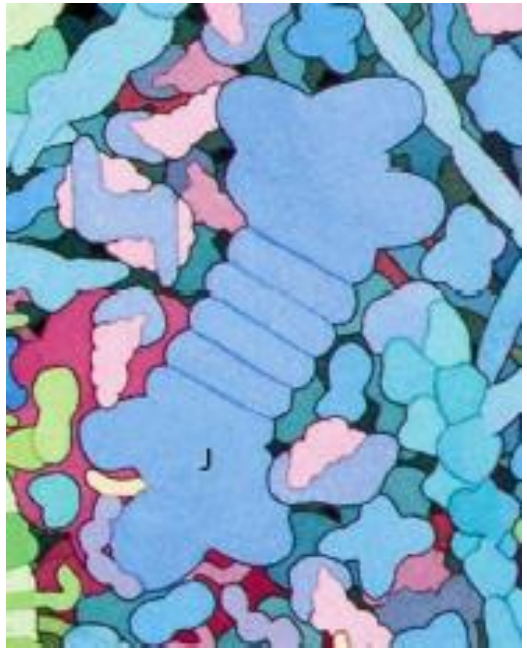
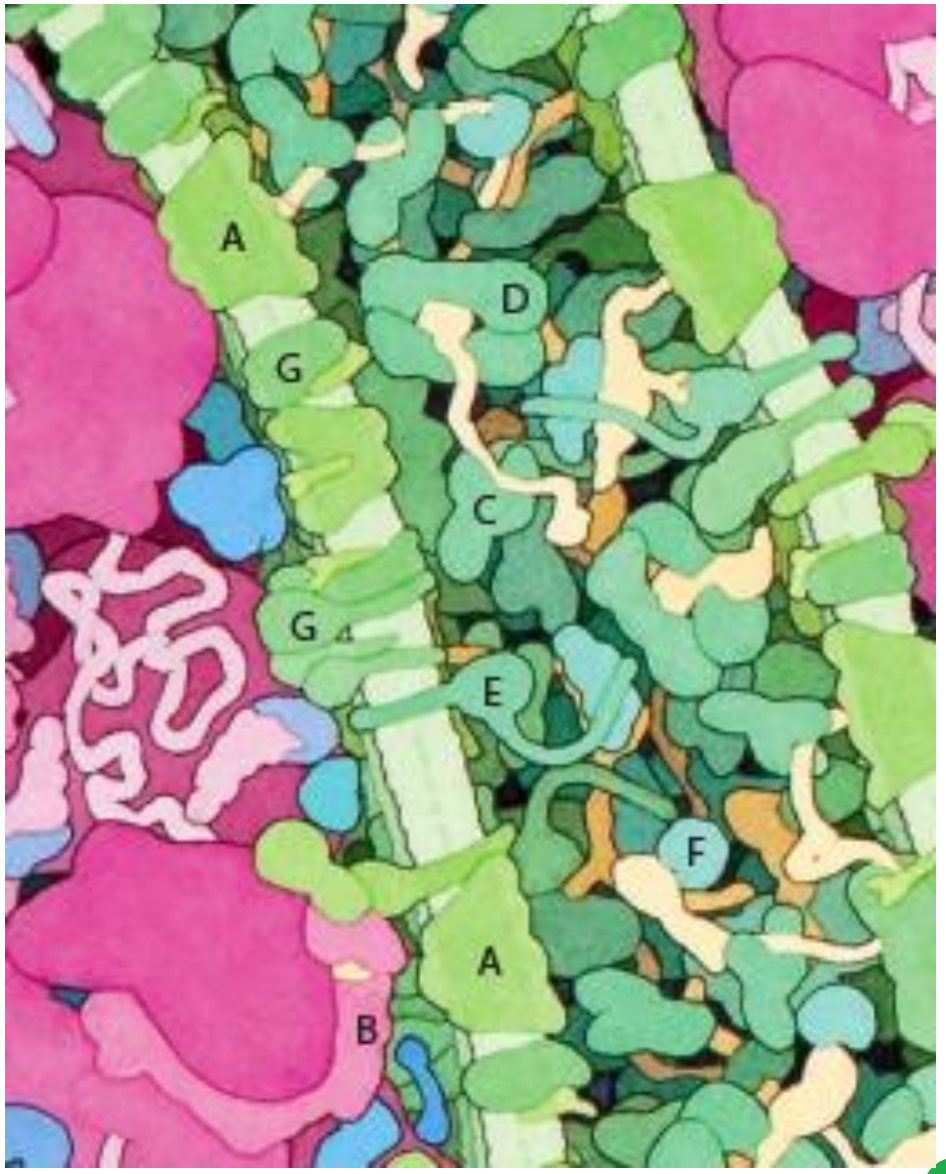
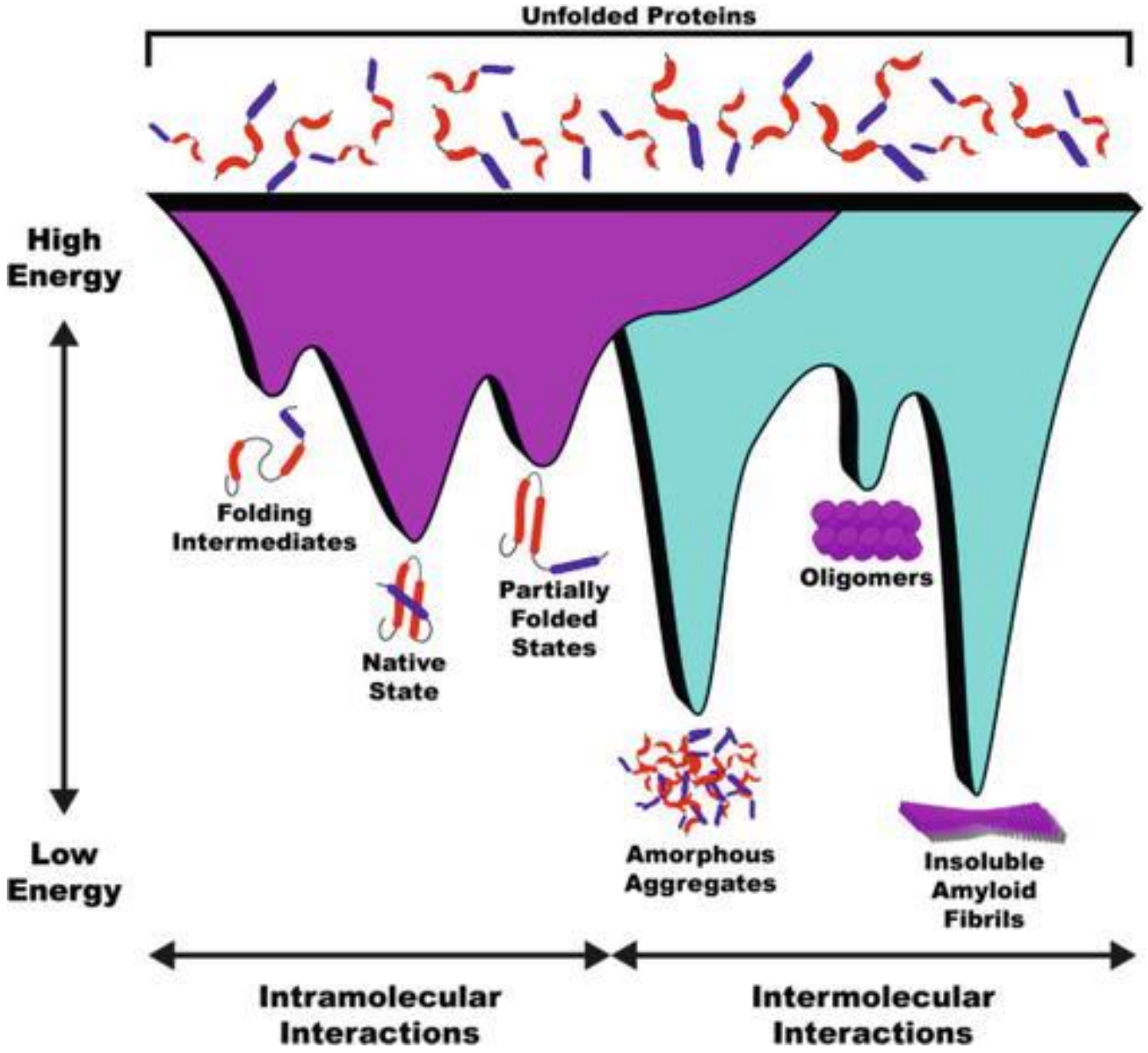
