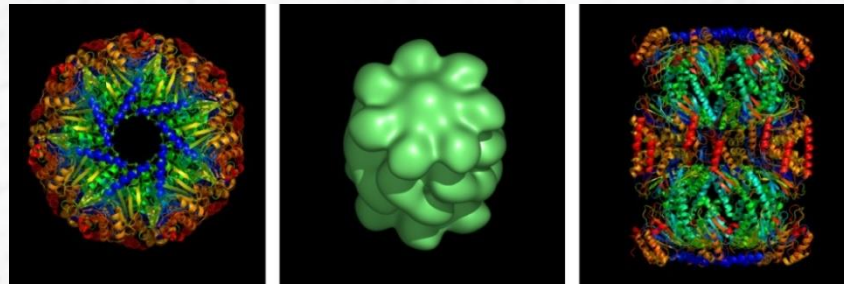


Proteasome 26S and Ubiquitin Proteasome system (UPS)



Protein biosynthesis and degradation are fundamental processes warrenting homeostasis

Protein synthesis

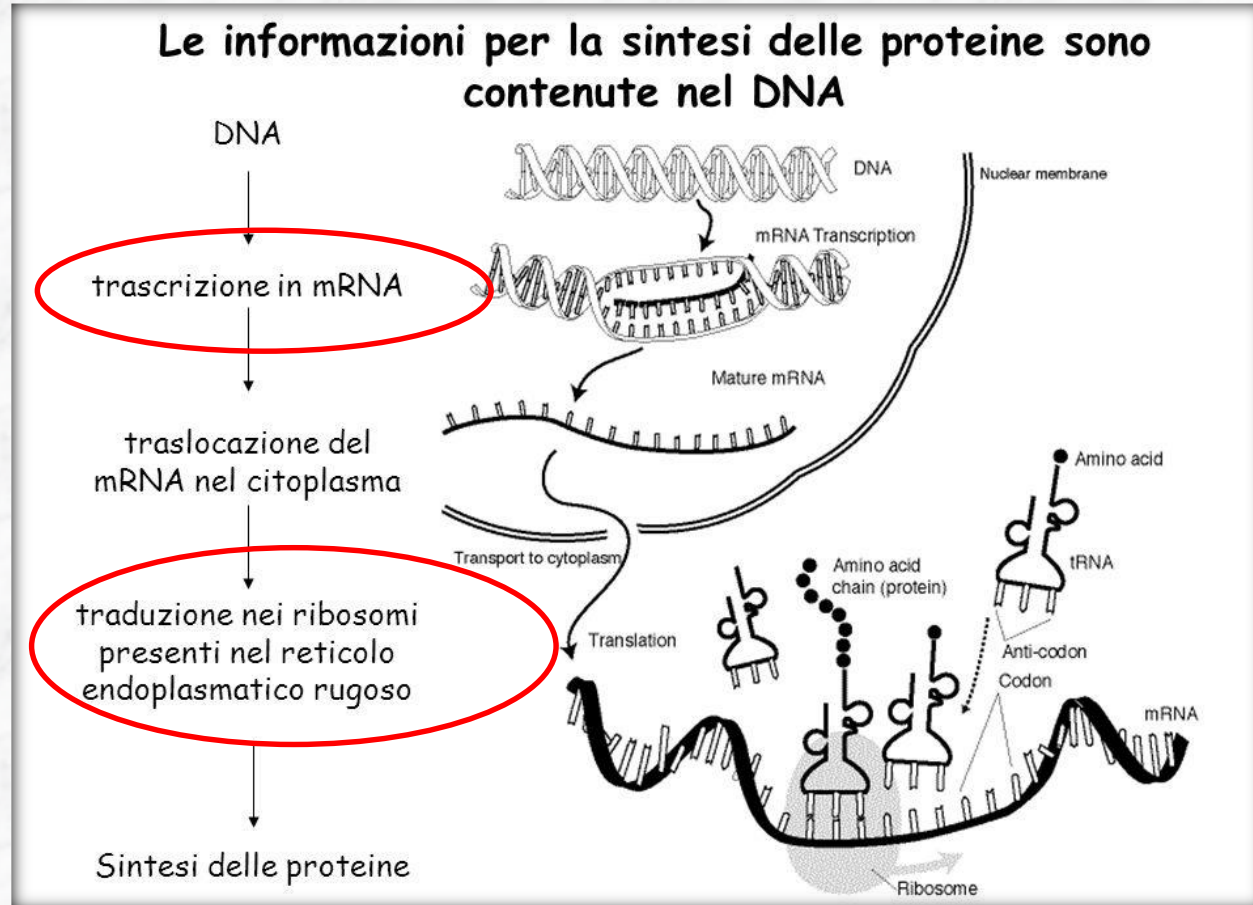
DNA

RNA

Protein structure

• Transcription

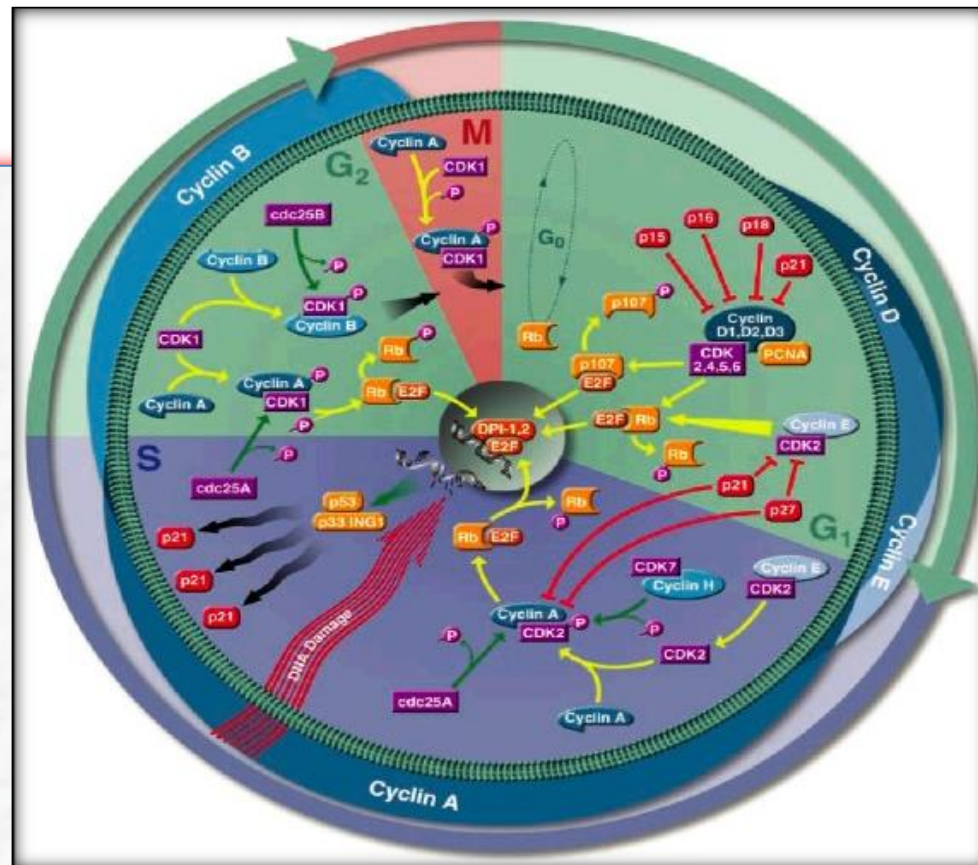
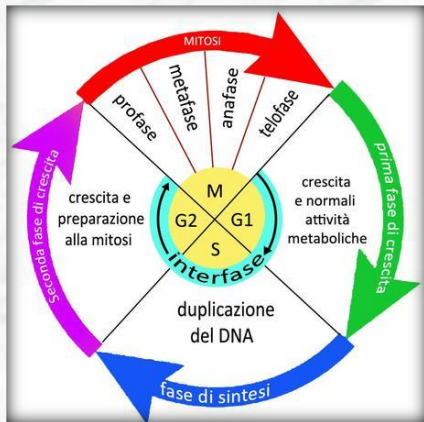
• Translation



Protein Turn-over

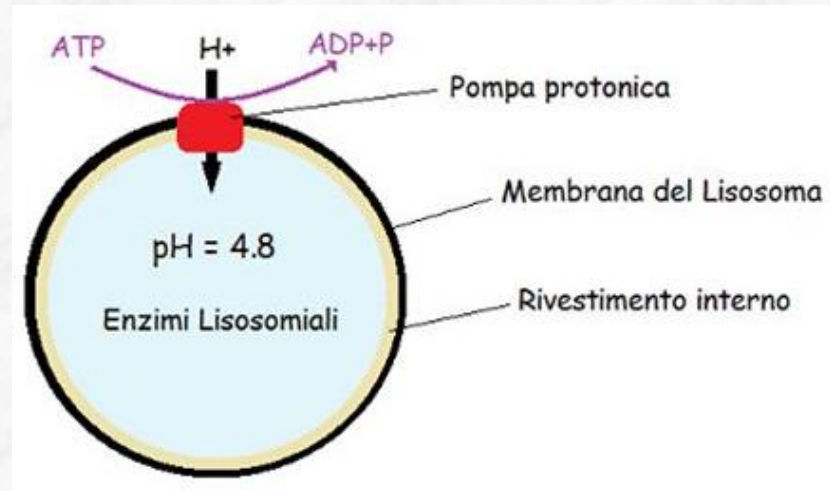
proteins are degraded and resynthesized.
