

1997 Nobel Prize in Physiology or Medicine

Dr. Stanley Prusiner

for the discovery of prions* - a new biological principal of infection

I. PRIONS - Definition

Prions are simple proteins that are much smaller than viruses. They are unique since they lack a genome. **All other known infectious agents contain genetic material.**

Prion Theory: Abnormal or “rogue” prion protein causes a conformational change in the normal prion protein, resulting in the accumulation of insoluble aggregates of the misfolded prion proteins.

II. PRION DISEASES

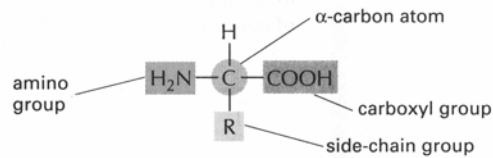
HUMAN	
KURU	Infection through ritualistic cannibalism
Iatrogenic Creutzfeld Jacob (iCJD)	Infection from prion-contaminated HGH, dura mater grafts, etc.
Variant CJD (vCJD)	Infection from bovine prions?
Familial CJD	Germline mutations in PrP gene
Gerstmann-Straussler-Scheinker Disease	Germline mutations in PrP gene
Fatal Familial Insomnia	Germline mutations in PrP gene (D178N and M129)
Sporadic CJD (sCJD)	Somatic mutation or spontaneous conversion of PrP ^c into PrP ^{sc}
ANIMAL	
Scrapie	Infection In Genetically Susceptible Sheep
Bovine Spongiform Encephalopathy	Infection With Prion-Contaminated Mbm
Transmissible Mink Encephalopathy	Infection With Prions From Sheep Or Cattle
Chronic Wasting Disease (Deer, Elk)	Unknown
Feline Spongiform Encephalopathy	Infection With Prion-Contaminated Mbm
Exotic Ungulate Encephalopathy (Greater Kudu, Nyala, Oryx)	Infection With Prion-Contaminated Mbm

III. PROTEIN STRUCTURE

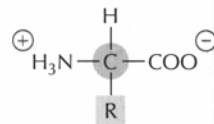
Primary Structure: the sequence of amino acids in a protein

THE AMINO ACID

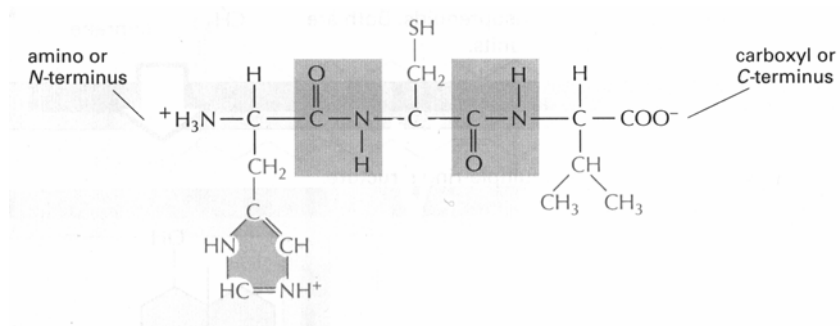
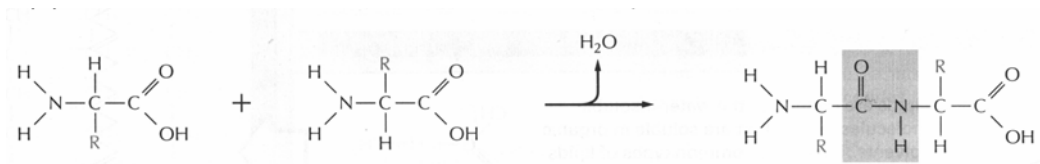
The general formula of an amino acid is



R is commonly one of 20 different side chains.
At pH 7 both the amino and carboxyl groups are ionized.



Amino acids are linked through peptide bonds to form proteins of varying lengths from as few as 10 amino acids to over 500



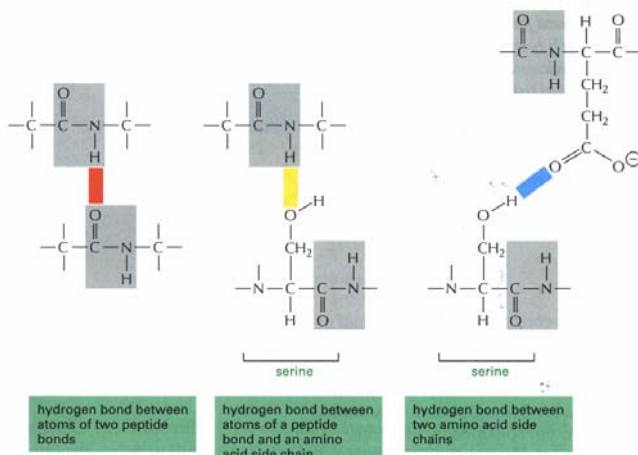
Secondary Structure: folding of a protein chain and interaction of side groups within the protein chain

