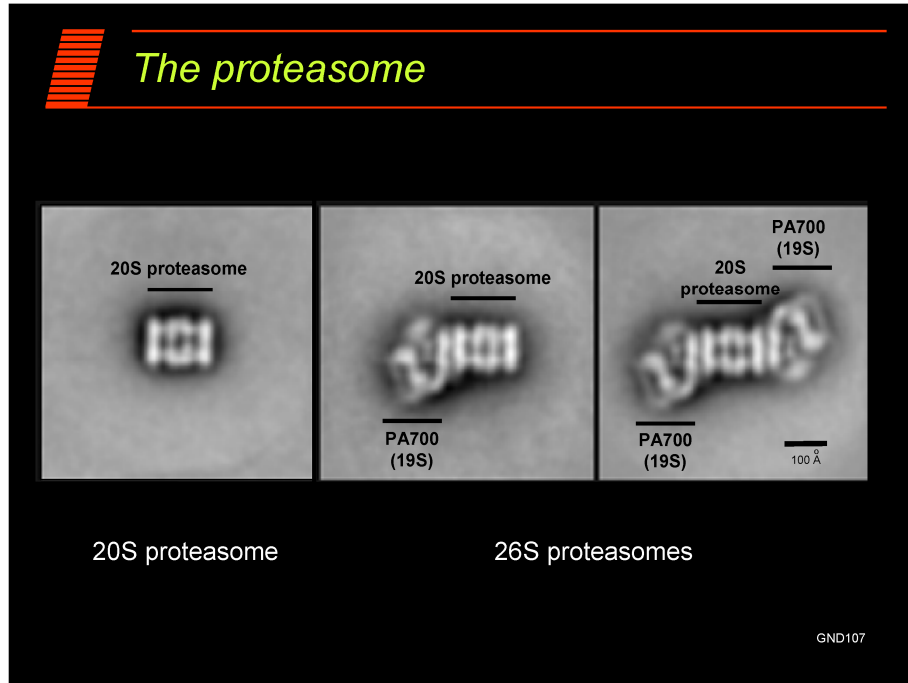
Lewy Bodies (PD)

Tau aggregates (AD)

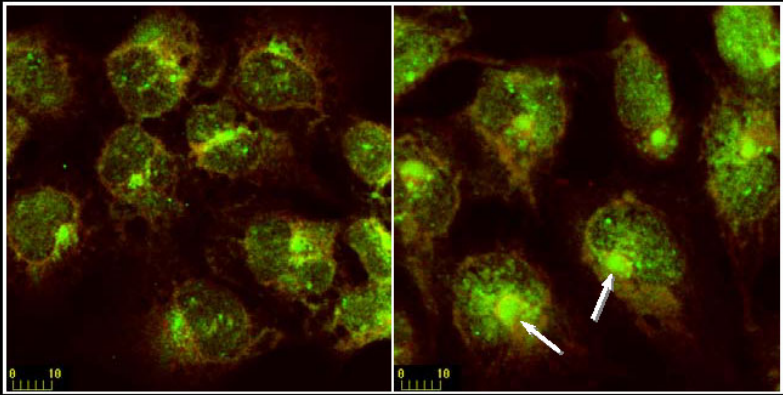
- Parkinson's disease (α -synuclein)
- ALS "Lou Gerhig's" disease (SOD)
- Alzheimer's disease (β -amyloid, tau)
- Huntington's disease (Huntingtin)
- Spinal-Bulbar Muscular atrophy (androgen receptor)
- Prion diseases "Mad Cow disease" (prion)
- *et al*

PD28





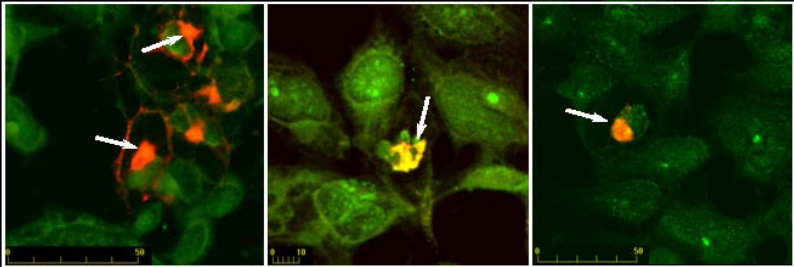
Protein aggregates form in response to inhibition of proteasome activity



- Lactacystin + Lactacystin


GND 209

Protein aggregates form in response to expression of mutant CFTR



PA700 PA28 Ubiquitin

GND 207



*Functional relationships between proteasome function
and neurological diseases*

- Proteasome function is inhibited in many neurological diseases.
- Inhibition of proteasome function in animals produces features of neurological diseases.