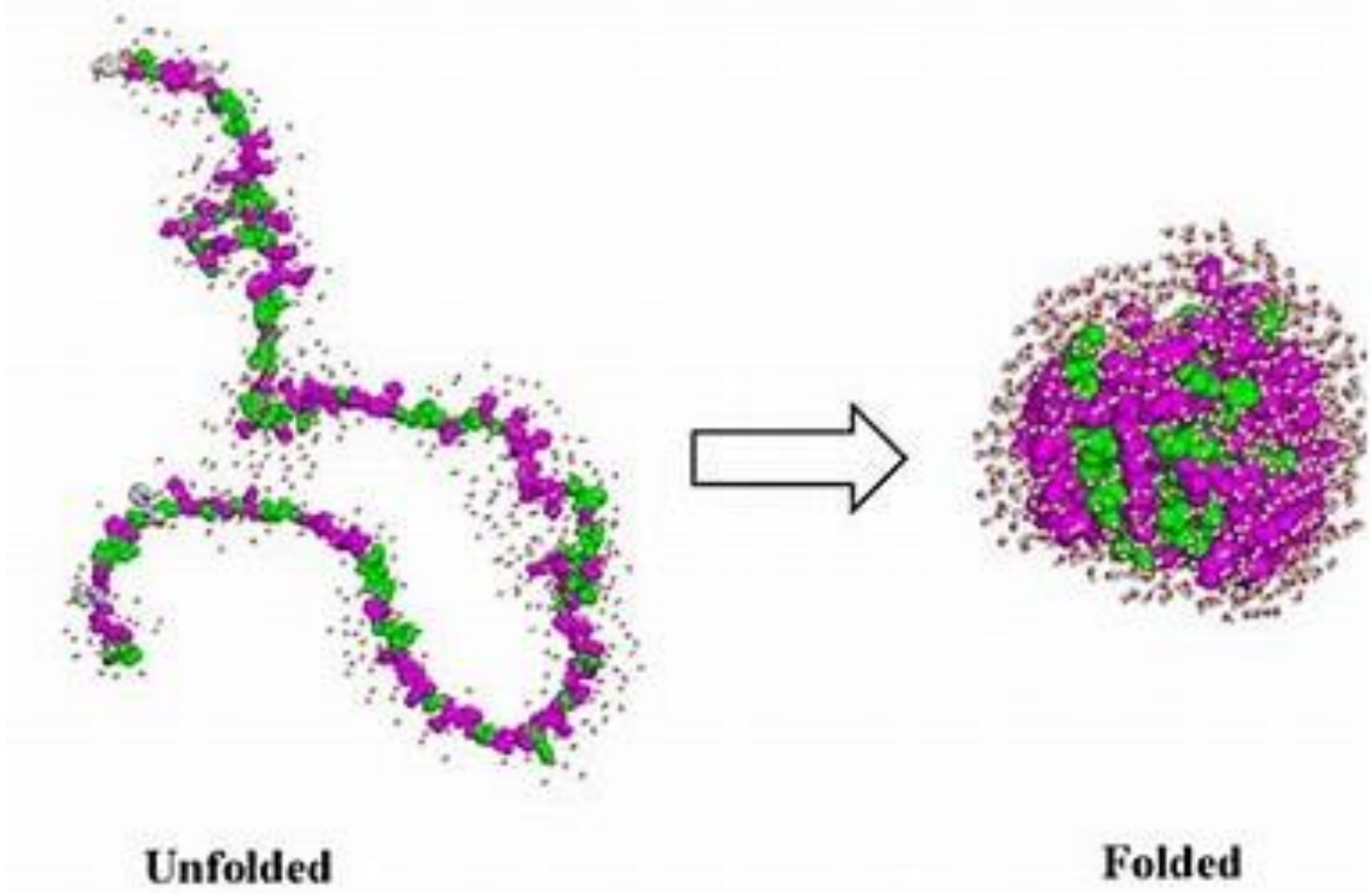
Chaperones and proteosomes… and why we need them