Degradation

– cellular cycle of eucariots is controlled by regulatory enzymes that are degraded in specific moments depending upon extracellular stimuli.



1- Lysosomes = are demolitors of garbage and extracellular substances.

Damaged proteins enter lysosomes via endocytosis where enzymes break peptidic bonds.



Mechanisms:

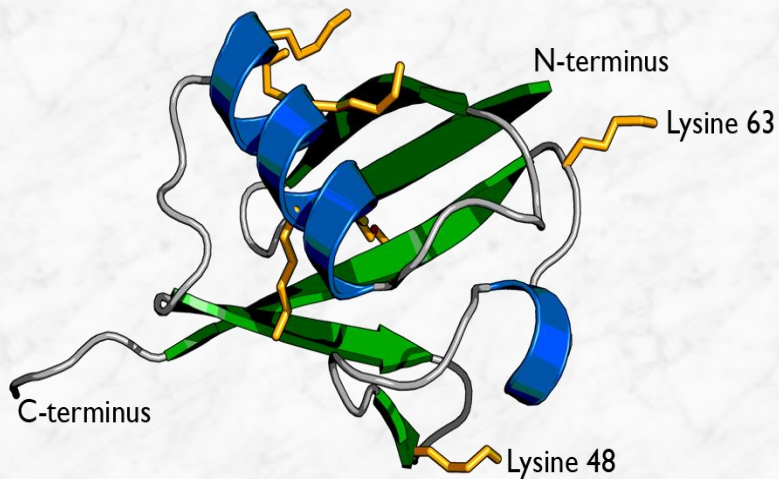
- Degradation by hydrolytic enzymes (acid hydrolases)
- They work at low pH (4,8 vs 7)

