LECTURE 1 – INTRODUCTION

1. **Choosing a disease**
   - Economic vs scientific issues
   - Have to recoup costs if development is to be *sustainable*
   - Therefore the ideal disease for drug discovery has:
     - Lots of patients
     - Someone is able to pay for treatment
       - Rich governments
       - Rich patients
   - Multiple effective drugs to treat HIV/AIDS
     - Initially affected economically privileged patients
   - Few effective drugs to treat malaria
     - Most patients in less economically well-off countries

2. **Hits and leads**
   - A compound that is identified in an assay with the desired activity
   - E.g. binds to a receptor with micromolar affinity or better = **HIT**
   - Success of hit in further
   - Biological characterization
   - E.g agonist versus antagonist
   - Chemical characterisation
   - E.g. ease of synthesis = **LEAD** (compound you can start investigating further)
   - What compounds do you synthesise and test?
   - How do you find hits?
     - How do you optimise the hits and come up with a lead?
   - Assume the compound is "out there"
     - How do you find it?
   - Molecular diversity

3. **Finding a hit**
   - Searching a "library" – collection of compounds (**SCREENING**)
     - Natural products
     - Artificially prepared library - combinatorial chemistry
   - Chemically modifying a natural ligand (**DESIGN**)
   - Designing a compound to fit a receptor (DESIGN)
4. **Optimising a lead (lead optimisation)**
   - Take a "hit" and examine pharmacological properties
   - Often ***in vitro*** – looking at: pharmacodynamics, signalling, pharmacokinetics
     - e.g. Receptor binding
     - e.g. Cellular function
     - e.g. Enzymatic stability
   - Sometimes ***in vivo*** – looking at in vivo pharmacology and pharmacokinetics
     - e.g. Animal model of disease
     - e.g. Pharmacokinetics (ADME)
   - When a hit fails some step, select a new compound
     - Chemically related analogue
   - And go through pharmacological studies again

- Hope to identify compounds that are
  - "Better" than initial hit
  - So much "better" that they become a lead
- **Things one may wish to optimise** (reflected in the assays)
  - Potency
  - Selectivity
  - Metabolic stability
  - Pharmacokinetic behaviour
  - Toxicity/safety
- How to optimise a lead:
  - Screening a "focussed" library
  - Natural products
  - Combinatorial chemistry
  - Chemically modifying a lead – medicinal chemistry
  - Redesigning to fit receptor

LECTURE 17-18 – STRUCTURE BASED DRUG DESIGN

- **What is a lead?**
- A new chemical entity that could potentially be developed into a new drug by optimising its beneficial effects and minimising its side effects
- Target validation establishes the relevance of a target in a certain disease pathway
- Drug discovery overview
  - What compounds do you synthesise and test?
    - How do you identify hits?
    - How do you select a lead?
    - How do you optimise the lead?
  - What aspect do you optimise?
    - A pharmacodynamic entity:
      - Affinity, potency, efficacy, selectivity
    - A pharmacokinetic entity:
      - A good lead compound shows good pharmacokinetics early on in the process of discovery
      - Oral bioavailability
      - Stability
      - Blood-brain barrier penetration
    - **ASSAY is important**
      - If you assay for oral bioavailability you are selecting for a compound that has good oral bioavailability
      - Need to have appropriate assays to ensure good drug discovery → critical to the success of drug discovery
  - How do you catch a drug **[lead]?**
    - **Screening**
      - 'catch' a broad range of molecules
      - May not catch the drug that you want
      - Currently high throughput screening is the main approach for the identification of lead compounds
    - **Design**

        - Trying to ‘catch’ a particular drug
        - Set out to design a particular drug
    - You will end up with a drug either way, but will you end up with the molecule you want?
- **Finding/discovering a lead compound (hit)**
    - Start with:
        - A **library**
            - A collection of **natural** products or **synthetic** compounds
            - Using combinatorial chemistry to create synthetic libraries of compounds
        - **Structural information**
            - Known **ligand** – e.g. substrate, NT, etc.
            - **Receptor** 3D structure