

# Collagen

7.88J Protein Folding

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## PDB Acknowledgements

The **Protein Data Bank** (PDB - <http://www.pdb.org/>) is the single worldwide repository for the processing and distribution of 3-D biological macromolecular structure data.

Berman, H. M., J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, and P. E. Bourne. "The Protein Data Bank." *Nucleic Acids Research* 28 (2000): 235-242.

(PDB Advisory Notice on using materials available in the archive: [http://www.pdb.org/pdb/static.do?p=general\\_information/about\\_pdb/pdb\\_advisory.html](http://www.pdb.org/pdb/static.do?p=general_information/about_pdb/pdb_advisory.html))

## PDB molecules and citations used in the "Collagen" Lecture Notes for 7.88J - Protein Folding

**PDB ID:** 1CGD

**JRNL reference:** Bella, J., M. Eaton, B. Brodsky, and H. M. Berman. "Crystal and molecular structure of a collagen-like peptide at 1.9Å resolution." *Science* 266 (October 7, 1994):75-8.

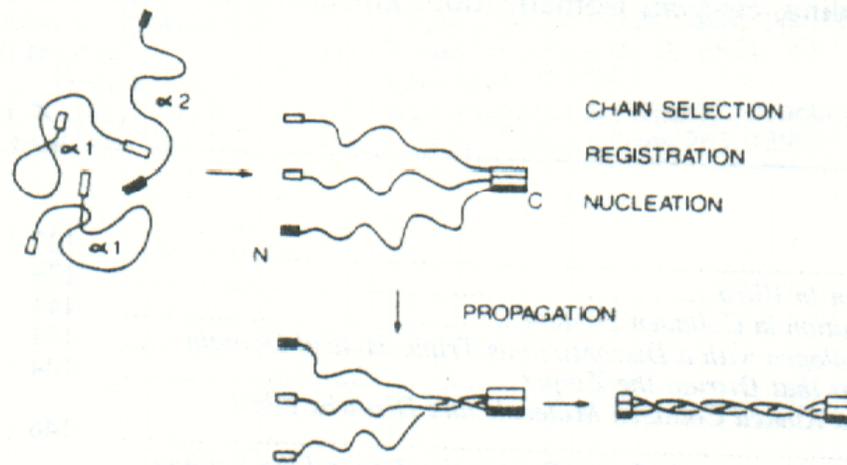
**Pages:** 16-17 ("Solved Structure – 1CGD")

# *Collagen*

- ❖ ~20% of all proteins in human body are collagen
- ❖ Extracellular matrix protein family
  - At least 21 different types of collagen
- ❖ Structural protein
  - Bone, tendon, cartilage, cornea, etc.
- ❖ Mutations in collagen responsible for
  - Osteogenesis imperfecta
  - Hereditary aortic aneurysm

# Pathway

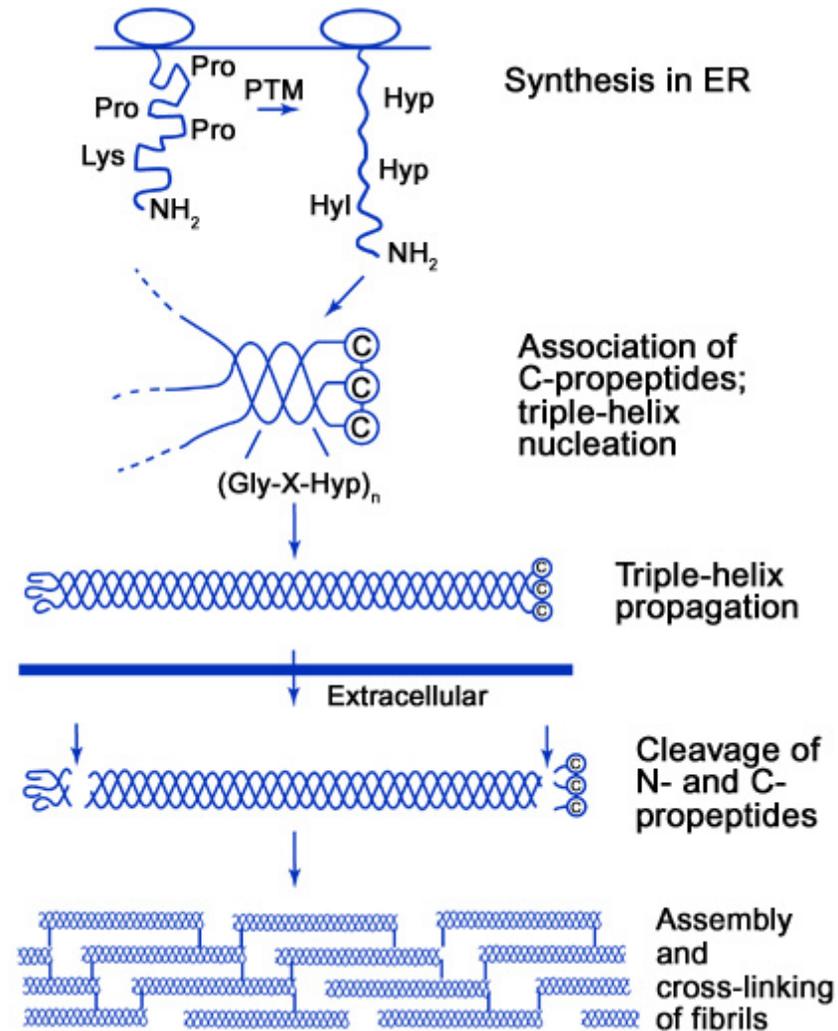
- ❖ Synthesized as longer precursors (procollagens) with globular extensions at both ends (propeptides)
- ❖ Propeptides form inter-chain disulfide bonds that align the chains prior to triple helix formation