2- Ubiquitin-Proteasome = Proteins are marked for degradation by chain of poly-ubiquitins (Ubq)

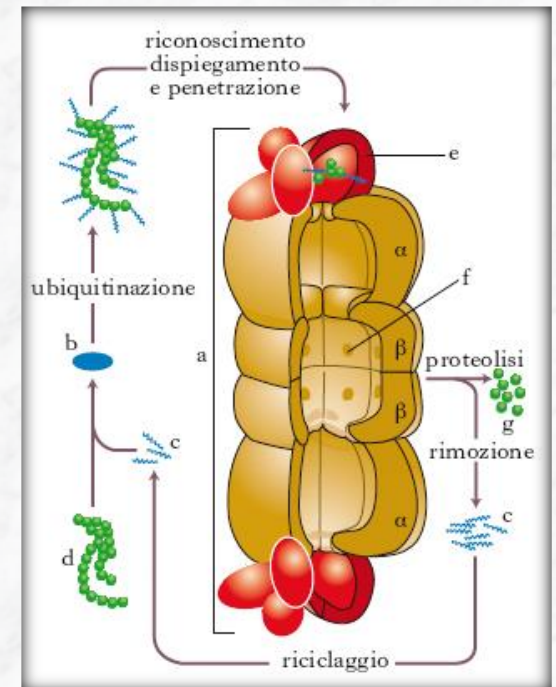
Proteasome 26S disrupts protein in peptides, then degraded in aa

Ubiquitin-Proteasome System (UPS)

