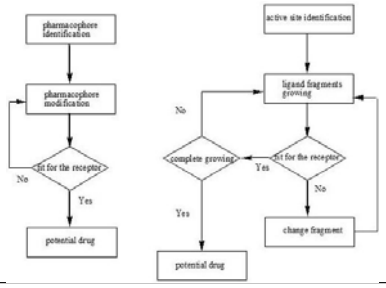
Drug design- Rational Approach

- **Drug design**, also sometimes referred to as **rational drug design**, is the inventive process of finding new medications based on the knowledge of the biological target.
- The drug is most commonly an organic small molecule which activates or inhibits the function of a biomolecule such as a protein which in turn results in a therapeutic benefit to the patient.
- In the most basic sense, drug design involves design of small molecules that are complementary in shape and charge to the biomolecular target to which they interact and therefore will bind to it.
- Drug design frequently but not necessarily relies on topology and computer modeling techniques

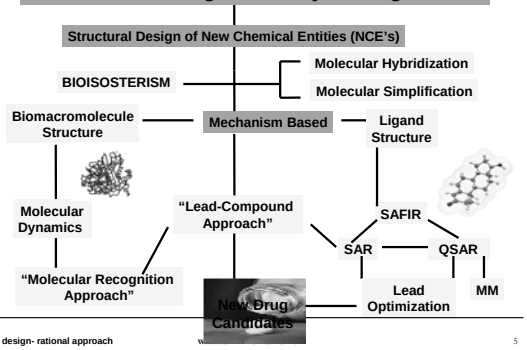
Drug design- Rational Approach

- In contrast to traditional methods of drug discovery which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value.
- In order for a biomolecule to be selected as a drug target, two essential pieces of information are required.
  - The first is evidence that modulation of the target will have therapeutic value. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states.
  - The second is that the target is "drugable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Drug design- Rational Approach



Rational Drug Discovery Strategies



Medicinal Chemistry

- "Medicinal chemistry is a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences.
- It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds,
  - The study of their metabolism,
  - The interpretation of their mode of action at the molecular level
  - The construction of structure-activity relationships."

Drug Discovery

Easy Synthetic Organic Chemistry

=

Medicinal Organic Synthesis

- **"… when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective … "**

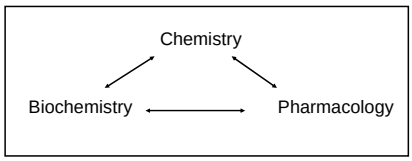
Sources of drugs

- **Animal** insulin (pig, cow)
  growth hormone (man)
- **Plant** digitalis (digitalis purpurea - foxglove)
  morphine (papaver somniferum)
- **Inorganic** arsenic mercury
  lithium
- **Synthetic** chemical (propranolol)
  biological (penicillin)
  biotechnology (human insulin)

Drug Discovery

- New drugs begin in the laboratory with scientists, including chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases.
- They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects.
- Out of every 5,000 new compounds identified during the discovery process, approximately five are considered safe for testing in human volunteers after preclinical evaluations.
- After three to six years of further clinical testing in patients, only one of these compounds on average is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines:

Drug Discovery



Drug discovery: Ideas → Drug candidates & biochemical tools

Drug development: Drug candidates → Drugs

Discovery vs. Development

- **Discovery** includes:
  - Concept, mechanism, assay, screening, hit identification, lead demonstration, lead optimization
  - In Vivo proof of concept in animals and concomitant demonstration of a therapeutic index
- **Development** begins when the decision is made to put a molecule into phase I clinical trials

Drug Discovery

- **Drug development** is a blanket term used to define the entire process of bringing a new drug or device to the market. It includes drug discovery/product development, pre-clinical research (microorganisms/animals) and clinical trials (on humans). Few people still refer to the drug development as mere preclinical development.

Basic Steps

- Choose a disease
- Choose a drug target
- Identify a “bioassay”
  bioassay = A test used to determine biological activity.
- Find a “lead compound”
  “lead compound” = structure that has some activity against the chosen target, but not yet good enough to be the drug itself.
- If not known, determine the structure of the “lead compound”
- Synthesize analogs of the lead
- Identify Structure-Activity-Relationships (SAR’s)

Basic Steps

- Structure-Activity-Relationship (SAR)
  - How does the activity change as structure is systematically altered?
- Identify the "pharmacophore"
  - pharmacophore = the structural features directly responsible for activity
- Vary structure to improve interactions with target
- Improve pharmacokinetic properties.
  - pharmacokinetic = The study of absorption, distribution, metabolism and excretion of a drug (ADME).

Basic Steps

- Patent the drug
- Study drug metabolism
- Test for toxicity
- Design a manufacturing process
- Carry out clinical trials
- Market the drug

What is a drug?

- A drug is a chemical/substance that is usually used to treat a disease/condition
- When administered appropriately causes a range of physiological and biochemical/molecular changes in a complex biological system that relate to its composition, structure and target

What is a drug?

- A drug is anything that affects the way an organism works.
- Drugs can be taken to enhance function, such as a student drinking caffeine to enhance alertness.
- For now we only consider drugs which are used to cure a disease.