Engel, J., and D. Prockop. "The zipper-like folding of collagen triple helices and the effects of mutations that disrupt the zipper", *Annu. Rev. Biophys. Biophys. Chem* 1991, **20**: 137-52.

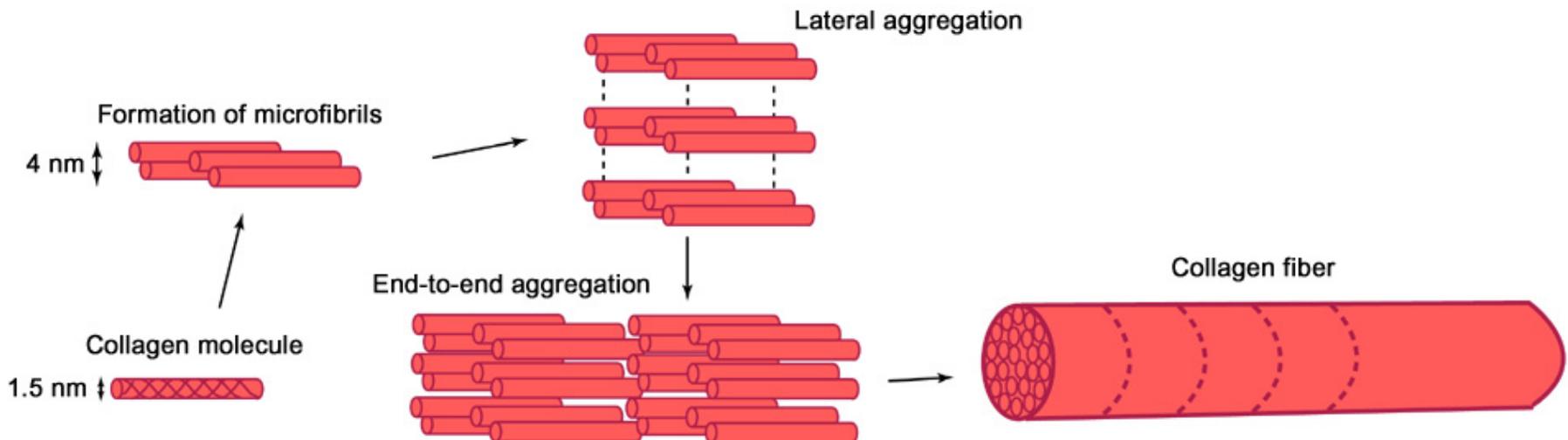
# Pathway

- ❖ Following exocytosis:
  - Propeptides cleaved off by extracellular enzymes
  - Triple-helix molecules polymerize into fibrils 50-200 nm long
  - Fibrils pack into fibers (stronger than steel of same size)
- ❖ When denatured, forms gelatin (missing propeptides lead to unordered cross-linking)



# Higher-Order Structure

- ❖ Levels: molecule => microfibril => fiber
- ❖ “Stagger” of molecules gives rise to “banding” observed in fiber