The amino acids within a protein chain are held together by strong covalent bonds, while the folding of the protein chain is determined by weak, noncovalent bonds:

Ionic bonds: interaction between charged side groups

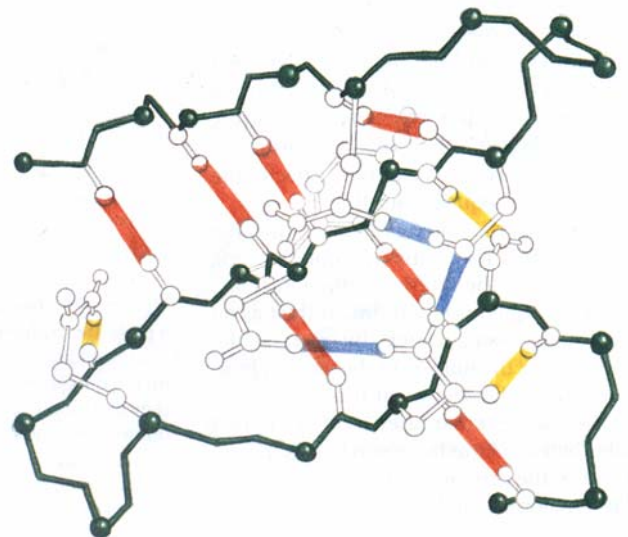
van der Waals forces: equilibrium of positive and negative repulsion of atoms

Hydrogen bonds: a hydrogen atom shared between two electronegative atoms



- H bonds between peptide bonds
- H bonds between a side chain and a peptide bond
- H bonds between two side chains