What is a Disease?

- A disease is often thought of as an infection, where a bacteria, virus, or other living thing invades the body.
- However, a disease is anything which affects the proper functioning of the body.
- It can be an infection, a genetic disorder, or the result of environmental conditions such as malnourishment, poisoning, or stress.

Modern drug discovery

Key stages:

- Programme selection (choosing a disease to work on)
- Identification and validation a drug target
- Assay development
- Identification of a "lead compound"
- Lead optimization
- Identification of a drug candidate
- Clinical trials
- Release of the drug
- Follow-up monitoring

Programme selection: decisions

In proposing a new research project one should consider:

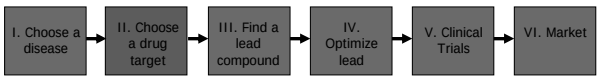
- **The medical need**
  – life threatening or self-limiting condition?
- **Availability of current therapy**
  – is level of satisfaction high or low?
  - A new drug may have advantages as it provides a new dosage form which results in a particular advantage to the patient (e.g. oral formulation vs. creams) or which requires less frequent dosing (once a day tablet).

Programme selection: decisions

- **Competitor activity.**
  - Will the proposed new drug:
    - Show increased selectivity for a particular biological mechanism?
    - Permit a novel approach to the management of the disease?
    - Optimum agents of a particular class may have been identified next therapeutic advance requires an alternative pharmacological approach. Must choose whether to seek improvements within an existing drug class or follow a novel approach.
- **Commercial opportunity**
  - Potential market (patient numbers)?
  - Duration of the proposed therapy?
  - Is the condition acute or chronic?
- **The product must of course be commercially viable!**

Drug Discovery

- General plan:



Target Identification

- Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease.
- Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease.
- Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

Drug targets

- Drug targets are most often proteins, but nucleic acids may also be attractive targets for some diseases.

TARGET MECHANISM

Enzyme Inhibitor	reversible or irreversible
Receptor	Agonist or antagonist
Nucleic acid	Intercalator (binder), modifier (alkylating agent) or substrate mimic.
Ion channels	Blockers or openers
Transporters	Uptake inhibitors

Target Prioritization/Validation

- To select targets most likely to be useful in the development of new treatments for disease, researchers analyze and compare each drug target to others based on their association with a specific disease and their ability to regulate biological and chemical compounds in the body.
- Tests are conducted to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells. Research scientists can then identify compounds that have an effect on the target selected.

Drug target validation

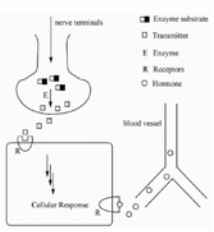
- A bio(macro)molecule may be involved in a disease process, but to be a drug target it has to be validated.
  - In other words shown to be critical in the disease process.

Useful techniques available are to validate a target are:

- **Gene knockout**:
  - Does removal of the gene that encodes the target protein result in, the death of a pathogen (disease causing microorganism)?
- **RNA interference (RNAi):**
  - Involves double-stranded ribonucleic acid (dsRNA) interfering with the expression of genes with sequences complementary to the dsRNA.
  - Results in a reduction of the production of the protein (target) in question.

Principles of drug action

- **Proteins (enzyme, receptor or ion channel) and nucleic acids form critical links in all "biochemical processes".**
- **When one of these links is malfunctioning then a disease state may arise.**
- **Modulating a malfunctioning biochemical process may alleviate the symptoms ("cure") of a disease state.**



Drug Design

There are two important aspects in drug design and drug strategies to improve :

- **Pharmacodynamics properties:** to optimize the interaction of the drug with its target.
- **Pharmacokinetics properties:** to improve the drug's ability to reach its target & to have acceptable lifetime.
  - Pharmacodynamics and pharmacokinetics should have equal priority in influencing which strategies are used and which analogues are synthesized.

Drug Discovery

- **Rational drug design**
  - **Understanding the cellular/molecular basis of diseases (eg receptors), using computer technology ⇒ 3D structure of receptor to design agonist drug**
  - **Propranolol (β blocker), cimetidine (H_2-antagonist)**
- **Prodrugs/analogs/metabolites of existing drugs**
  - **aspirin (salicyclic acid); paracetamol (phenacetin)**
- **Serendipity – a chance observation**
  - **Penicillin, cisplatinum, valproate, sildenafil**
- **Genomics – information on genes to identify drug targets**
  - **Gene therapy, siRNA**

Drug Discovery

Drug development time-line :

- Discovery + basic research
- Preclinical studies (animal) → Regulatory review
- Clinical testing
  - Phase 1
  - Phase 2
  - Phase 3 → Regulatory review
- Pre-launch activities
- Launch
- Post-marketing studies (phase 4)

10 – 12 years

And costs > US$800 M

Drug Discovery

- **Development from herbal/traditional remedies**
  - **Morphine from opium poppy**
  - **Digoxin/digitoxin from foxgloves**
  - **Salicyclic acid (aspirin) from willow bark**
- **Empirical approach**
  - **Development of models felt to be predictive of activity ⇒ screening of large number of compounds**
  - **Anticancer drugs (eg., taxol), cyclosporin,**