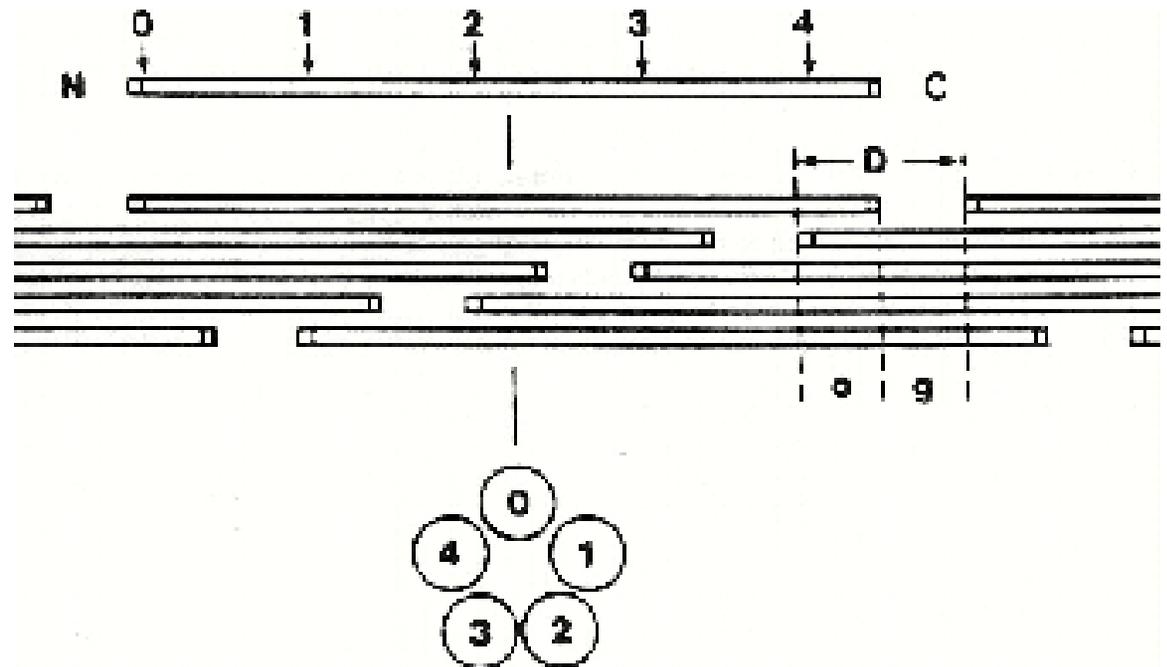


# Packing of Collagen Molecules

❖ 5 molecules/microfibril

❖  $D/2$  offset

❖ Gaps: locus of mineral deposition



# Molecular Structure

- ❖ Triple helix
  - Rod-like bundle
  - Right-handed supercoil: 100A repeat
  - Length: 2800 A (~1000 aa)
- ❖ Each chain is extended, left-handed helix
  - 3.3 residues per turn (3.6 in  $\alpha$ -helix)
  - 2.9 A rise per residue (1.5 in  $\alpha$ -helix)
  - 9.6 A rise per turn (5.4 in  $\alpha$ -helix)
- ❖ Helices do not form in isolation
- ❖ Chains are staggered by one residue