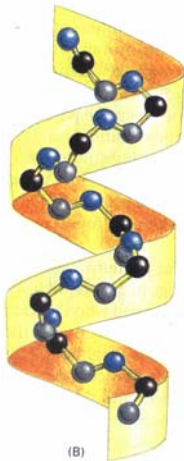
LYSOZYME



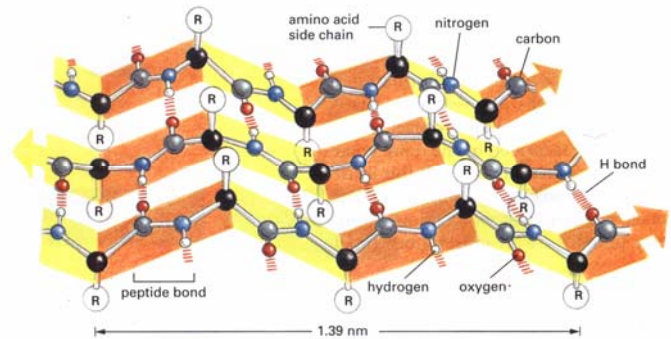
PROTEIN FOLDING

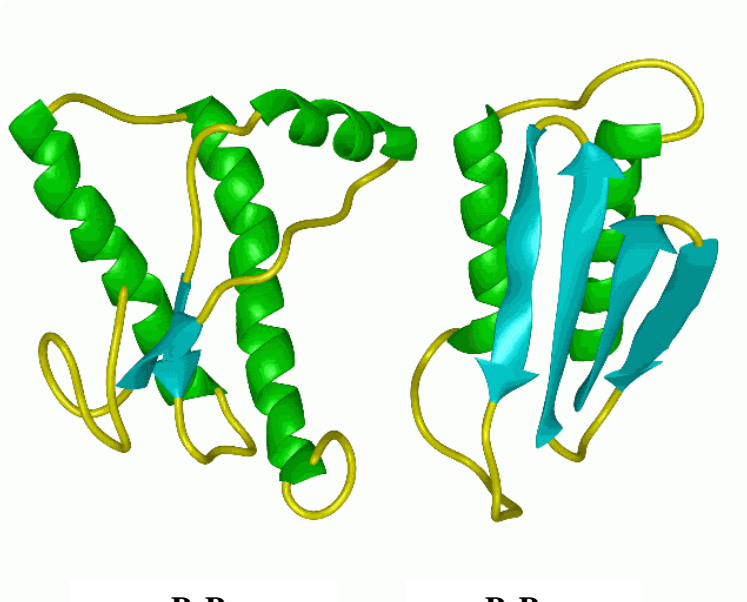
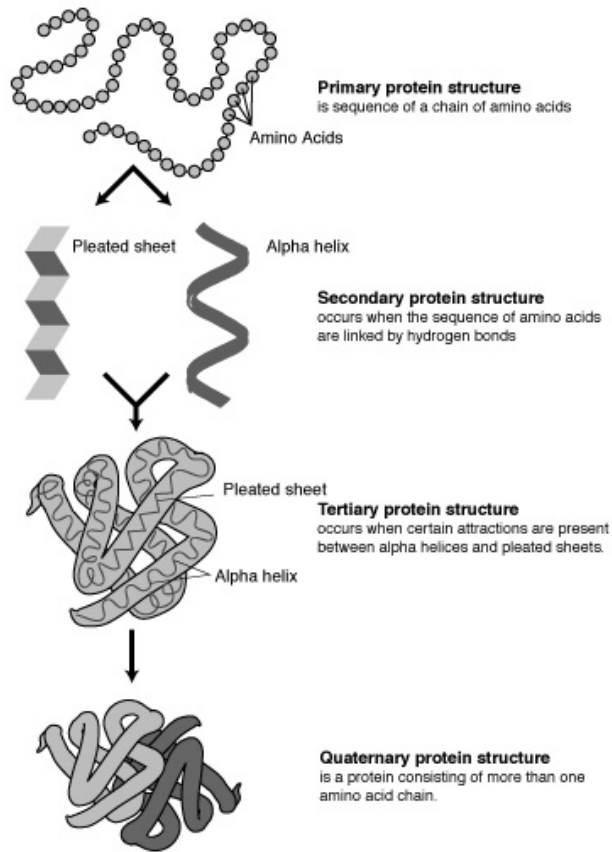
- Most protein molecules fold up spontaneously into precise conformations determined by the amino acid sequence
- More than 100 types of protein folds have been discovered by x-ray diffraction analysis
- Two patterns are particularly common since they involve H bonds between the peptide bonds:

α -HELIX



β -SHEET





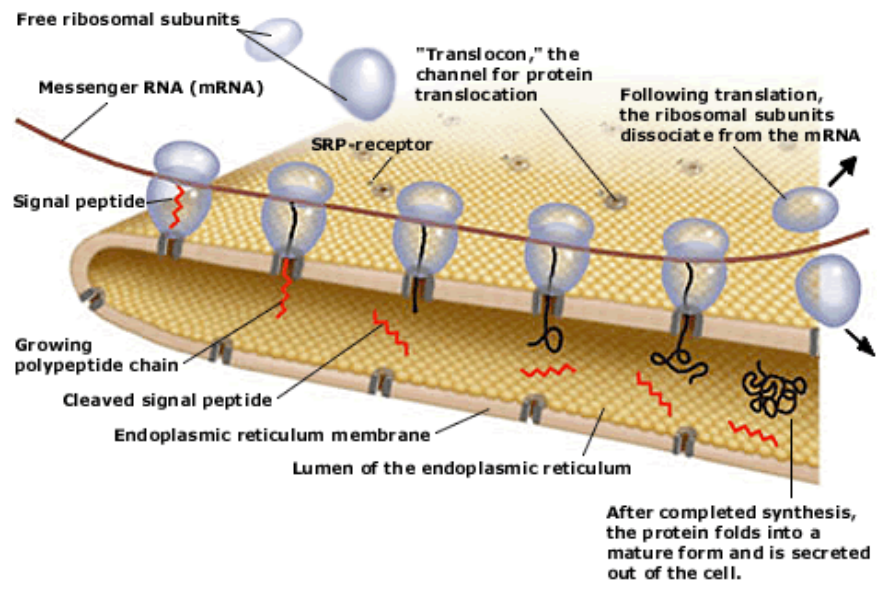
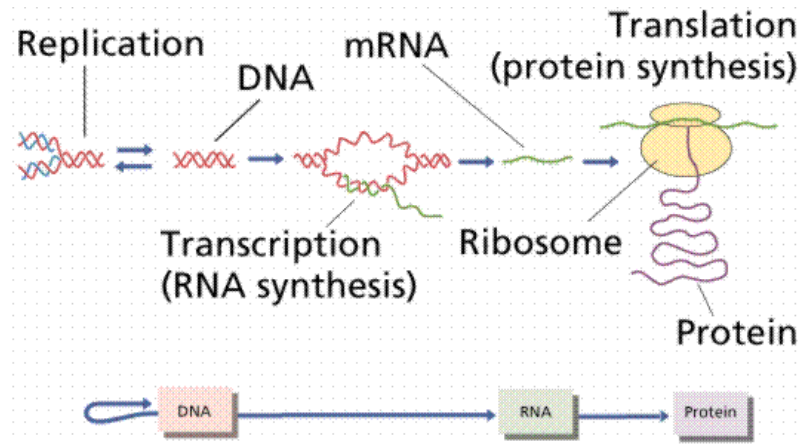
PrPc

