## Drug Designing

Drug designing is another area of biotechnology research, which is being actively pursued. Several approaches are being used for this purpose and some of them will be briefly described in this section to give an elementary idea about this important and fascinating area of research. However, all these approaches are based on an exercise where we first acquire knowledge

about active site that needs to be attacked by the drug and then utilize this information to design a drug that will not only bind to the chosen site but will also possess all other properties required of a drug. Therefore, drug designing will involve atleast three steps: (i) Knowledge will have to be acquired about the site structure, upto the level of atomic resolutions, so that the accessible surface, which needs to be attacked, is known; (ii) A ligand will have to be designed that will fit the binding site; for this purpose the steric outline of the ligand should be complementary to the site and, therefore, these complementary features will have to be built in the ligand at appropriate positions. This should result in the maximum interactions between atoms of the ligand and the site, and is mainly achieved with the help of computer-aided methods. (iii) Once the ligand is designed to fit the binding site, ligand needs to be modified to have pharmacological and toxicological properties, while maintaining its affinity for the binding site. This and the above step (ii) will require three dimensional constructions. Computers have provided methods which will allow automated site-directed drug designing.

**Drug designing by blocking enzyme activity**

Since most drugs act by modifying or blocking the activity of an enzyme, a deeper understanding of suitably chosen target enzymes should lead to major advances in rational drug designing. Following two examples will illustrate the utility of drug designing as an important area of biotechnology research.

**Trimethoprim (TMP).** This clinically important antimicrobial drug provides an important example to demonstrate drug designing. This drug inhibits the enzyme **dihydrofolate reductase (dHFR)** in bacteria and is frequently used to treat urinary tract infections, but in high concentrations it attacks even human dHFR, thus becoming harmful (toxic), if used by the patient. In view of this, the structures of different dHFRs have been compared, so that TMP with greater specificity for bacterial enzyme may be designed. Since TMP shows flexibility in its three dimensional structure in association with enzyme dHFR, efforts have been made to synthesize TMP, which will have a rigid three dimensional structure in association with bacterial enzyme dHFR, so that it may not be able to attack human dHFR.

**Inhibitor of renin.** Inhibitors of the enzyme *'renin'* are also being actively modelled. The enzyme catalyses the first in a series of reactions that lead to elevated blood pressure. Models of renin have been prepared on the basis of known structures of similar other proteins like aspartic proteinase and pepsin. This led to the designing of nonpeptide inhibitors that mimic intermediate product in the reaction of renin with its substate, so that native renin will not function. These inhibitors may be useful for treating hypertensions.

**Drug designing through blocking hormone receptors**

Drugs have also been produced through a study of receptor molecules that are responsible for the disease, followed by identification of chemicals that will block such receptors. Utilizing this strategy, atleast two drugs were developed by **Dr. James Black** (of UK), who shared with **Drs. G. Elion** and **G. Hitchings** (of USA), the 1988 Nobel Prize for Physiology and Medicine. These two medicines are briefly described in the following text.

**Propranolol.** This drug is widely used for treating heart disease and high blood pressure. Heart diseases result due to the presence (in excess) of hormones '**norepinephrine**' and '**epinephrine**', due to their role in contraction and relaxation of cardiac muscles. These hormones act through two receptors $\alpha$ and $\beta$. The drug '**propranolol**' is a '**blocker**' and relaxes the heart muscles. It has been shown that the drug not only cures the heart diseases but reduces the death rate of heart disease survivors by 25%. The drug is also used for treatments of '**angina pectoris**' and '**high blood pressure**'. Obviously by blocking the receptor '$\beta$', the drug inhibits the activity of hormones which act through a receptor molecule.

**Cimetidine.** This drug is antiulcer and is used for treatment of ulcers. Ulcers result from acid production due to histamine release in the stomach and therefore attempts were made to treat these ulcers through antihistamines that were earlier used to combat respiratory allergies. These antihistamines proved ineffective for ulcer treatment and **James Black** attributed this to use of receptors that were different in stomach lining and respiratory tract. He was able to characterize histamine receptor of stomach lining and called it **$H_2$ receptor**, which is blocked by the drug '**cimetidine**', thus leading to healing of ulcers by preventing acid production due to nonavailability of histamine. Therefore 'cimetidine' marked the beginning of a new era in ulcer treatment, since earlier ulcers, that did not heal, had to be removed surgically.

**Drug designing through inhibition of nucleic acid synthesis**

Through their detailed studies of antimetabolites or inhibitors (they block key enzymes) of DNA synthesis, **G. Elison** and **G. Hitchings** (both of USA) were able to develop drugs for treating '**cancer**', '**gout**' ,'**malaria**' and viral infections such as '**herpes**'. They found that there are drugs like '**6-mercaptopurine**' and '**thioguanine**' which inhibit DNA synthesis leading to inhibition of cell division and therefore are effective in cancer chemotherapy. Another drug developed by them is '**azathioprine**' used to fight transplant rejection, or diseases like rhematoid arthritis, in both cases the drug acting through attacking the immune system (immunosuppressive effect).

Elion and Hitchings also studied the differences in nucleic acid synthesis of prokaryotes and human cells, which led to the development of durgs like '**pyramethamine**' for malaria, '**trimethoprim**' for bacterial