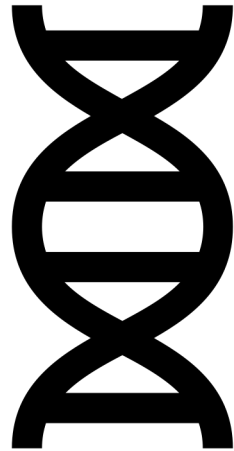
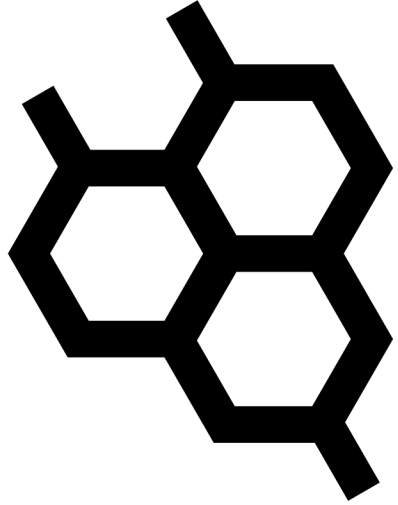


Zoo 642

(Advanced Cytology)

The Ubiquitin-
Proteasome
System



Outlines

- ❖ **Protein degradation (Proteolysis)**
- ❖ **The main protein degrading systems.**
- ❖ **The Ubiquitin-Proteasome System.**
- ❖ **26S proteasome & ubiquitin structure**
- ❖ **The enzymatic are required in Ubiquitination pathway.**
- ❖ **Ubiquitin proteasome pathway.**
- ❖ **Different ubiquitin linkages.**

Protein degradation (Proteolysis)

- ❖ Proteolysis is the **breakdown** of proteins into **smaller polypeptides** or **amino acids**.
- ❖ Proteolysis is usually catalyzed by enzymes known as **proteases**.
- ❖ The content of any protein in a cell based on relative rate of protein synthesis and protein degradation and that rate must be **balanced**, because a small decrease in synthesis or a small acceleration of degradation, if sustained, can result in a marked loss of mass in the organism.
- ❖ **Cellular protein content = synthesis rate – degradation rate**

Protein degradation (Proteolysis)

- ❖ Protein degradation is **very important** , involved in regulating cellular process such as growth and atrophy, transcription, rate of metabolic pathway and some disease status such as cancer.
- ❖ Cells **quickly remove** the failures of their translation processes such as denatured or misfolded proteins or fail to be assembled properly as well as proteins containing oxidized or other abnormal amino acids, then return them back to the cytosol for degradation.

The main protein degrading systems

- 1) The ubiquitin-proteasome pathway.
- 2) lysosomal system pathway.
- 3) calpain system pathway.

Activation of these systems or other is increased under catabolic conditions associated with muscle atrophy such as cancer, AIDS, kidney disease and diabetes mellites.

The main protein degrading systems

❖ The calpain and lysosomal pathway are deal with :

long-lived proteins such as: structural protein, contractile protein and membrane protein.

❖ The ubiquitin-proteasome pathway is involved in:

- degrade abnormal or short-lived proteins and Farther destruction of protein fragments.

The Ubiquitin-Proteasome System

- ❖ They got it for their work on the discovery of ubiquitin-mediated protein degradation and characterization of the ubiquitin proteasome system (UPS).
- ❖ These new inhibitors represent a new class of anticancer agents.