43% α -helix
3% β -sheet

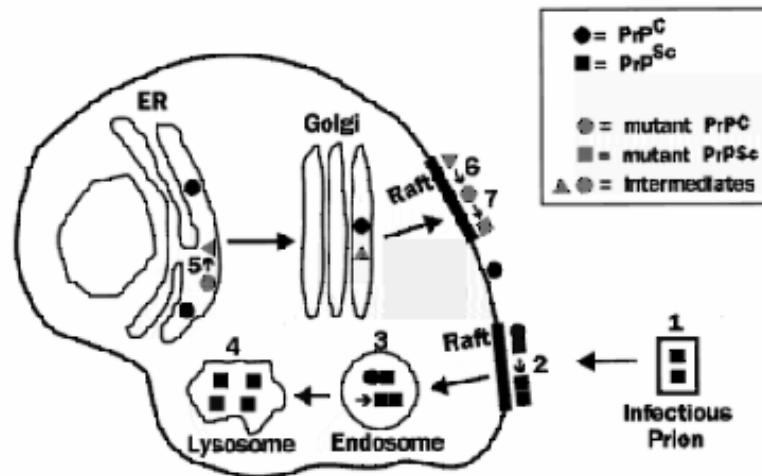
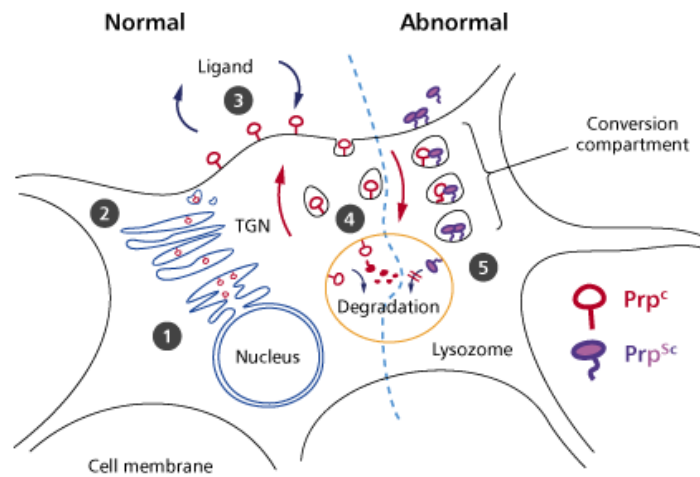
PrPsc