# Sequence

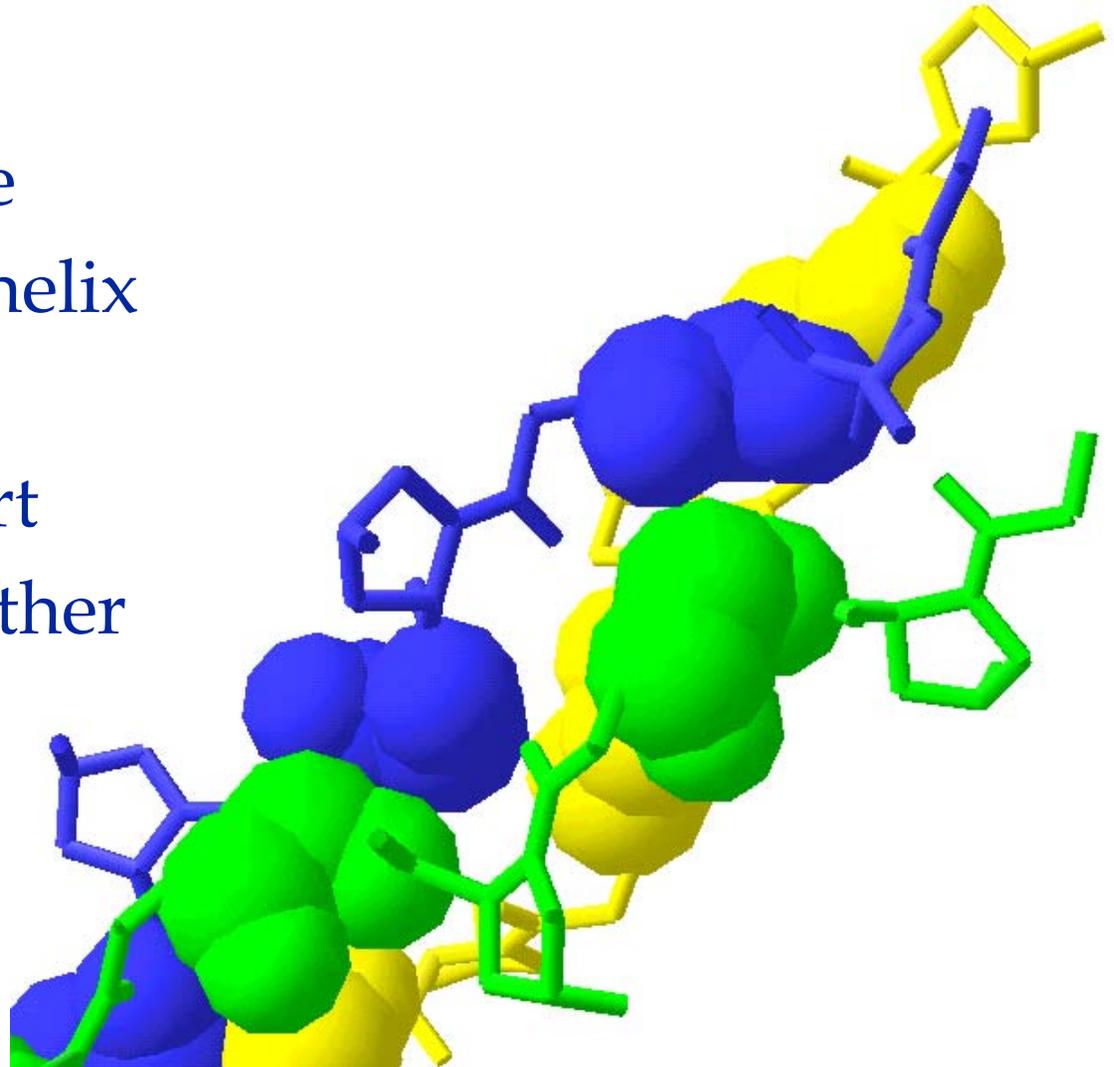
- ❖ Glycine at every third residue
  - (Gly -X - Y)<sub>n</sub>
  - X often proline (Pro)
  - Y often hydroxyproline (Hyp)
    - ◆ In collagen Pro & Hyp constitute about 20% (40% ?) of all residues
- ❖ Glycine at center of triple helix
- ❖ Pro & Hyp side-chains fully exposed to solvent

The corresponding figure that illustrates these points may be found in:

Introduction to protein structure / Carl Branden, John Tooze. New York : Garland Pub., 1991.

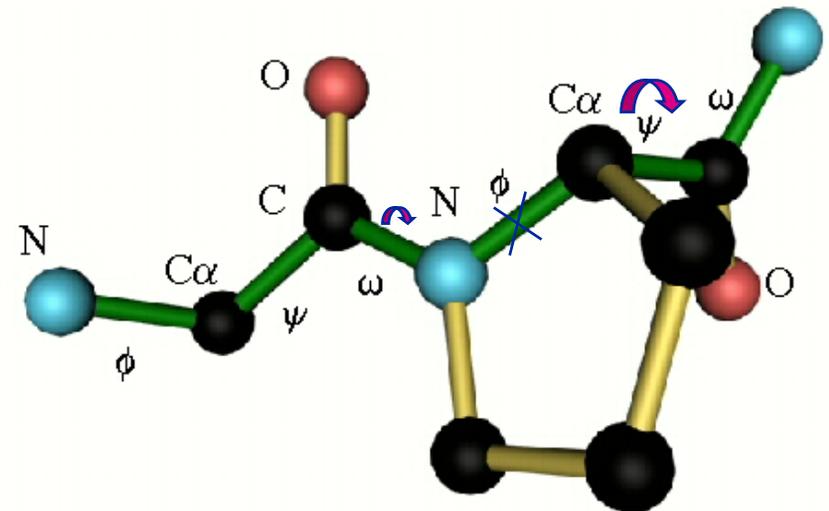
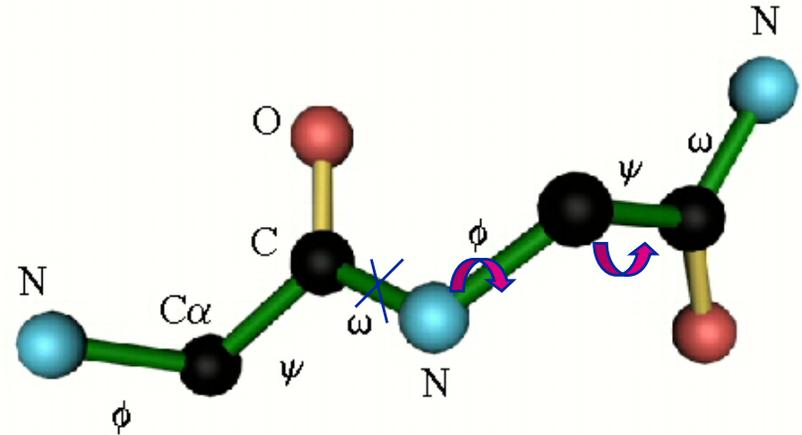
# *Glycines*