The Nobel Prize in Chemistry 2004



Aaron Ciechanover



Avram Hershko

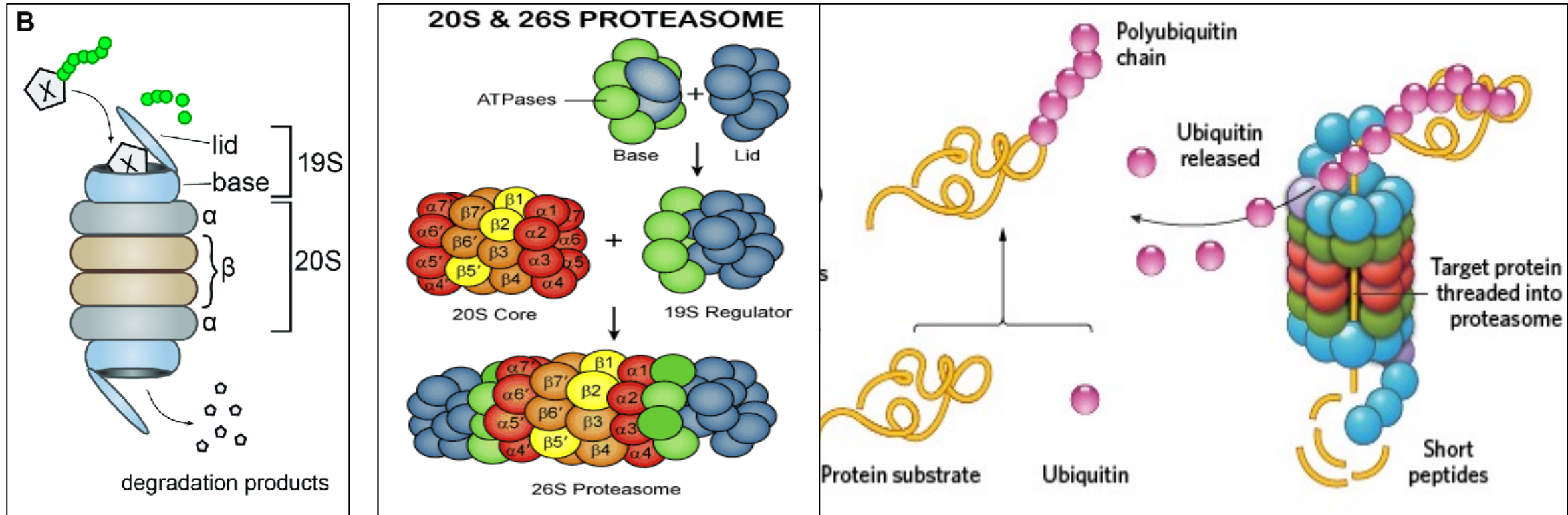


Irwin Rose

The Ubiquitin-Proteasome System

- ❖ It plays a major role in targeting and degrading cellular protein.
- ❖ The pathway must recognize and label a specific protein for degradation then carry out the process.
- ❖ The recognition part is based on marking a protein known as **ubiquitin**.
- ❖ Ubiquitinated proteins are subsequently degraded to small polypeptides by **a large, multi-subunit protease complex**, called **the 26S proteasome** complex.