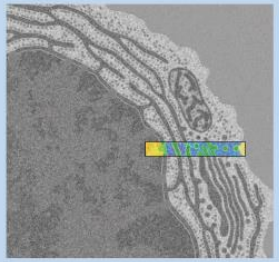

Unfolded Proteins
High Energy
Low Energy
Folding Intermediates
Native State
Partially Folded States
Oligomers
Amorphous Aggregates
Insoluble Amyloid Fibrils
Intramolecular Interactions
Intermolecular Interactions

Where does protein folding happen?



Let’s find those places in the Goodsell Landscape

Tour of a Human Cell

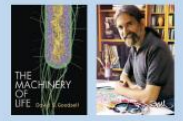


This illustration simulates what we would see if we could magnify a portion of a living cell by 1,500,000 times. At this magnification, atoms would be about the size of a grain of salt, cells would be the size of huge buildings, and you would be roughly one-fourth the size of the earth in height, allowing you to walk across the continent in a few steps. All of the macromolecules in the cell are shown, including proteins, nucleic acids, carbohydrates and lipid bilayers, but all of the smaller molecules have been omitted for clarity. In reality, the empty spaces in this picture are filled with water, ions, sugars, ATP, and many other small molecules.

The narrow strip is taken from a plasma cell (shown above), a cell from the blood that is dedicated to the production of antibodies. The entire process of antibody production is shown, starting from the gene in the nucleus, proceeding to synthesis in the endoplasmic reticulum, continuing to processing in the Golgi, and finishing with transport and secretion at the cell surface.

