Drug discovery: Past and present

Drug discovery in earlier days was made by random screening of higher plants. Crude plant drugs like opium, senna, belladonna, reserpine, ephedrine, etc., were in use for centuries. With the serendipitous discovery of penicillin came the screening of microorganisms, resulting in a large number of antibiotics from bacterial and fungal sources. Prototypes of these antibiotics enabled medicinal chemists to modify them and yield better antibacterials with improved therapeutic profiles.

Thousands of new organic compounds are synthesized and subjected to pharmacological screening. This process of random screening, though inefficient, has led to the identification of new lead compounds. Optimization of the lead compounds has resulted in good clinical drug candidates. Sulfanilamide testifies this, as many sulfonamides have resulted in drugs ranging from antibacterial through anti-malarial, anti-diabetic, diuretic, and sulfas with activity for typhoid fevers. Automated high-throughput screening systems have increased the efficiency of random screening. Combinatorial chemistry has accelerated synthetic methods and facilitated synthesis of a huge library of compounds which is subjected to high throughput screening for deciphering the biological activity of the compounds. Although synthesis was fast, this technique has not produced compounds with the status as drugs.

Rational design of drugs evolved from observations made on correlating certain physicochemical properties of the organic molecules with biological potency. Optimization of the compounds by incorporating the favorable substituent resulted in better drug-like molecules. X-ray crystallography and NMR techniques have enabled to provide information of the structure of enzymes and other drug receptors. Many drugs like ACE inhibitors have come to clinical practice from such information. Thus, it was realized that inhibition of strategic enzymes would result in stopping the proliferation of bacteria, viruses, and even cancer cells.

The field of biotechnology has revolutionized the drug discovery process. Recombinant DNA-driven drug discovery process is beginning to add new avenues for some old drugs. In its infancy, genetic engineering was considered useful only for the production of therapeutic proteins. Insulin, for example, previously prepared by isolation of pancreatic tissue of bovine or porcine species, can now be prepared identical to human insulin by biotechnology. Companies like Genentech and Biogen were founded solely with this objective. However, proteins do not make ideal drugs, being difficult to administer, rapidly cleared, and potentially immunogenic. Despite these disadvantages, a rapidly increasing number of "biopharmaceuticals" including recombinant proteins, therapeutic monoclonal antibodies, and even antisense oligonucleosides have been approved for indications ranging from metastatic breast cancer (Herceptin) to rheumatoid arthritis (Remicade, Enbrel).

Hence, these developments reflect the revolution that has occurred in the drug discovery process.

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