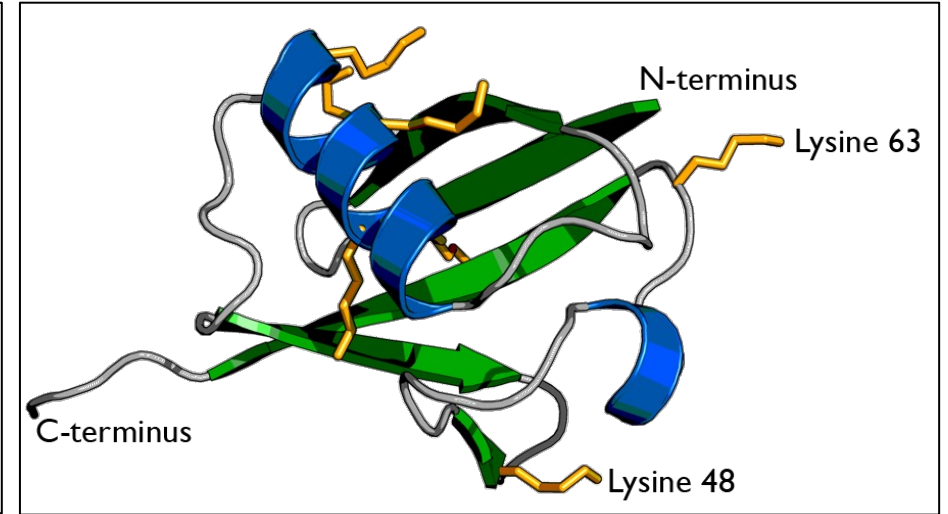
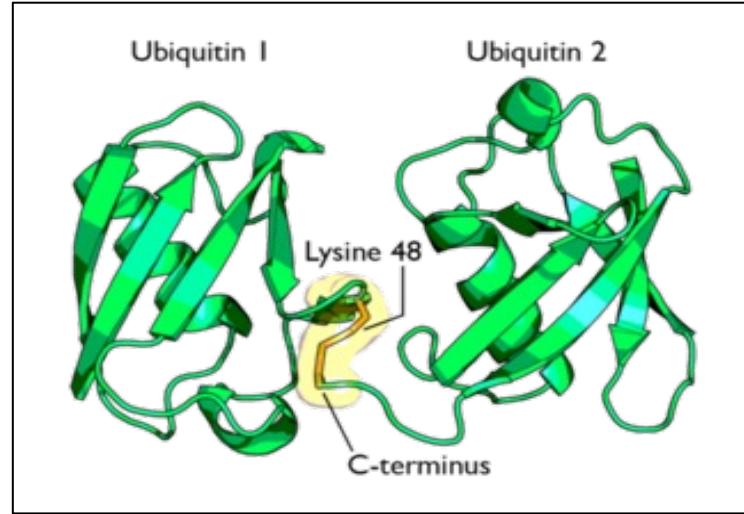
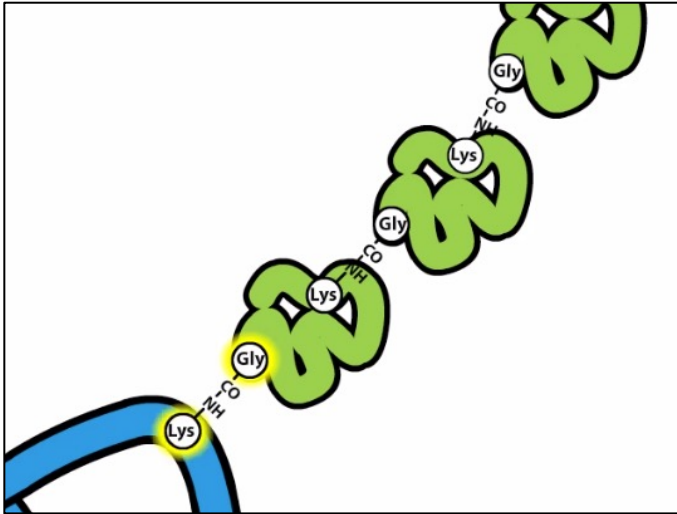
26S proteasome structure



26S proteasome structure

- ❖ Each proteasome consists of a **central hollow cylinder** (the 20S core proteasome) formed from multiple protein subunits that assemble as a cylindrical stack of four heptameric rings.
- ❖ Some of these subunits are distinct proteases whose active sites face the cylinder's inner chamber.
- ❖ Each end of the cylinder is normally associated with a large protein complex (the 19S cap) containing approximately 20 distinct polypeptides.
- ❖ The cap subunits include at least six proteins that hydrolyze ATP; located near the edge of the cylinder, these ATPases are thought to **unfold the proteins** to be digested and move them into the **interior chamber for proteolysis**.

Ubiquitin Structure



- ❖ **Ubiquitin** is composed of 76 amino acids. Its **C-terminus** is a critical **glycine** that is required for its conjugation to other Ub molecules and substrates, and it contains internal **lysine** residues (**N-terminus**) that are used in the creation of polyubiquitin chains.

Ubiquitin

- ❖ **Ubiquitin** is released in the process, so it can be reused in another cycle.
- ❖ **Ub** conjugation to cellular proteins also can be reversed by the many **deubiquitinating enzymes** in cells.
- ❖ At least **4 ubiquitins** are added to the target protein, generating a poly ubiquitinated protein.
- ❖ Both of the attachment of ubiquitin and the degradation of marked proteins require **energy in the form of ATP**.

Three enzymatic components are required to link chains of Ub onto proteins

1- ubiquitin-activating enzyme (E1).

Activation of Ub at its C-terminus to start conjugate onto proteins (uses ATP).

2- ubiquitin-conjugating enzyme (E2).