UBIQUITIN



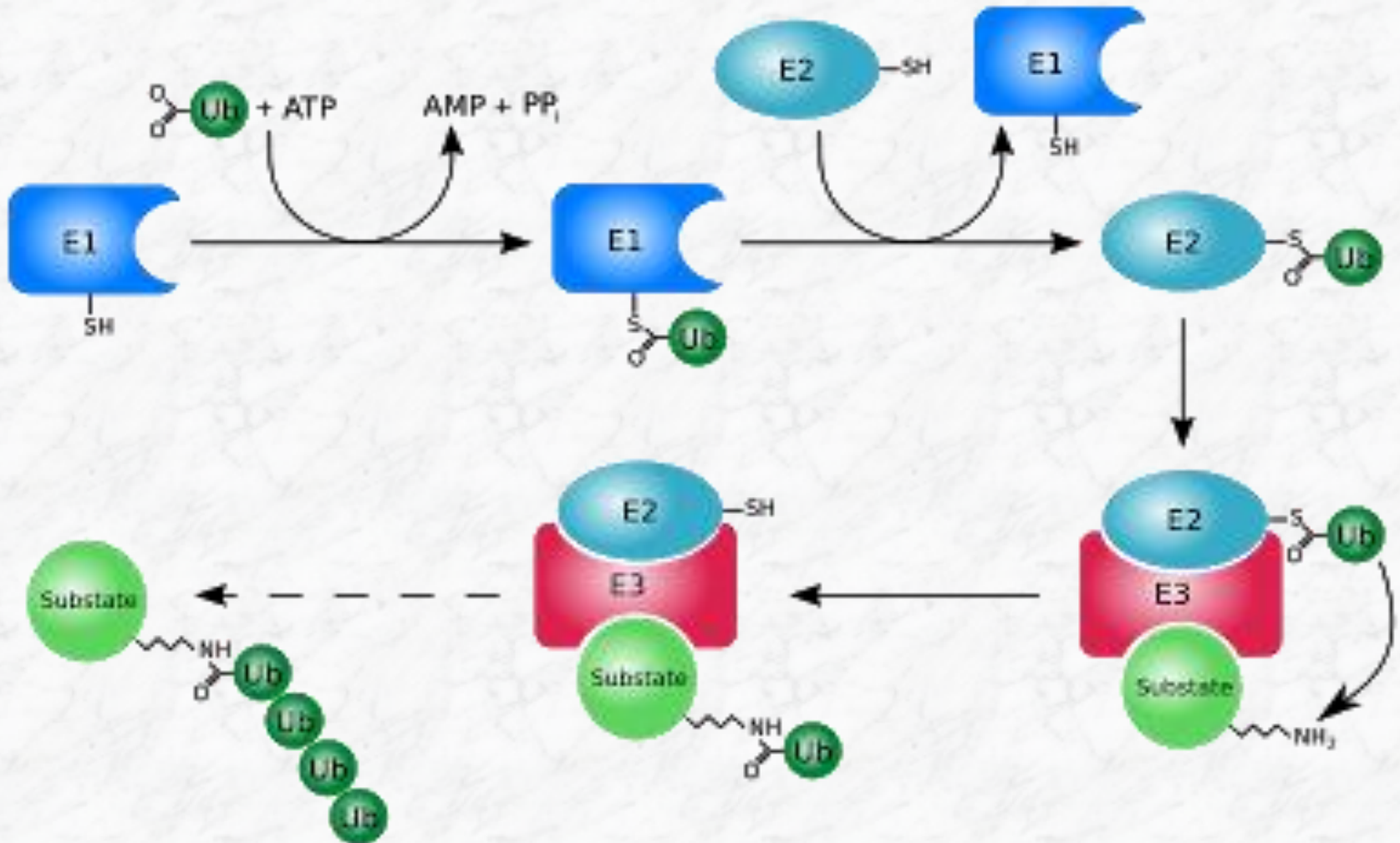
PROTEASOME 26S

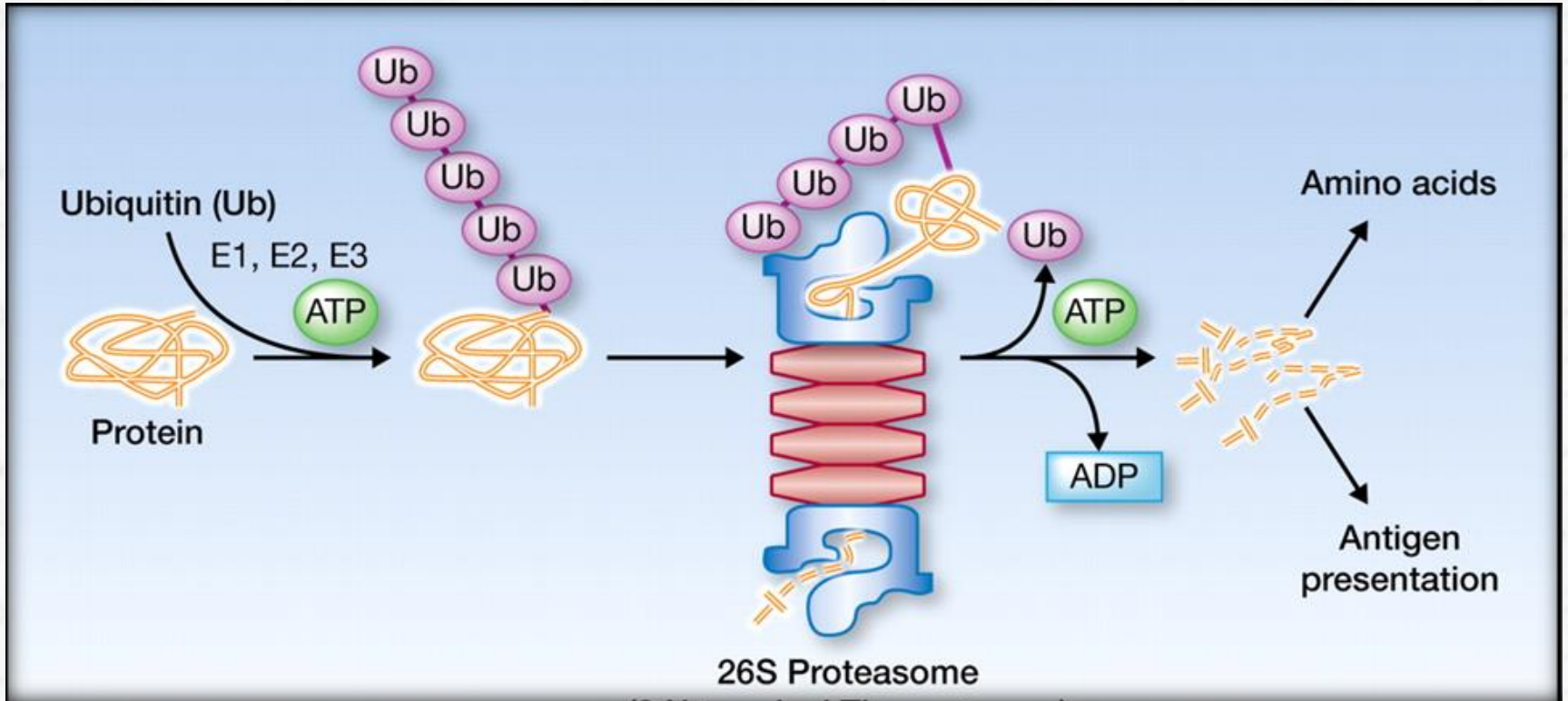


Bond between COOH terminal of Ubq and the NH₂ terminal of a lysine of the protein to be destroyed, ATP dependent reaction

