Drug Discovery and Synthesis

Target Identification

A drug target is a specific macromolecule, or biological system, which the drug will interact with. Most research is carried out on diseases which afflict “first world” countries and avoid those only affects a small subset of the population (e.g. cancer, cardiovascular diseases, depression, diabetes, flu, migraine, obesity). Pharmaceutical companies avoid products that would be consumed by individuals of lower economic status (i.e. a disease which only affects third world countries).

In the past, many medicines (and lead compounds) were isolated from plant sources. Since plants did not evolve with human beings in mind, the fact that they posses chemicals which results in effects on humans is incidental. Sometimes this can happen through incidental observation.

Having the genetic code for the production of an enzyme or a receptor may enable us to over-express that protein and determine its structure and biological function. If it is deemed important to the disease process, inhibitors (of enzymes), or antagonists or agonists of the receptors can be prepared through a process called rational drug design. In a process called “combinatorial chemistry” large numbers of compounds can be prepared at one time. Selectivity is important: targeting a bacterial enzyme, which is not present in mammals, or which has significant structural differences from the corresponding enzyme in mammals.

Resource Identification

Potential resources for novel drugs:

* Natural products (plants, microbes, the marine world, and animals)
* Screening synthetic banks

Pharmaceutical companies have prepared thousands of compounds stored (in the freezer), cataloged and screened on new targets as these new targets are identified

* Computer-Assisted Drug Design

If one knows the precise molecular structure of the target (enzyme or receptor), then one can use a computer to design a perfectly-fitting ligand.

* Serendipity: a chance occurrence

Ex. Penicillin discoveryanddevelopment of Viagra to treat erectile dysfunction

Finding a hit compound

In vitro (cell-based) laboratory assays are developed to measure the effect of potential therapeutics. Using the in vitro laboratory assay, 5,000-10,000 new and previously developed compounds are tested for biological activity. On average, 250 of the compounds tested possess the desired activity and are now designated as “hits” A hit compound refers to primary active compound(s), with non-promiscuous binding behavior, exceeding a certain threshold value in a given assay(s). The ‘active’ is followed up with an identity and purity evaluation, an authentic sample is then obtained or re-synthesized and activity confirmed in a multi-point activity determination to establish the validity of the hit (validated hit).

Finding the lead compound

A handful of the most promising hits are chosen for chemical modification to improve target specificity, potency, chemical and metabolic stability, water solubility, and other pharmacological parameters. Improved hits are now known as “lead compounds”. A lead compound is a prototypical chemical structure or series of structures that demonstrate activity and selectivity in a pharmacological or biochemically relevant screen. This forms the basis for a focused medicinal chemistry effort for lead optimization and development with the goal of identifying a clinical candidate. A distinct lead series has a unique core structure and the ability to be patented separately.