30% α -helix
43% β -sheet

IV. PrP Synthesis



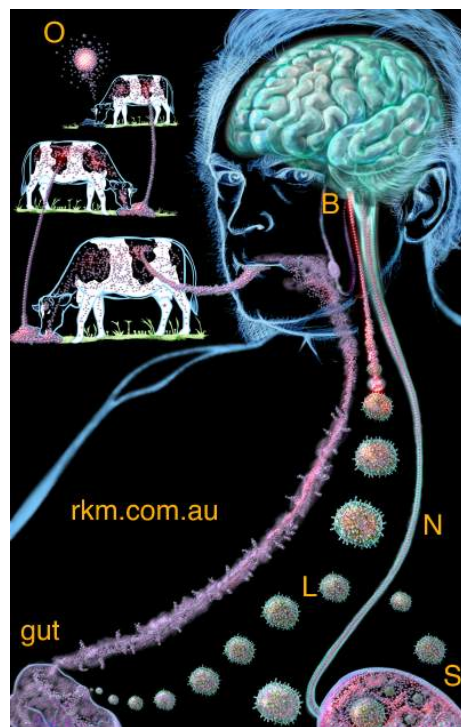
V. PrP Metabolism

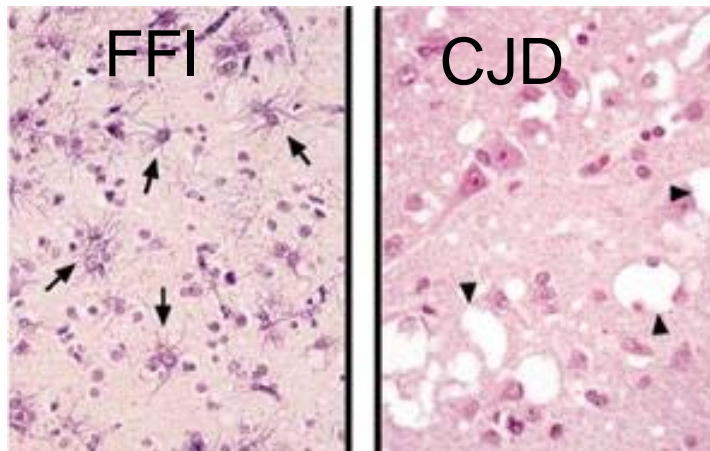
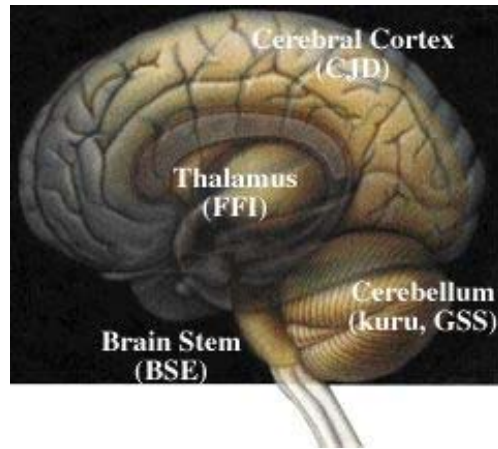


In infectious prion diseases, PrP^{Sc} binds to the normal PrP^C on the surface, converts it to PrP^{Sc}, and the abnormal PrP^{Sc} is delivered to lysosomes. These abnormal proteins are stable, accumulate, and ultimately destroy the cell.

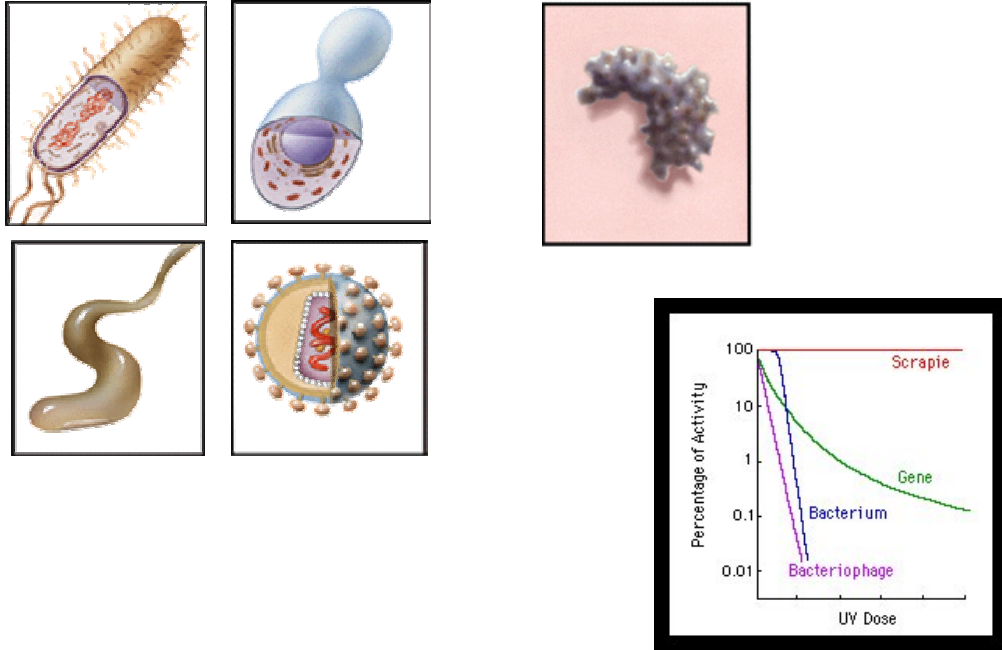
How can you get Mad Cow disease by eating beef?

- Humans acquire prions by eating contaminated meat.
- In the human gut (bottom left) prions may be taken up by lymphoid tissues (Peyer's patches).
- The prions are then ferried around the body in lymphocytes "L".
- Prion replication is thought to occur in lymphoid tissues, especially the spleen "S".
- Nerves "N" that supply the lymphoid tissues then allow prions to travel back up them to the brain.





Prions – novel infectious agents differing from all other known pathogenic agents



Nobel Prize Winners Associated with the Prion Story:

- Linus Pauling – discoverer of the α -helix (Chemistry, 1954)
- Carlton Gajdusek – discoverer that Kuru is spread from human to human through eating of human brains (Physiology or Medicine, 1976)
- Eric Kandel – has proposed that self-perpetuation of normal prions may form basis for information storage – i.e. memory (Physiology or Medicine, 2000)