3 enzymes are involved

**E1 = ubiquitin activating enzyme ; E2 = ubiquitin conjugating enzyme
E3 = ubiquitin ligase enzyme**





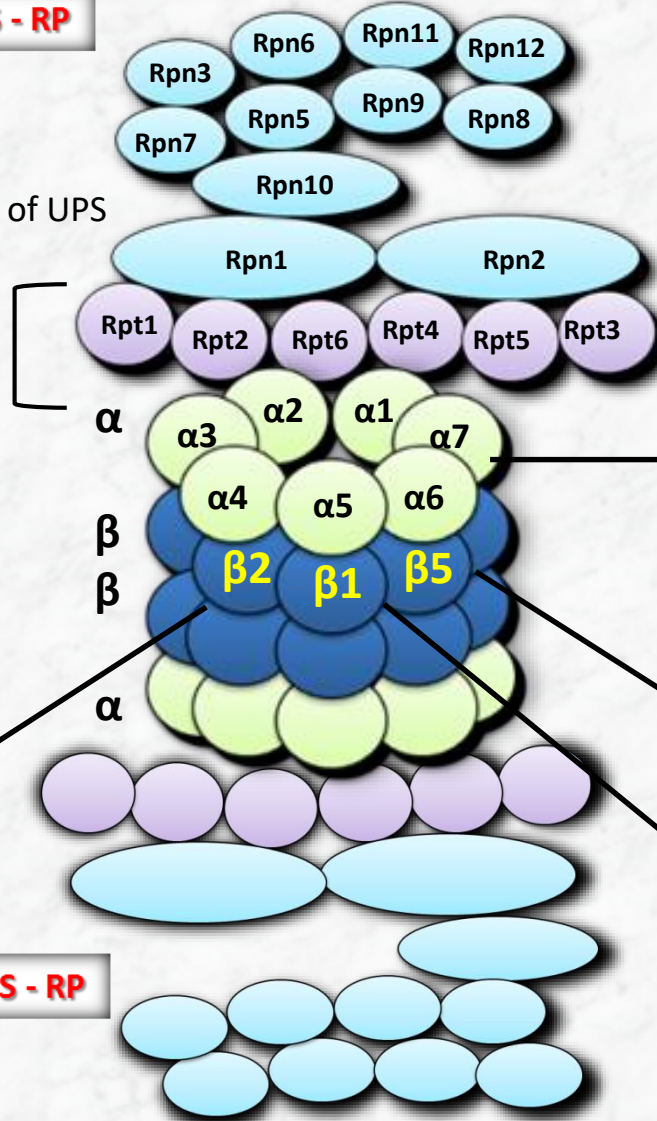
Regulatory Particle: 19 S - RP

Rpt-family subunits

Translocation of protein into the core of UPS

Rpn-family subunits

Tagging the ubiq-protein and then cut the tail.



Core Particle: 20 S - CP
($\alpha_7, \beta_7, \beta_7, \alpha_7$)

7 α subunit types

Pore for the passage of protein into the proteolytic room

β_5 = chymotrypsin-like activity

β_1 = caspase-like activity

β_2 = trypsin-like activity

Regulatory Particle: 19 S - RP

- Cellular Cycle regulation
- Cellular development
- Stress response
- Neuronal web
- Modulation of membrane receptors
- DNA repair, transcriptional regulation
- Long term memory
- Circadian rythms
- neuroimmuno and inflammatory stimuli
- Organelles biogenesys

Rapid protein degradation

**Protein to be eliminated is tagged by means of a covalent bond with Ubq
And addressed towards proteolysis by the 26S.**

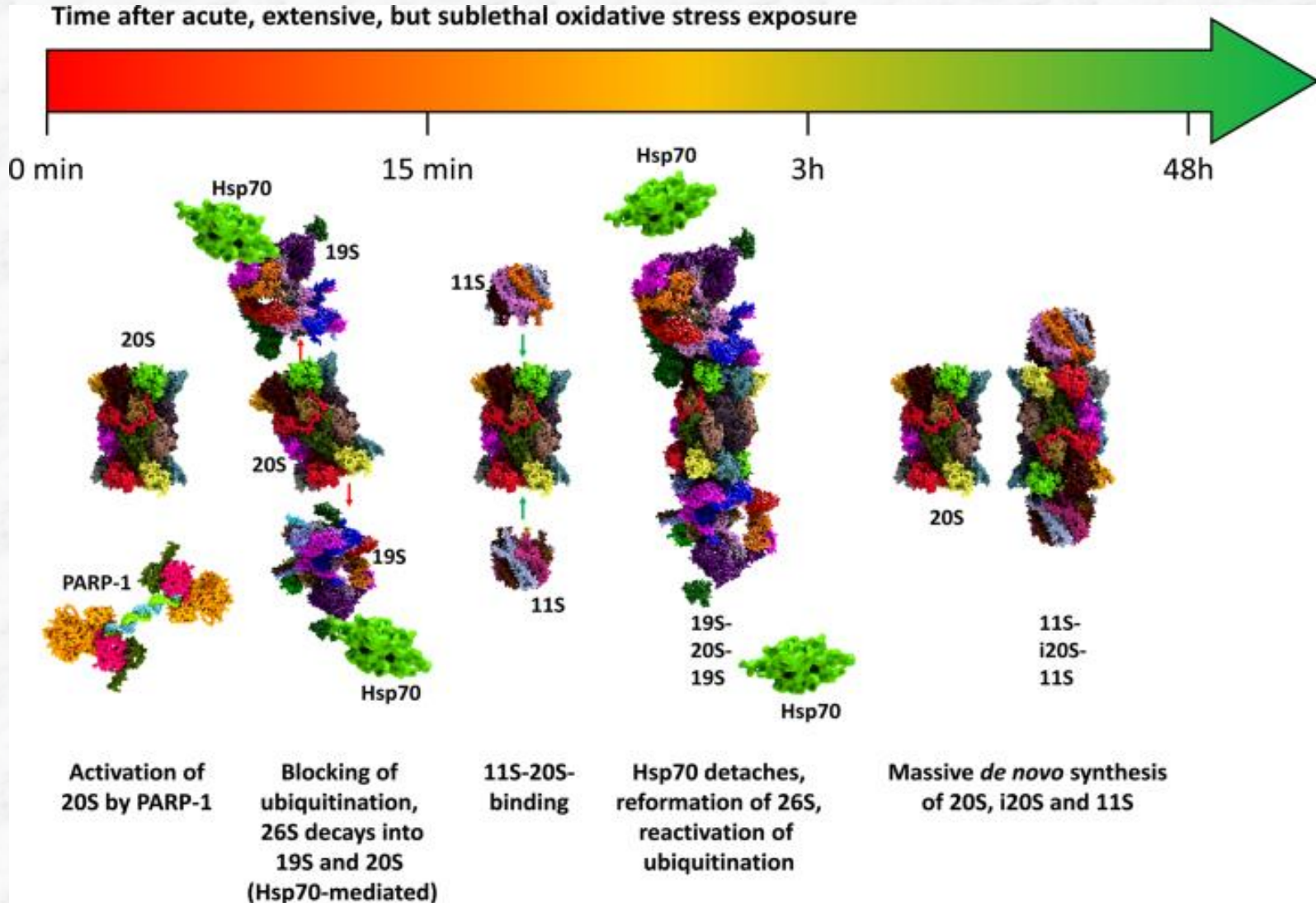
This mechanism has something to do with epigenetics