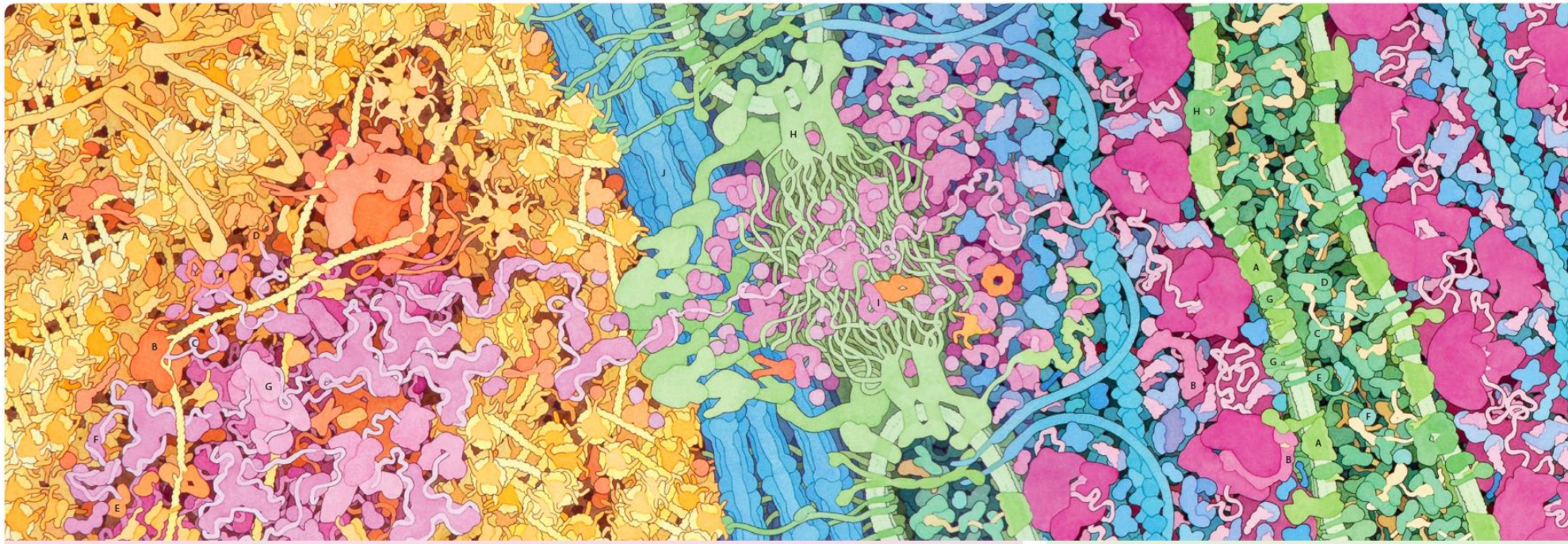
The Machinery of Life

This image is taken from *The Machinery of Life* by David S. Goodsell. It reveals a previously unseen level of biological scale. Light and electron microscopy may be used to explore the ultrastructure of cells, and X-ray crystallography and NMR spectroscopy may be used to reveal the atomic structure of individual purified molecules, but there is currently no way to observe directly the structure of living cells at the molecular level. Instead, this illustration is synthesized by combining experimental data on cellular ultrastructure, the atomic structure of molecules, and bioinformatics.



To purchase this book, visit springer.com or your favorite bookseller.

3-D Molecular Designs
...where molecules become real™
www.3dmoleculardesigns.com



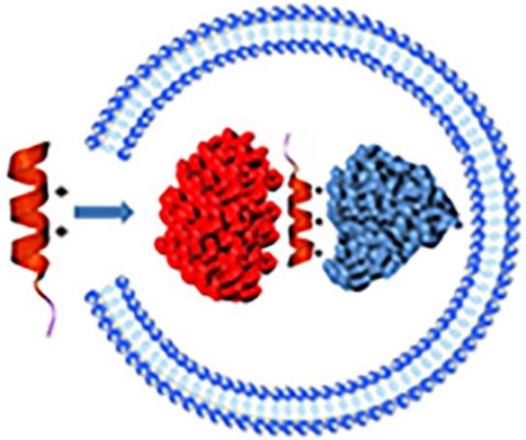
Nucleus. The nucleus is the cell’s library, storing the delicate strands of DNA and protecting them from the rigors of the cytoplasm. Much of the DNA is wrapped around histone proteins to form small nucleosomes (A) that compact and protect the DNA. When the DNA is needed, it is unwrapped, unwound, and read by RNA polymerase (B) to create a messenger RNA (C). The RNA molecules are then processed: capping enzymes (D) protect one end and polyadenylate polymerase (E) adds a repeated string of adenine nucleotides to the other end, which is then protected by the polyadenylate binding protein (F). Our DNA must also be edited by large spliceosome complexes (G) to remove intron regions that do not encode proteins. Once the RNA is properly edited, it is delivered out of the nucleus through nuclear pore complexes (H). These pores span the double-layered nuclear membrane and control the traffic of a diverse collection of importin proteins (I), which carry other molecules in and out. The nuclear membrane is strengthened inside by criss-crossed layers of lamin protein filaments (J).

Endoplasmic Reticulum. With so many compartments, our cells need ways of sorting and transporting new proteins to their proper destinations. For many proteins, such as the antibodies made by this plasma cell, the journey starts with the endoplasmic reticulum. The endoplasmic reticulum is an interconnected series of tubules and sacs. The membrane surrounding the endoplasmic recticulum is filled with transport proteins (A) that bind to ribosomes and guide new proteins inside as they are being made. The transporter finds new p signal sequence of amino acids. This signal seque ribosome, and it is quickly recognized by a signal delivered to the endoplasmic reticulum surface. off when the protein is fully synthesized and safe collection of chaperonins such as BiP (C), Grp94 (

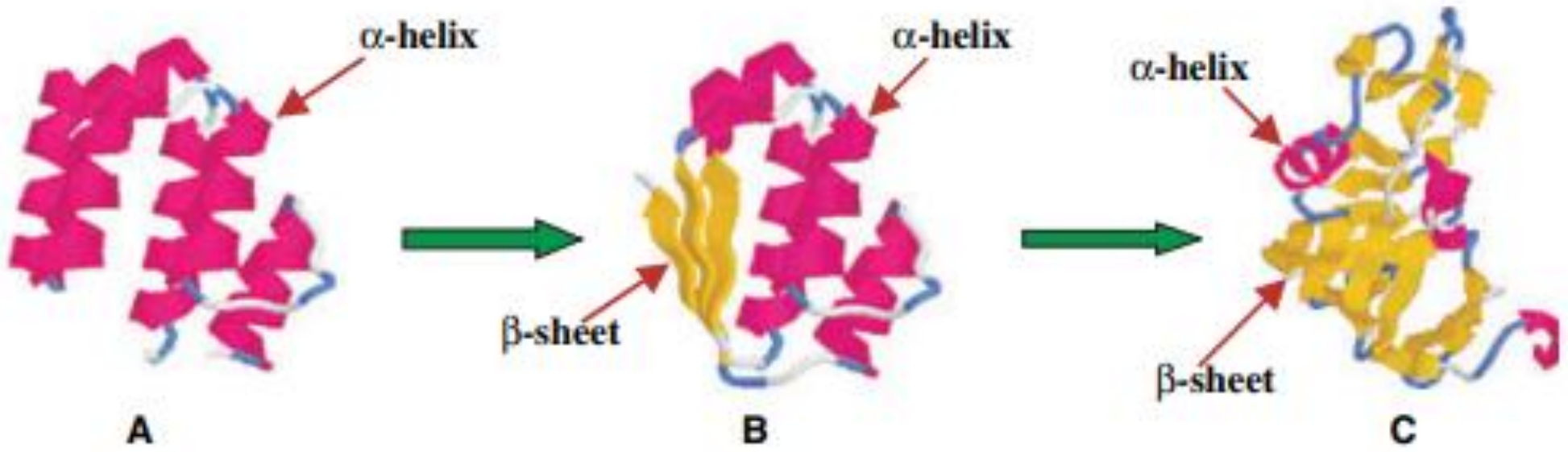
The Problem…

What happens to protein folding when you have a long peptide chain?
Titin has at least 27,000 sidechains