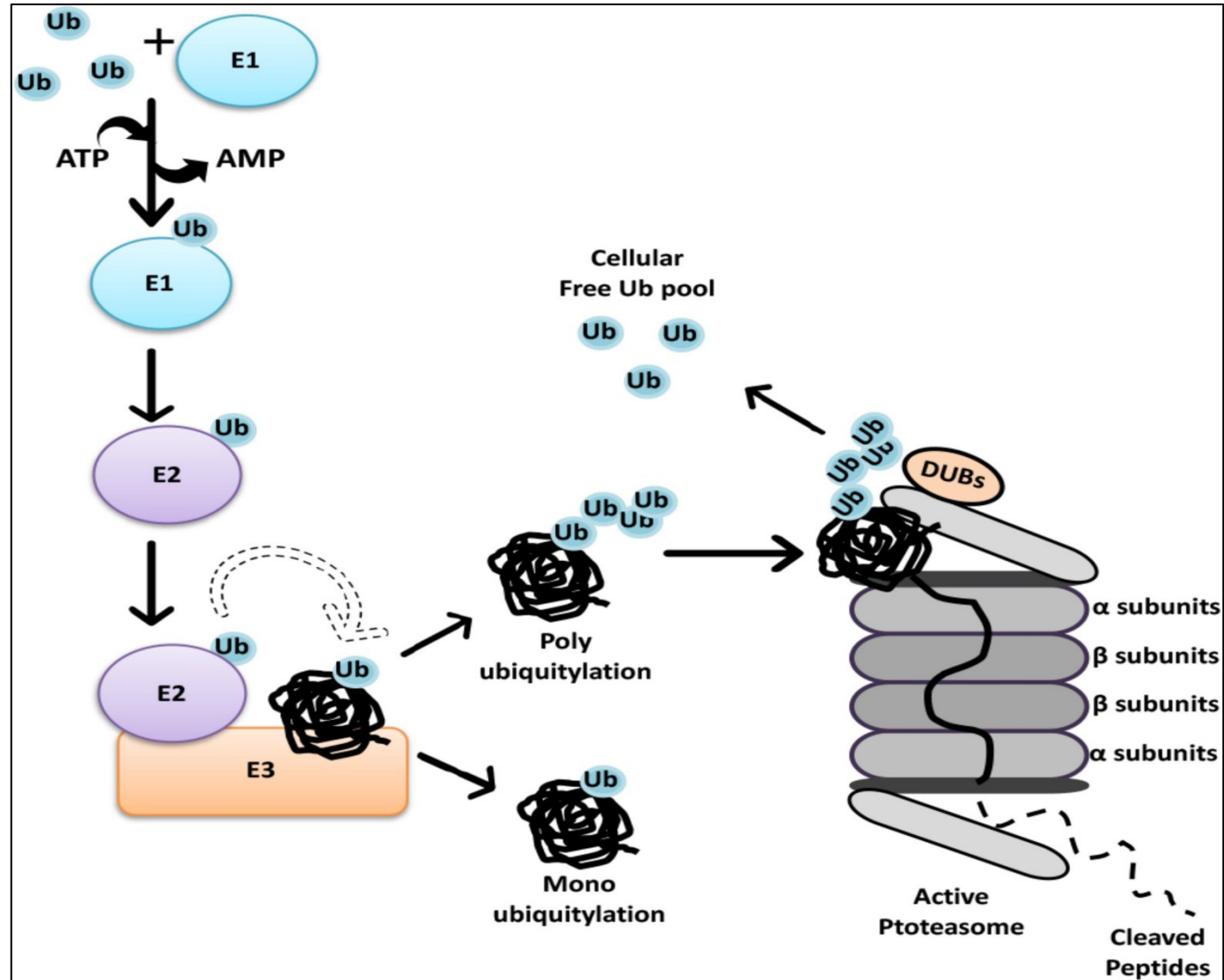
The ubiquitin is then transferred to a second enzyme.