- ❖ On the inside of the triple helix
- ❖ Staggered wrt to Gly's on other chains



# Proline (Pro)

- ❖ Increases “stiffness” of chain
  - Eliminates one rotational degree of freedom ( $\psi$ -angle)
  - Slightly increases another ( $\omega$ -angle)
  
- ❖ Promotes an extended (not globular) conformation

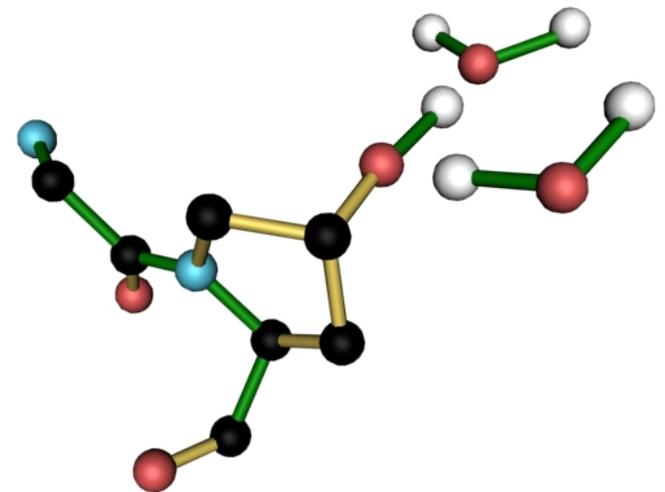
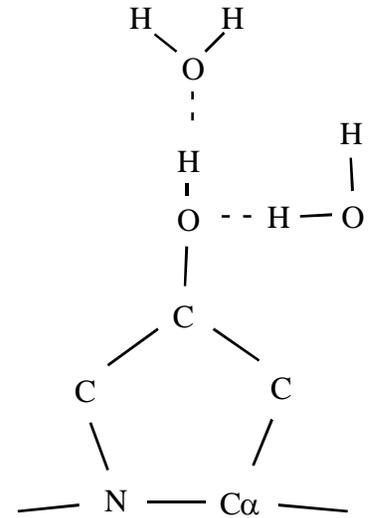


# *Key Features of Collagen*

- ❖ High content of Hyp residues
- ❖ Unique interaction with water

# Hydroxyproline (Hyp)

- ❖ Produced from Pro by post-translational modification
- ❖ Is unusual, always found in triple helix domains in animal proteins, rarely in other proteins
- ❖ Provides binding sites for water molecules
  - Important to stability