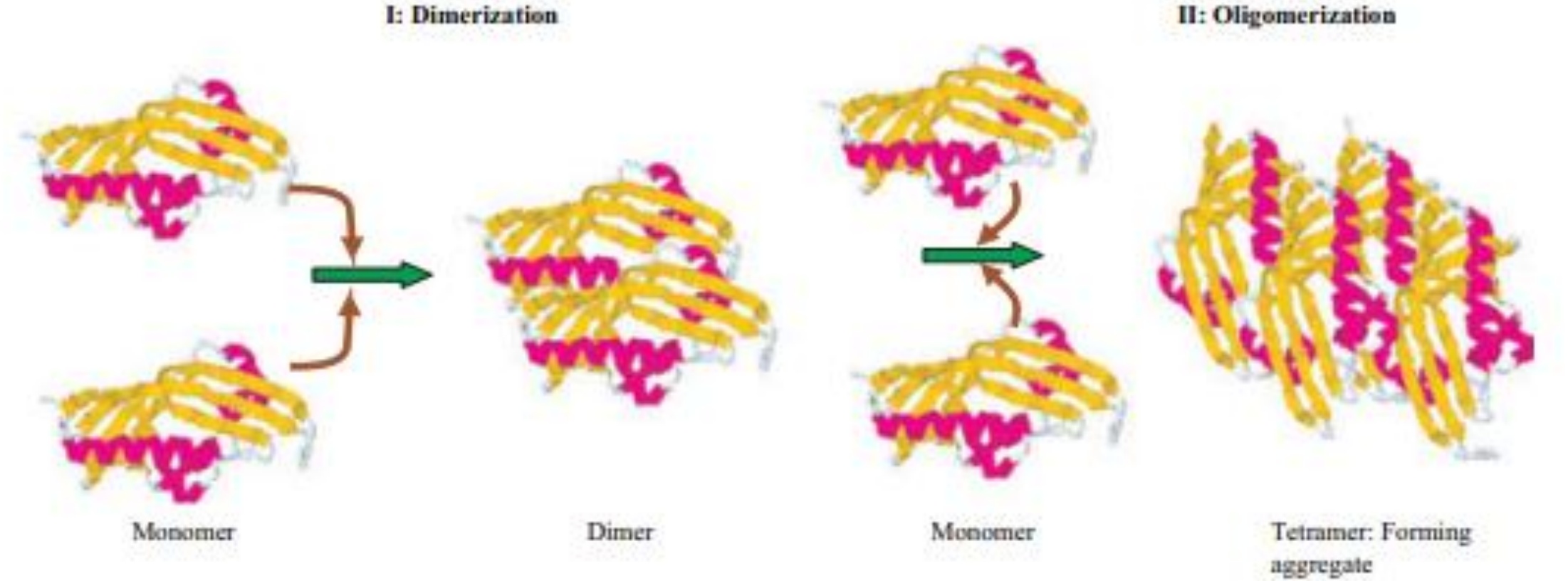
What about an increase in temperature?
Chemical exposure?
Radiation?



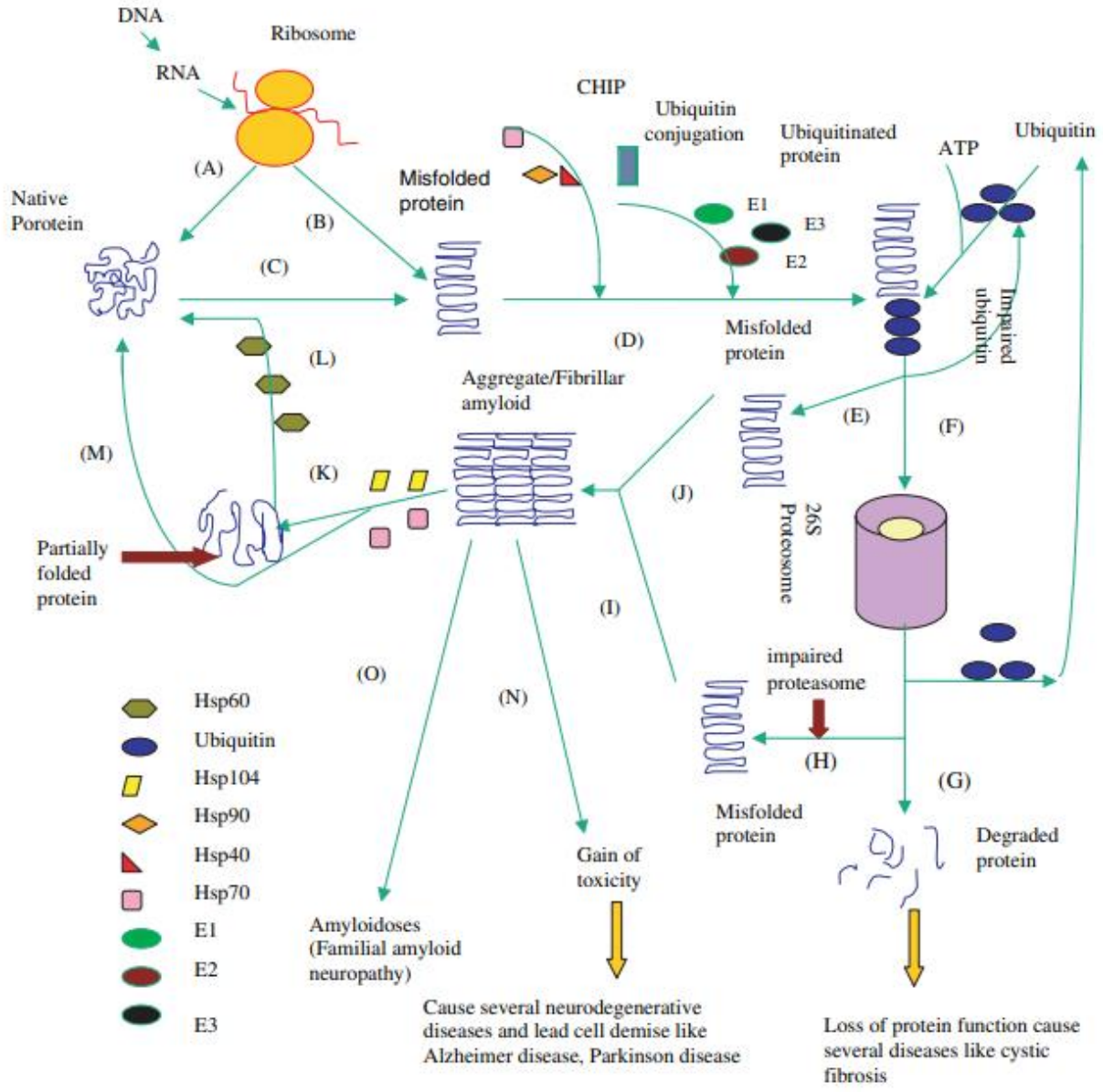
Protein misfolding is detrimental to cellular function…



