MACROMOLECULAR CRYSTALLOGRAPHY AND DRUG DESIGN

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Knowledge of three-dimensional structure of proteins provides a basis for rational design of novel therapeutic agents. Since the specific binding of a potential drug to the macromolecular target depends on an exact match of the interacting surfaces and of the electrostatic potentials, these feature have to be known in great detail in order for the design process to be successful. Therefore, the structure of the protein has to be determined at the highest possible resolution. X-ray crystallography is the method of choice to achieve this, and the resolution can usually be further improved by application of synchrotron radiation. In addition, both the wavelength tunability and the intensity of synchrotron radiation offer other advantages for protein crystallography, which will be discussed.

As examples for the use of synchrotron radiation and macromolecular crystallography in the drug discovery process our efforts to design novel inhibitors of HIV protease will be discussed. In addition, structural studies on bacterial elongation factors, which are potential targets for novel antibiotics, will be presented We determined some of the relevant structures by using diffraction data collected at the XRD beamline of Elettra.

Knowledge of the three-dimensional structure of proteins is also required when they are subjected to alterations by protein engineering. In the protein engineering cycle, the protein is modified by site-directed mutagenesis and the resulting variant is characterized chemically , structurally, and, if appropriate, pharmaceutically. As an example of this approach, our successful design of insulins with prolonged activity will be described. Again, this project has benefited a lot from the usage of synchrotron radiation, the first of these modified insulins is now entering phase II clinical trials.