# *Hydrogen Bonding Pattern*

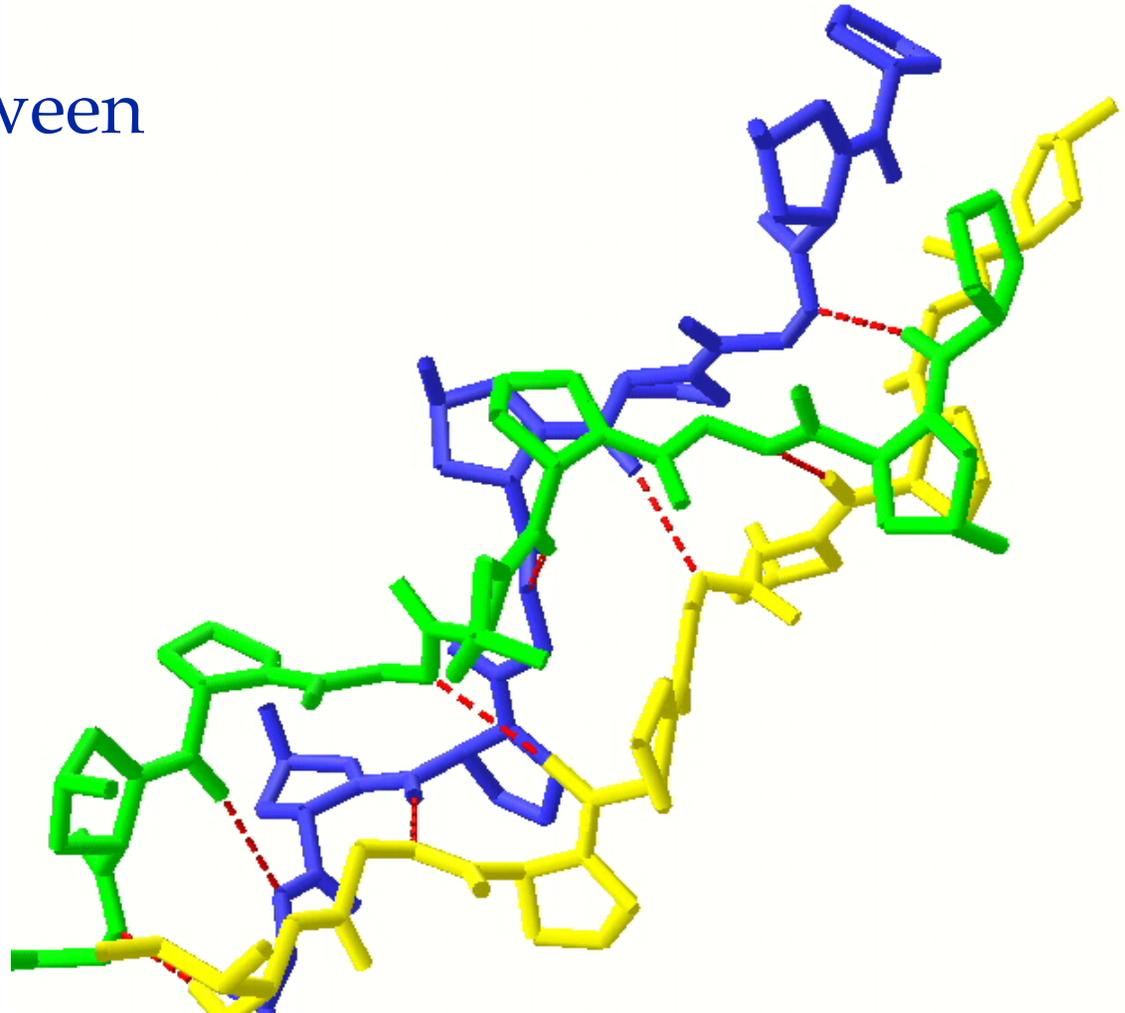
- ❖ H-bonds between
  - Gly N - H
  - Pro C=O

The corresponding figure that illustrates these points may be found in:

Introduction to protein structure / Carl Branden, John Tooze. New York : Garland Pub., 1991.

# 3D Hydrogen Bonding Pattern

- ❖ H-bonds between
  - Gly N - H
  - Pro C=O



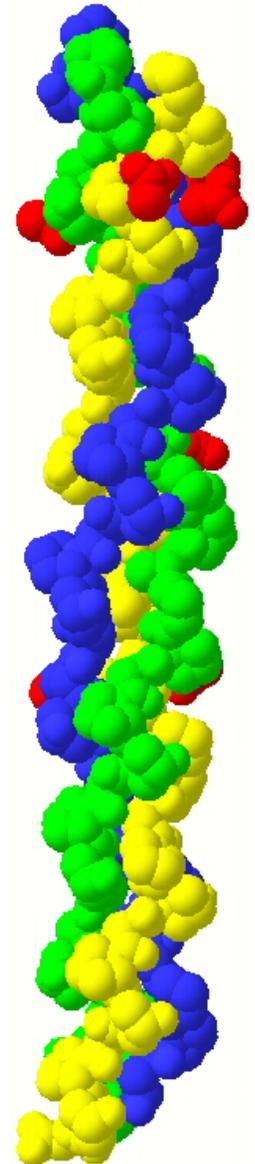
Principles of icosahedral virus structure published by Caspar and Klug, Cold Spring Harbor Laboratory Press, Symp. Quant. Biol. vol 27, 1962.

# *Solved Structure -1CGD*

- ❖ Gly → Ala  
(single aa substitution, all 3 chains)
- ❖ Formed crystals instead of fibrils
- ❖ 3 chains – triple helix
- ❖ 30 residues (not 1000 !)
- ❖ T<sub>m</sub>: 62 °C → 29 °C !!!