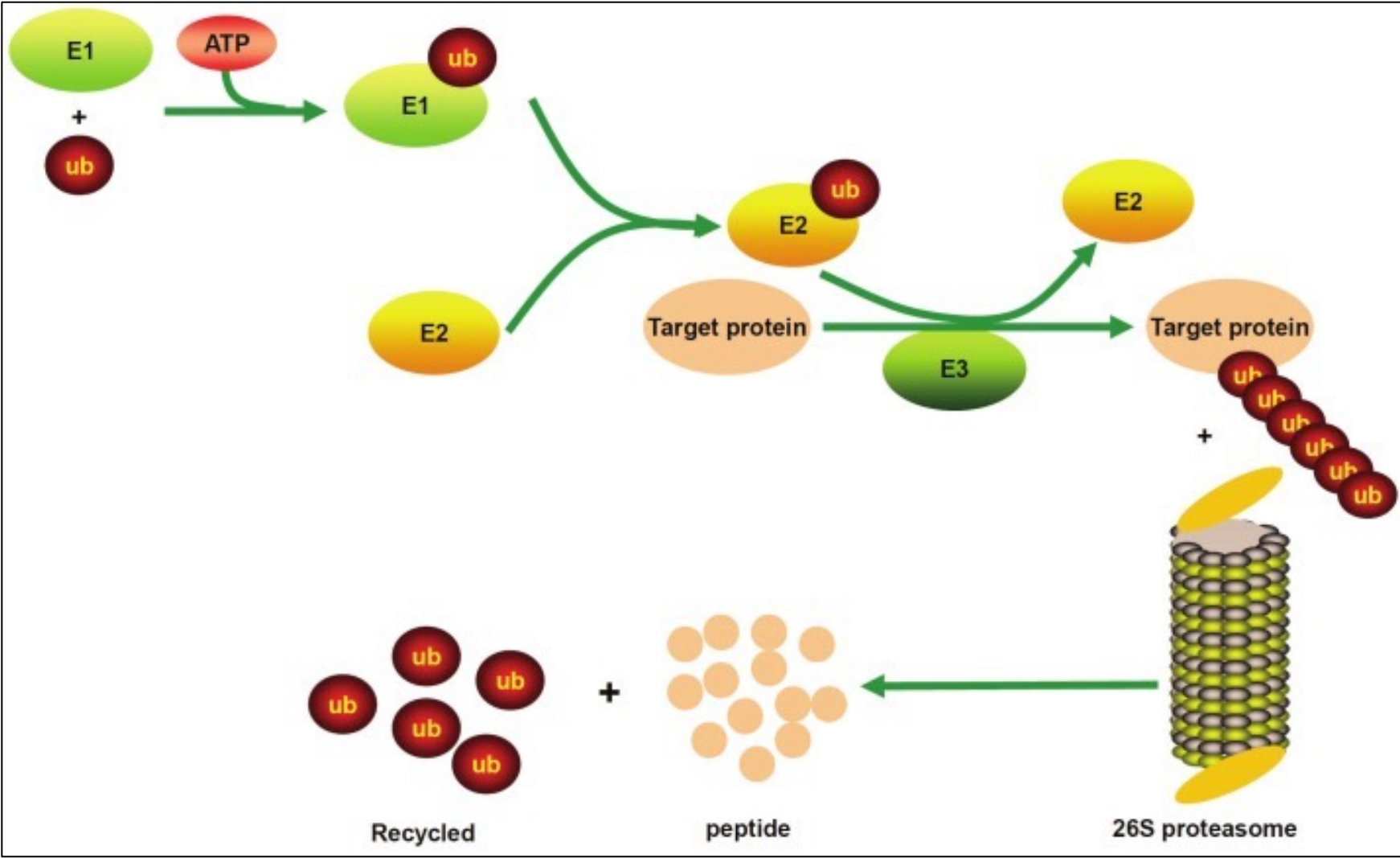
3- ubiquitin ligase (E3).

The final transfer of ubiquitin to the **target protein** is then mediated by this enzyme (responsible for the recognition of appropriate substrate proteins).

- ❖ Multiple ubiquitins are then added, and the polyubiquitinated proteins are degraded by a **protease complex (the proteasome)**.

Ubiquitin proteasome pathway





Different ubiquitin linkages do different thing!