**This mechanism is very important because its malfunction is involved in
tumoral progression**

Genetic diseases

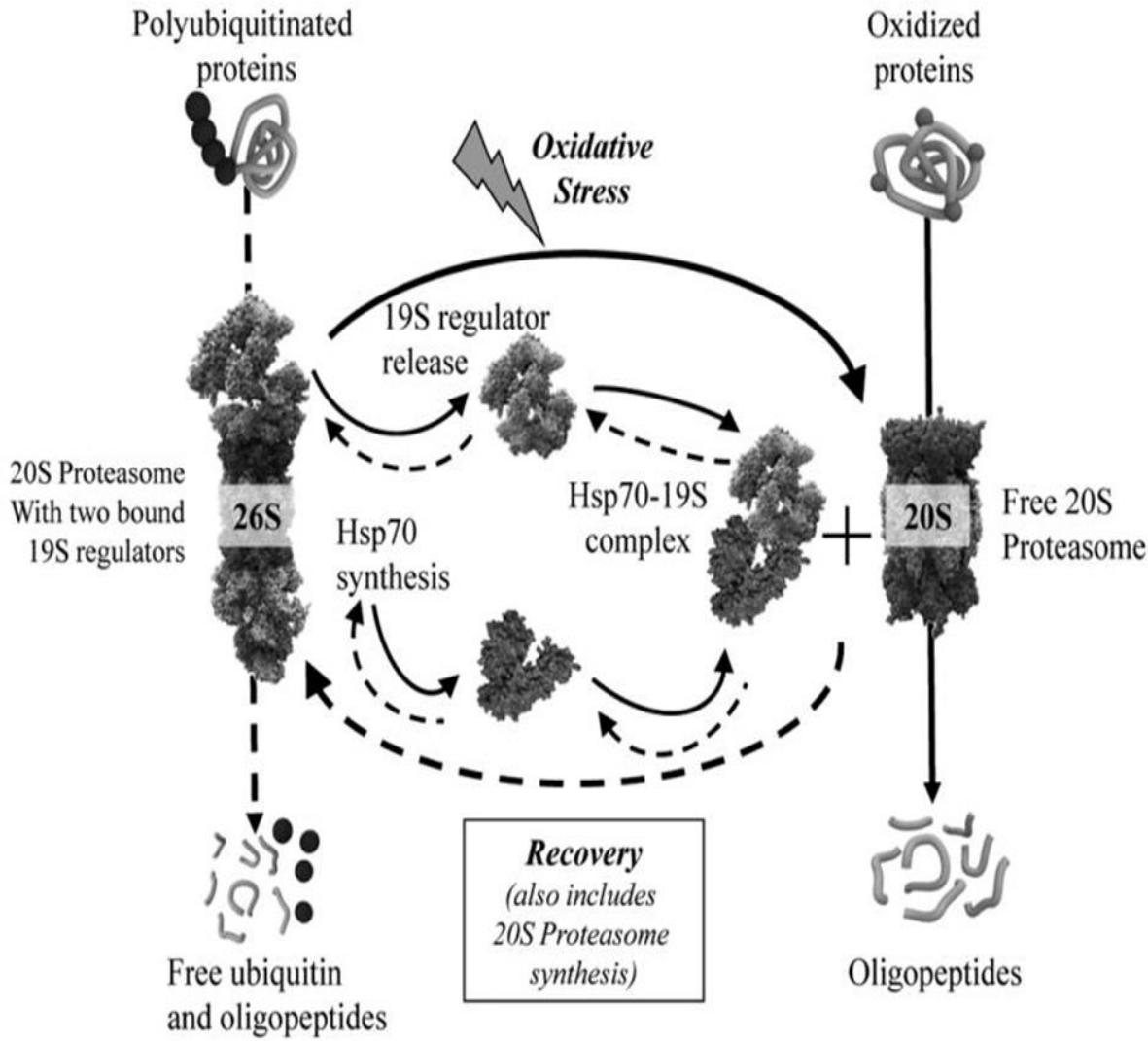