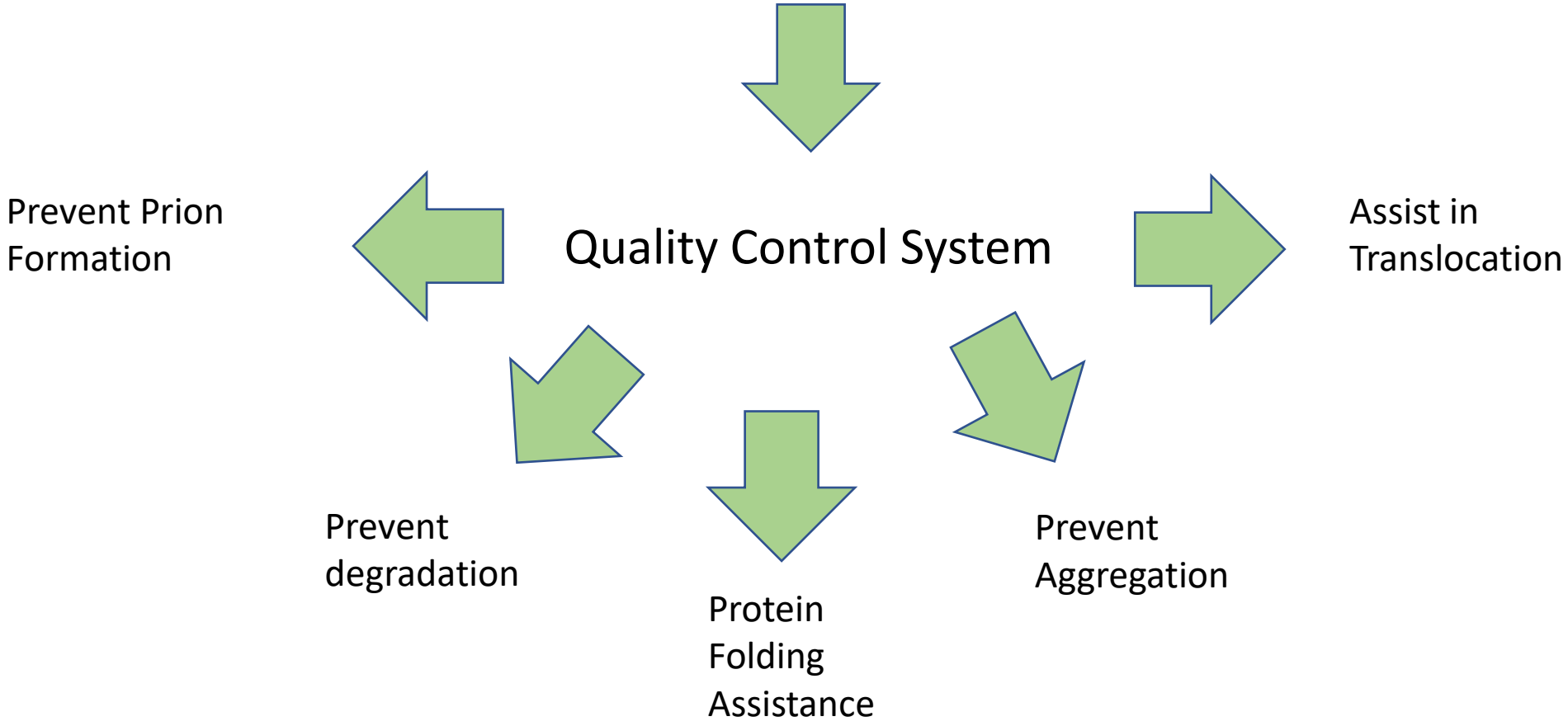
… and can lead to cell death



Life is complicated!

