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:

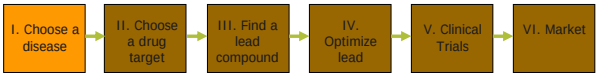
- Programme selection (choosing a disease to work on)
- Identification and validation a drug target
- Assay development
- Identification of a "lead compound"
- Lead optimization
- Identification of a drug candidate
- Clinical trials
- Release of the drug
- Follow-up monitoring

Modern drug discovery

- **Target Profile**
  - Intended therapeutic site of action and clinical outcome
- **Lead Identification**
  - Identified candidate compounds with potential drug activity commensurate with profile from a library of actives (hits)
- **Lead Optimization**
  - Identification / modification of lead compounds for best action / least side effects, etc
- **Combinatorial Chemistry**
  - Generation of active compounds (hits) from a library of building blocks
- **Structure-Activity Relationship**
  - Determination of the relationship between a specific chemical structure and a pharmacological action

Drug Discovery

- General plan:



Programme selection: decisions

In proposing a new research project one should consider:

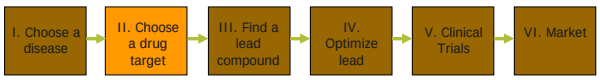
- **The medical need**
  – life threatening or self-limiting condition?
- **Availability of current therapy**
  – is level of satisfaction high or low?
  - A new drug may have advantages as it provides a new dosage form which results in a particular advantage to the patient (e.g. oral formulation vs.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

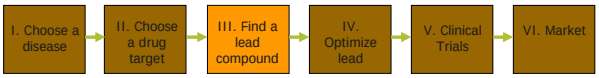
- A bio(macro)molecule may be involved in a disease process, but to be a drug target it has to be validated.
  - In other words shown to be critical in the disease process.

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.

Drug Discovery

- General plan:



Lead Compounds

- New projects can be divided into those which have “lead compounds” on which to base the design of novel analogues, and those which do not.
- A *lead compound* is:
  - “a compound from a series of related compounds that has some of a desired biological activity. This molecule can be characterized, and modified to produce another molecule with a better profile of wanted properties to unwanted side effects”
  - A*lead compound* is a first foothold on the drug discovery ladder
  - It takes much more effort to make a *lead compound into a drug candidate*

Lead Identification

- A lead compound or substance is one that is believed to have potential to treat disease.
- Laboratory scientists can compare known substances with new compounds to determine their likelihood of success.
- Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug.
- Testing is then done on each of these molecules to confirm its effect on the drug target.

Lead Optimization

- Lead optimization compares the properties of various lead compounds and provides information to help biopharmaceutical companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines.
- Often during this same stage of development, lead prioritization studies are conducted in living organisms and in cells in the test tube to compare various lead compounds and how they are metabolized and affect the body.

Identification of lead compounds

- Lead compounds may be identified by chance, e.g.:Penicillin (antibiotic) – discovered by Fleming(and others).
- An inactive compound’s structure was misassigned and “shelved” and the project was wound up. The compound was unearthed in a lab tidy some years later and tested in a new project. Was found to be effective as a treatment for short-term anxiety. First in the class of benzodiazepines.
  - Librium (anxiolytic) – discovered by Sternbach.