Neurodegenerative diseases

Chronic pain



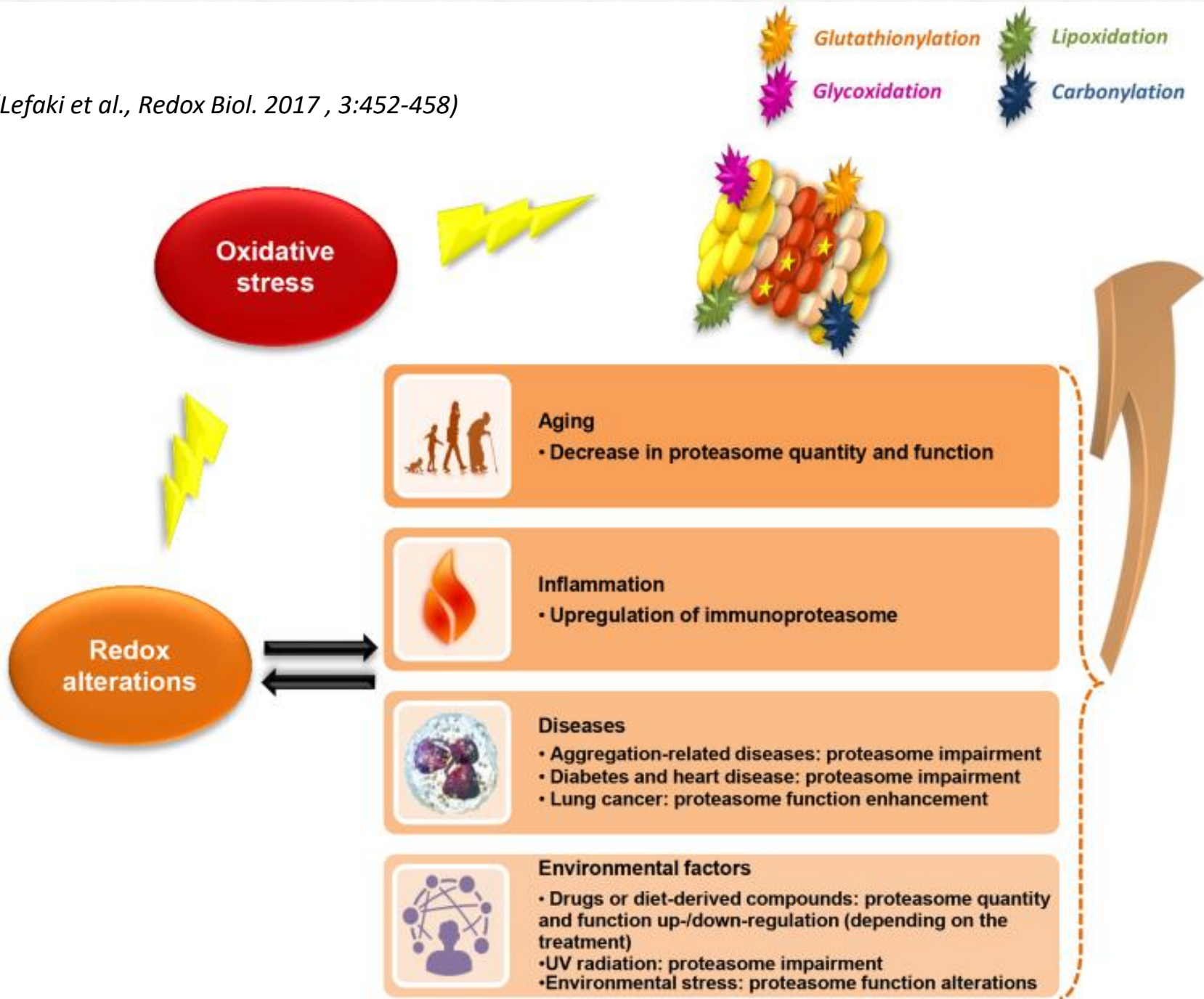
(Korovila, et al. Redox Biol. 2017, 13:550-567)

