Medicinal Chemistry & Drug Discovery
Section 2.1.1 – Targets & Crystals

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Learning goals

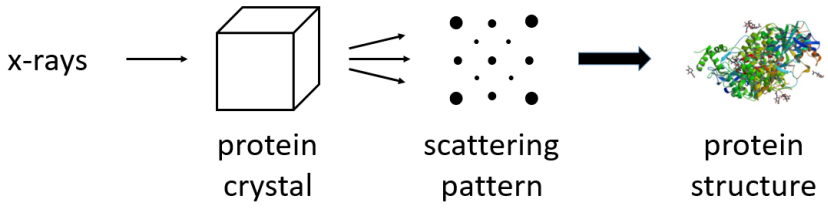
- summarize x-ray crystallography
- use the Protein Data Bank to search protein structures

Vocabulary

- x-ray crystallography
- scattering pattern
- Protein Data Bank

Drugs interfere with proteins – enzymes or receptors – in biological pathways. Proteins are large biopolymers made from the 20 natural amino acids. Proteins, especially the functional parts of a protein, have a well-defined structure. Because a protein has a specific shape, drugs that act on the protein need a specific shape, a shape that complements the protein's shape. Therefore, if we can determine the shape of a protein (our target), we can better understand the ideal shape and structure of a possible drug. This idea is very important for target-based drug discovery. There are many methods for determining a protein's structure, and the most common is likely **x-ray crystallography**.

X-ray crystallography is a technique that requires purified protein crystals. Indeed, a limitation of x-ray crystallography is not all proteins form crystals appropriate for analysis. Regardless, very many drug targets work quite well. The protein sample is placed in the path of an x-ray beam. The x-rays pass through the sample and are scattered by the electrons in the protein. The scattering pattern can be used to determine the three-dimensional structure of the protein.



The Research Collaboratory for Structural Bioinformatics **Protein Data Bank**, the RCSB PDB or just **PDB**, is a repository of protein structures, mostly x-ray. Each protein has a 4-character code. For example, the code for a structure of lysozyme is 3LZT. Any protein structure that has been reported in the literature will likely be included in the PDB. Protein structural information is extremely useful for finding molecules that will affect a protein, a drug target.