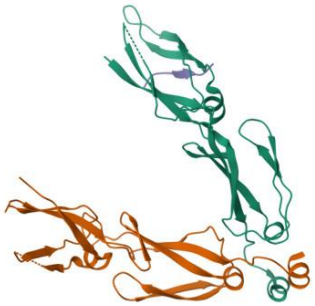


Molecular Chaperones

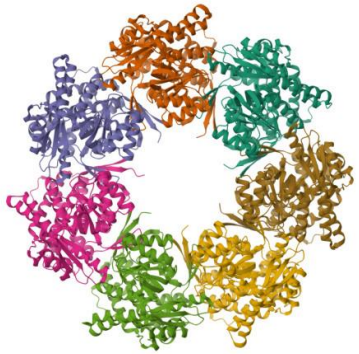


Chaperones

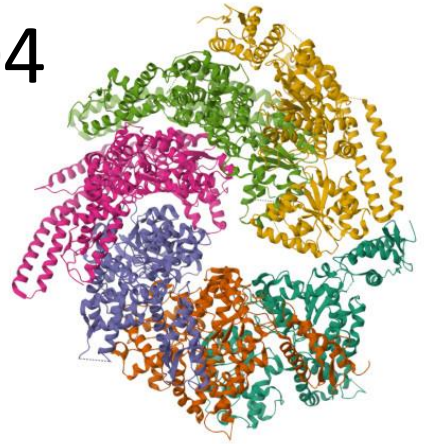
Holdases
HSP40

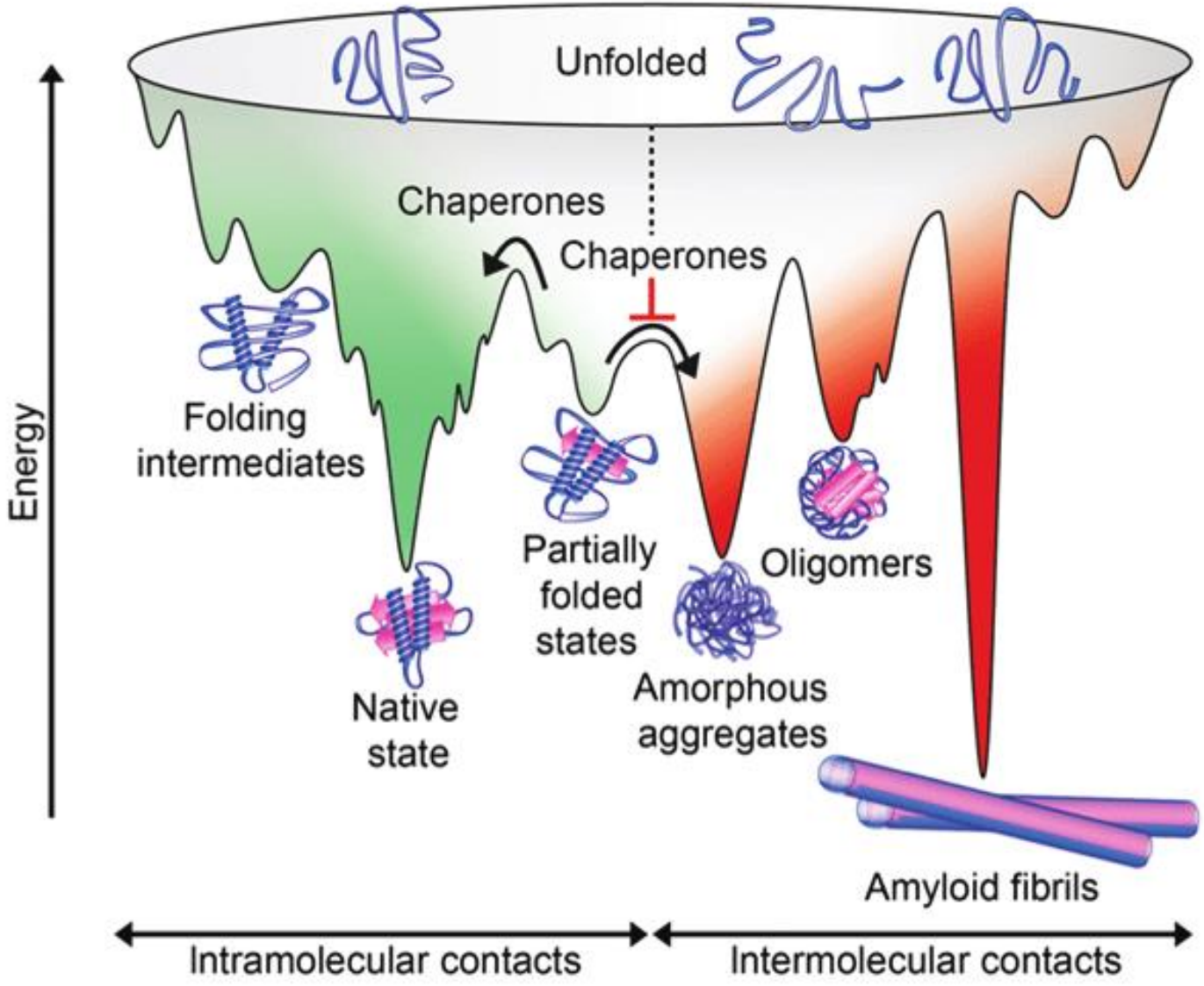


Foldases
HSP60



Disaggregases
HSP104

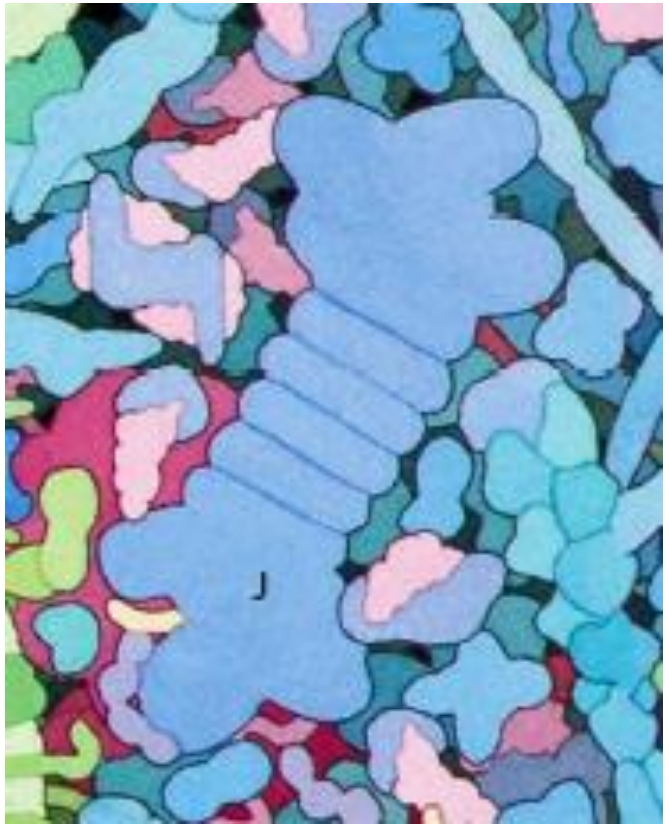



Unfolded
Chaperones
Chaperones
Energy
Folding intermediates
Partially folded states
Oligomers
Native state
Amorphous aggregates
Amyloid fibrils
Intramolecular contacts
Intermolecular contacts

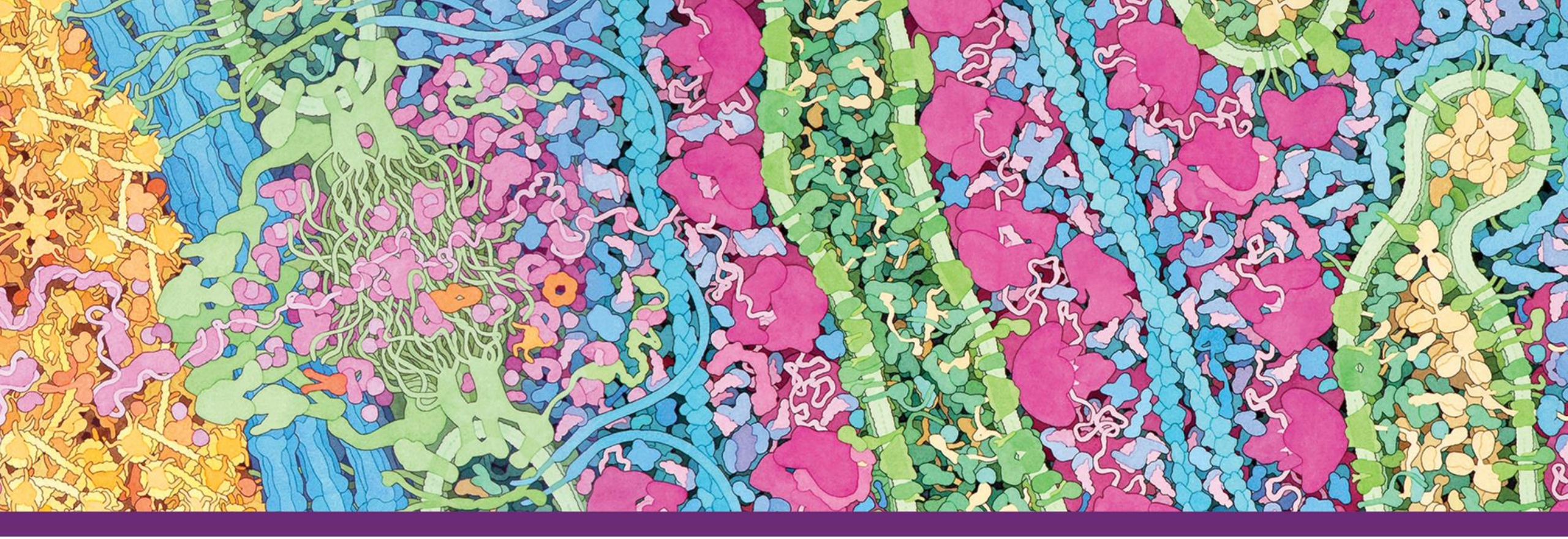
Failure to refold?

- Recycle it in the Proteasome!
- Marked with ubiquitin … another complicated process

- Failure in the proteasome?
- Alzheimer’s
- Parkinson’s
- Huntington's
- … and about 50 other diseases



- Protein-misfolding diseases and chaperone-based therapeutic approaches (wiley.com)
- Protein Misfolding and Degenerative Diseases | Learn Science at Scitable (nature.com)
- PDB-101: Molecule of the Month: Chaperones (rcsb.org)
- PDB-101: Molecule of the Month: Hsp90 (rcsb.org)



3d molecular designs

Transforming Science Learning