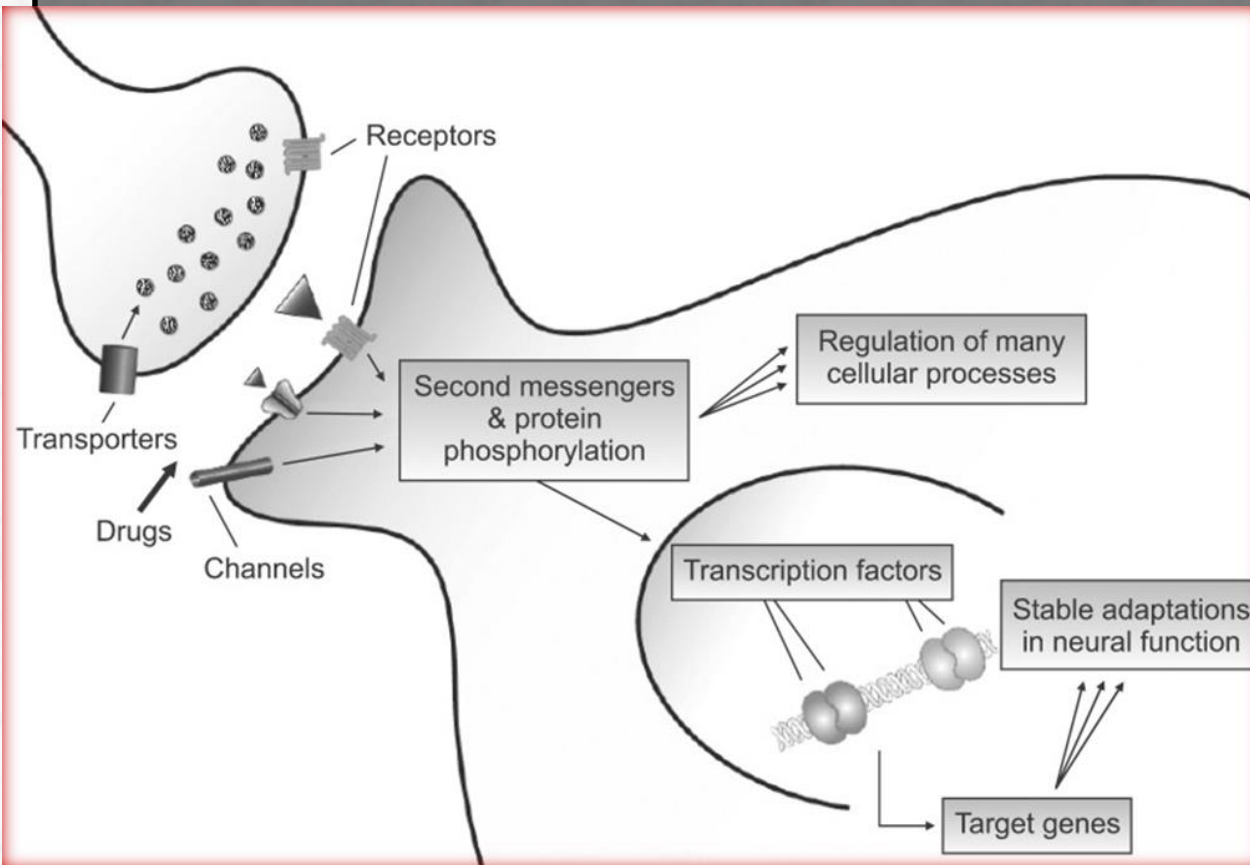
HSP70-mediated Dissociation of the 26S Proteasome During Oxidative Stress



(Grune et al., *Free Radic Biol Med.* 2011. 51:1355-1364.)

(Lefaki et al., Redox Biol. 2017, 3:452-458)





- Neurotransmitter receptors
- Ion channels
- Neurotrophic factors
- Second messengers
- Protein kinases
- Enzymes
- Transcription factors
- Rna Pol.II
- Epigenetic mechanisms

UPS Inhibitors as antineoplastic:

Bortezomib = first iUPS approved in human (2003) → multiple mieloma

Carfizomib = mieloma multiplo

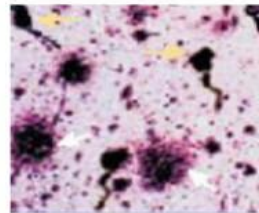
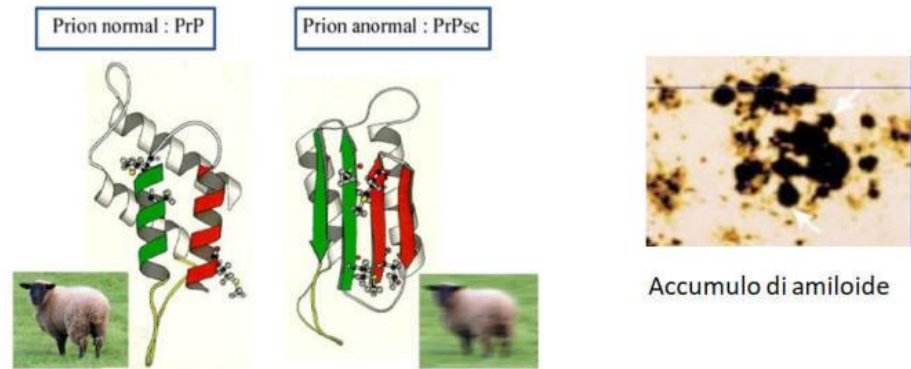
Ixazomib = mieloma multiplo

Side effects: Neuropathic pain

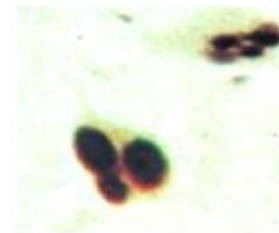
3- Neurodegeneration

In stress conditions UPS can be damaged inducing an increase and accumulation of toxic proteins leading to

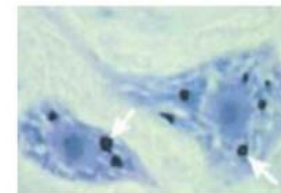
- Alzheimer D
- Parkinson D



Placche e grovigli in Alzheimer



Corpi di Levi nel Parkinson



Aggregati nella SLA

Malattie neurodegenerative

CNS Neurol Disord Drug Targets. 2013 Oct 28. [Epub ahead of print]

α -Synuclein Ubiquitination and Novel Therapeutic Targets for Parkinson's Disease.

Rott R, Szargel R, Shani V, Bisharat S, Engelender S.

Department of Pharmacology, The Rappaport Faculty of Medicine and Research Institute, Technion-Israel Institute of Technology, Bat-Galim, Haifa 31096, Israel. simone@tx.technion.ac.il.

Drug addiction



Neuropsychopharmacology (2013) 38, 778–790

© 2013 American College of Neuropsychopharmacology. All rights reserved 0893-133X/13

www.neuropsychopharmacology.org

A Critical Role for Protein Degradation in the Nucleus Accumbens Core in Cocaine Reward Memory

DA can i UPS



Neurodegeneration.