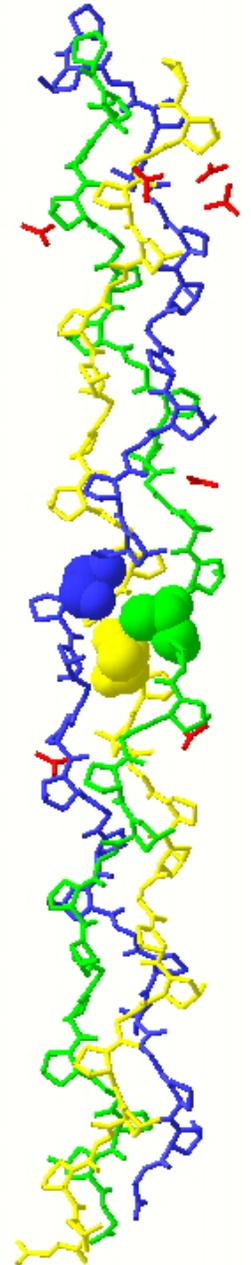
Bella, J., M. Eaton, B. Brodsky, and H. M. Berman. “Crystal and molecular structure of a collagen-like peptide at 1.9Å resolution.” *Science* **266** (October 7, 1994) :75-81.

Principles of icosahedral virus structure published by Caspar and Klug, Cold Spring Harbor Laboratory Press, Symp. Quant. Biol. vol 27, 1962.



# Solved Structure – 1CGD

|    | Chain 1 |     |            |    | Chain 2 |     |            |    | Chain 3 |     |            |  |
|----|---------|-----|------------|----|---------|-----|------------|----|---------|-----|------------|--|
| 1  | Pro     | Hyp | Gly        | 31 | Pro     | Hyp | Gly        | 61 | Pro     | Hyp | Gly        |  |
| 4  | Pro     | Hyp | Gly        | 34 | Pro     | Hyp | Gly        | 64 | Pro     | Hyp | Gly        |  |
| 7  | Pro     | Hyp | Gly        | 37 | Pro     | Hyp | Gly        | 67 | Pro     | Hyp | Gly        |  |
| 10 | Pro     | Hyp | Gly        | 40 | Pro     | Hyp | Gly        | 70 | Pro     | Hyp | Gly        |  |
| 13 | Pro     | Hyp | <b>Ala</b> | 43 | Pro     | Hyp | <b>Ala</b> | 73 | Pro     | Hyp | <b>Ala</b> |  |
| 16 | Pro     | Hyp | Gly        | 46 | Pro     | Hyp | Gly        | 76 | Pro     | Hyp | Gly        |  |
| 19 | Pro     | Hyp | Gly        | 49 | Pro     | Hyp | Gly        | 79 | Pro     | Hyp | Gly        |  |
| 22 | Pro     | Hyp | Gly        | 52 | Pro     | Hyp | Gly        | 82 | Pro     | Hyp | Gly        |  |
| 25 | Pro     | Hyp | Gly        | 55 | Pro     | Hyp | Gly        | 85 | Pro     | Hyp | Gly        |  |
| 28 | Pro     | Hyp | Gly        | 58 | Pro     | Hyp | Gly        | 88 | Pro     | Hyp | Gly        |  |



Principles of icosahedral virus structure published by Caspar and Klug, Cold Spring Harbor Laboratory Press, Symp. Quant. Biol. vol 27, 1962.

# *Hydrogen Bonding Pattern - 1CGD*

- ❖ At Gly → Ala substitution site
  - triple helix “unwinds” slightly
  - H-bonds broken
  - 4 Water molecules establish bridges between the groups with the broken H-bonds

The corresponding figure that illustrates these points may be found in:

Introduction to protein structure / Carl Branden, John Tooze. New York : Garland Pub., 1991.

# *Types of Water Bridges*

Table 2 may be found on page 896 of:

Bella, J., B. Brodsky, and H. M. Berman. "Hydration structure of a collagen peptide." *Structure* **3** (September 15, 1995): 893-906.

# *Location of Water Bridges*

Figure 2 may be found on page 897 of:

Bella, J., B. Brodsky, and H. M. Berman. “Hydration structure of a collagen peptide.” *Structure* **3** (September 15, 1995): 893-906.

# *Interchain & Intrachain Water Bridges*

- ❖ A: interchain,  
1 water molecule
- ❖ B: interchain,  
2 water molecules
- ❖ C: Intrachain,  
3 water molecules
- ❖ D: Intrachain,  
network of water

Figures may be found in:

Bella, J., M. Eaton, B. Brodsky, and H. M. Berman. "Crystal and molecular structure of a collagen-like peptide at 1.9Å resolution." *Science* **266** (October 7, 1994): 75-81.

# *Water Bridges*

Images may be found in:

Bella, J., B. Brodsky, and H. M. Berman. “Hydration structure of a collagen peptide.”  
*Structure* **3** (September 15, 1995): 893-906.

