As a review, we have already seen amino acids, which are the building blocks of proteins. Amino acids link together to form the functionalized backbone of a protein. The order of the amino acids determines the primary structure of the protein. Sections of the protein assume folding patterns called secondary structure. Examples of secondary structure include the α-helix and β-sheet.

Within a complete protein are several different secondary structures. The overall three-dimensional arrangement of the secondary structures in a protein defines the shape, or tertiary structure, of the protein. An example of a complete protein is shown below. The protein is the enzyme adenosine deaminase (PDB: 3EWC).

Within the different secondary structures of 3EWC are pockets and cavities. These cavities create opportunities for smaller molecules, including drugs, to interact tightly with the protein and affect the protein's function. Remember that proteins are frequent targets for drugs. In the very middle of the structure of 3EWC is a bound molecule, visible in the center of the structure. This bound molecule blocks the function of adenosine deaminase and inhibits its function.

Since tertiary structure describes the three-dimensional shape of a protein, it may not be obvious that proteins can have another level of structure. The final level, quaternary structure, accounts for the fact that many proteins aggregate with other proteins in order to become fully functional. The relative interaction and arrangement of the different proteins within a multi-protein complex is quaternary structure.

An example of quaternary structure can be seen in alcohol dehydrogenase (PDB: 1AGN). Upon first glance, the structure of alcohol dehydrogenase appears unremarkable, but the protein is actually a dimer of two identical proteins (a homodimer). The Protein Data Bank
visualization software allows one to color the two proteins differently by selecting the Subunit button. The left image below is the original view of the dimer while the right image reflects different coloring for each protein subunit – one red and the other green-gray.

Protein structures are determined primarily through the interpretation of X-ray crystallographic data. X-ray data is obtained by passing X-rays through a crystallized protein. The X-rays are scattered by the electrons in the protein and create a diffraction pattern. The pattern can ultimately be interpreted to discover the structure of the protein.

Interpreting X-ray crystallographic data is not easy. The diffraction data is converted to an electron density map, which shows the location of different atoms within the protein. The clarity of the atom positions depends on the quality of the density map. A high quality map is said to have higher resolution. Resolution is listed as a number with angstrom units (Å). A smaller number denotes higher resolution. Crystal structures with a resolution of 2.0 Å or less are considered to be high resolution structures.

Examples of electron density maps of the same structure at different resolutions are shown below. Each atom is fairly distinct up to a resolution of 2.0 Å. At 3.0 Å and above, structural details become much less clear, and accurately assigning the structure of the protein becomes more difficult. (Images of electron density maps used with permission of Paul Emsley, Cambridge University.)
Although correctly assigning a structure to a protein can be a challenge, knowing the structure of a protein target is invaluable for medicinal chemists. Understanding the folding of a protein and its potential binding sites can guide the design of drugs that will effectively target the protein.