Ubiquitin-Mediated Protein Degradation

from the lab to the bedside

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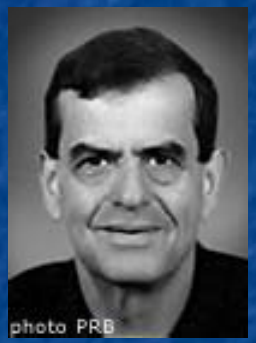
The Nobel Prize in Chemistry 2004

"for the discovery of ubiquitin-mediated protein degradation"



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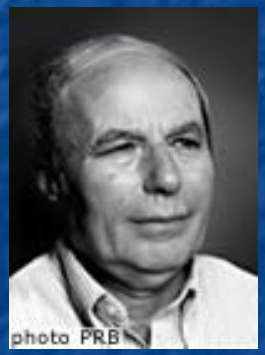

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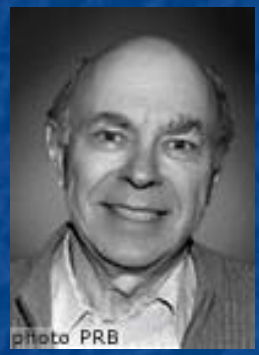

Irwin Rose

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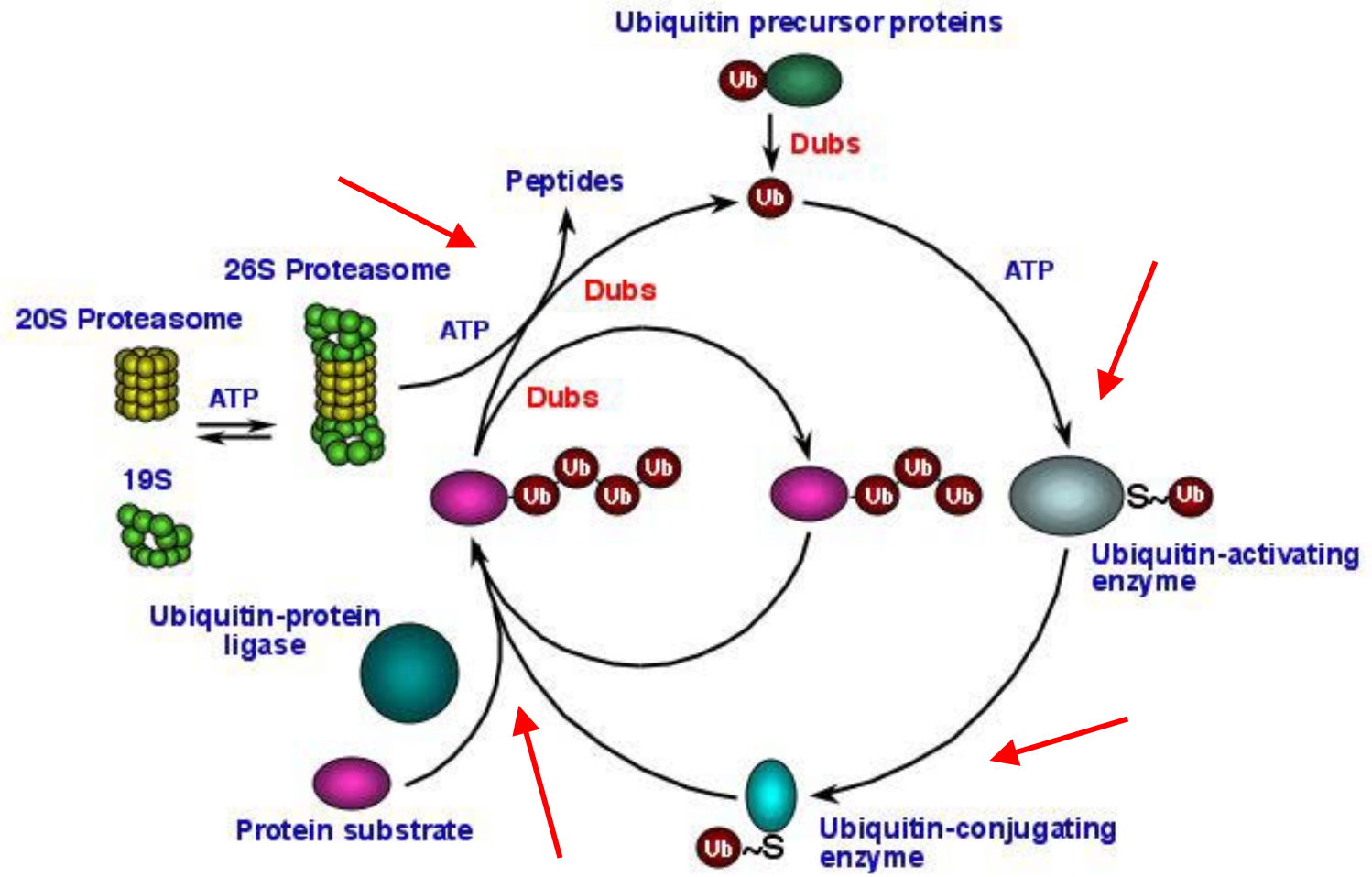
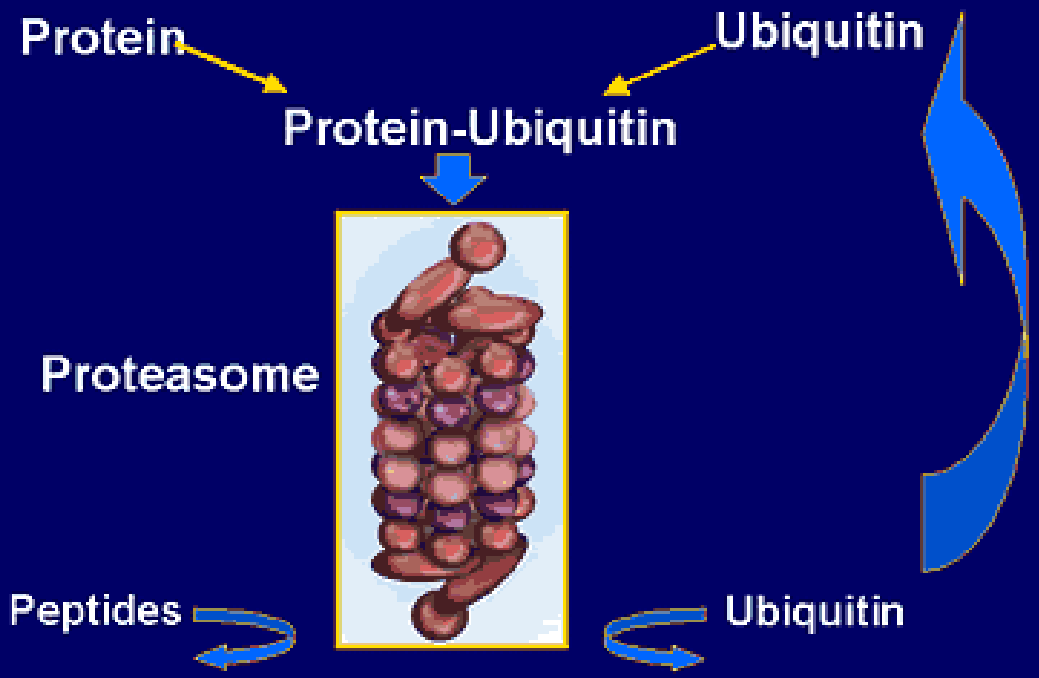
History

- In the seventies – great interest in protein synthesis
- “proteolysis is unregulated”
- Hershko – aimed to understand the paradox of why intracellular proteolysis required enregy
- 1978 – 1982: isolation and characterization of the ATP-dependent ubiquitin-mediated protein degradation pathway

The Ubiquitin-Proteasome Pathway



Ubiquitin-Proteasome Pathway



Biological functions

- Cell cycle regulation
- Transcription regulation
- DNA repair
- Signal transduction
- Metabolism
- Receptor modulation
- Immune response
- Quality control

Clinical relevance

- Cancer
- Muscular and neurological diseases
- Immune and inflammatory responses
- Cystic fibrosis

Therapeutic interventions

- Proteasome inhibitors -Bortezomib (Velcade™)

- Ubiquitin ligase inhibitors (E3):
  - Skp2
  - MdM2
  - BRCA1/BRAD1

Conclusions

- The ubiquitin - proteasome pathway has a critical role in maintaining cell's homeostasis
- Involved in the development and progression of diseases
- Development of novel therapeutic interventions
- Good research can be done with minimal funding

Thank you