# *Hydration Shell*

Image may be found in:

Bella, J., Brodsky, B. and Berman, H.M., “Hydration structure of a collagen peptide”, *Structure*, **3**:893-906, September 15, 1995.

# *Packing of Triple Helices*

- ❖ Hexameric

- ❖ Anti-parallel

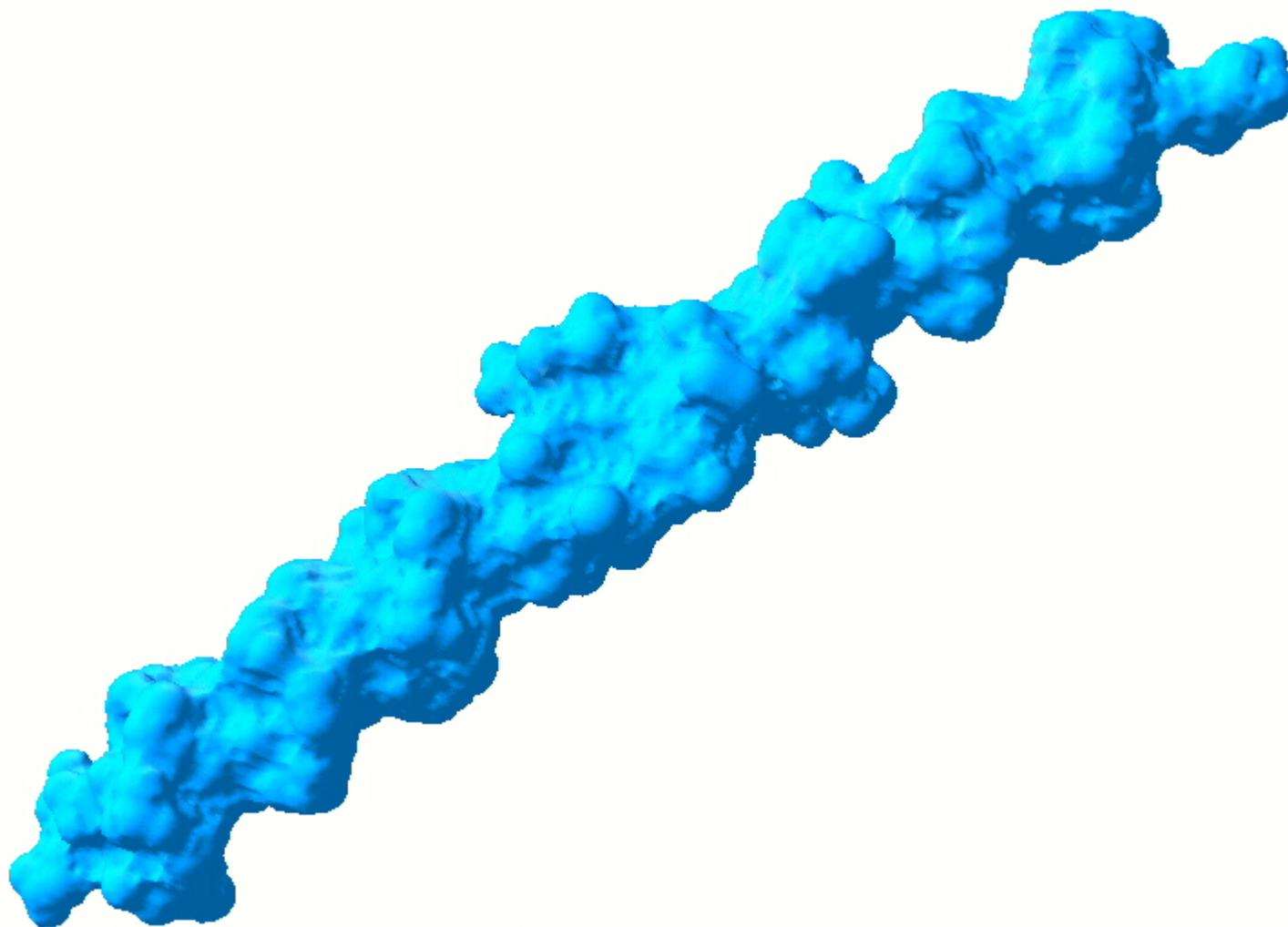
Corresponding image may be found in:

Bella, J., M. Eaton, B. Brodsky, and H. M. Berman. "Crystal and molecular structure of a collagen-like peptide at 1.9A resolution." *Science* **266** (October 7, 1994): 75-81.

- ❖ Separation distance  
between axes (14 Å)  
too large for direct contact

- ❖ Water matrix

# *Molecular Surface*



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7.88J / 5.48J / 10.543J Protein Folding and Human Disease  
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