Drug Discovery and Development

How are drugs discovered and developed?
Sources of drugs

**Animal**
- insulin (pig, cow)
- growth hormone (man)

**Plant**
- digitalis (digitalis purpurea-foxglove)
- morphine (papaver somniferum)

**Inorganic**
- lithium

**Synthetic**
- chemical (propranolol)
- biological (penicillin)
- biotechnology (human insulin)
How a new drug development proceeds?

• Idea or Hypothesis
• Design and synthesis of substances
• Studies on tissues and whole animals (preclinical studies)
• Studies in man (clinical studies)
• Grant of an official license to make therapeutic claims and to sell
• Post-licensing (marketing) studies of safety and comparisons with other medicines.
Drug Discovery

• General plan:

1. Choose a disease
2. Choose a drug target
3. Find a lead compound
4. Optimize lead
5. Clinical Trials
6. Market

For a New Chemical Entity (NCE)
– More than 10 years
– More than $500 million
– More than 10000 tested compounds
– For one drug!
Basic Steps

• Choose a disease
• Choose a drug target
• Do 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)
Choosing a Disease

• Pharmaceutical companies must make a profit to exist
• Pharmaceutical companies will, therefore, avoid products with too small a market (i.e. a disease which only affects a small subset of the population)
Choosing a Disease

• Pharmaceutical companies will also avoid products that would be consumed by individuals of lower economic status (i.e. a disease which only affects third world countries)

• Most research is carried out on diseases which afflict “first world” countries: (e.g. cancer, cardiovascular diseases, depression, diabetes, flu, migraine, obesity).
Choosing the Bioassay

**In vitro testing**
- Has advantages in terms of speed and requires relatively small amounts of compound.
- Speed may be increased to the point where it is possible to analyze several hundred compounds in a single day (high throughput screening).
- Results may not translate to living animals

**In vivo tests**
- More expensive
- May cause suffering to animals
- Results may be clouded by interference with other biological systems
TECHNIQUES OF DISCOVERY

• MOLECULAR MODELLING – AIDED BY THREE DIMENTIONAL COMPUTER GRAPHICS;
• ALLOWS THE DESIGN OF STRUCTURES BASED ON NEW AND KNOWN MOLECULES TO ENHANCE THEIR DESIRED & TO ELIMINATE THEIR UNDESIRED PROPERTIES TO CREATE HIGHLY SELECTIVE TARGETED COMPOUNDS.
• **COMBINATORIAL CHEMISTRY**—RANDOM MIXING AND MATCHING OF LARGE NUMBERS OF CHEMICAL BUILDING BLOCKS TO PRODUCE LIBRARIES OF ALL POSSIBLE COMBINATIONS.

• GENERATES BILLIONS OF COMPOUNDS, SCREENED BY HIGH-THROUGHPUT SCREENING (THOUSANDS A DAY). IF POSITIVE RESPONSE, TRADITIONAL LABORATORY METHODS.

• **BIOTECHNOLOGY**—PROTEINS AS DRUGS, USE OF RECOMBINANT DNA TECHNOLOGY / GENETIC ENGINEERING TO CLONE AND EXPRESS HUMAN GENES.
Preclinical Studies in animals

• **Pharmacodynamics**: To explore actions relevant to the proposed therapeutic use
• **Pharmacokinetics**: how the drug is distributed in and disposed of by the body
• **Toxicology**: whether and how drug causes injury (in vitro tests and intact animals)
  -- single-dose studies - acute toxicity
  -- repeated dose studies – sub-acute chronic or long term toxicity

--- Done in 2 species – rodent and non-rodent
--- Clearance from Institutional Animal Ethic Committee required
Special toxicity study

• Carcinogenecity
• Teratogenecity
• Mutagenecity
• Local toxicity – dermal, ocular, inhalational, vaginal & rectal
• Effect on reproductive performance
Reducing animal usage

- **REPLACEMENT**: use non-animal tests if possible (cheaper, less trouble, less variable but not possible for everything at this time)
- **REDUCTION**: get the statistics right, don’t replicate work unnecessarily, don’t over-breed
- **REFINEMENT**: reduce suffering and severity of procedure, pay attention to housing, stress, husbandry and rich environments, proper analgesia and pre- and post-operative care.
- According to Good Laboratory Practice (GCP)
Rational Introduction Of a new drug to man

• When studies in animals predict that a new molecule may be a useful medicine i.e. effective and safe in relation to its benefits, then time has come to put it to test in man.
Clinical testing (trials)

- **Phase I** – Human Pharmacology (Healthy volunteers – 20-50 subjects)
- **Phase II** - Therapeutic Exploration (patients – 50-400)
- **Phase III** – Therapeutic Confirmation (large scale multi-centre; 250-1000)
- **Phase IV** - Therapeutic Use (post-registration monitoring)

{Phase 0, Microdosing}
Clinical Trials

• **Phase I**: Drug is tested on healthy volunteers,
• **P/K, P/D (biological effects), tolerability, safety, efficacy.**
• To determine safe clinical dose range.
• If drug is expected to have significant toxicity, volunteers with that disease are taken rather than healthy volunteers, (anti-cancer, drugs for AIDS)
• These trials are **non-blind** or **open-label**; both the investigator and the subject know what is being given.
• Phase II:

• Drug is tested on small group of patients with the target disease.

• P/K, P/D, dose range, safety and efficacy may involve comparison with a control.
• **Phase III:** Drug is tested on much larger group of patients and compared with existing treatments and with an inert control. These are randomised double-blind trials.

• Takes 5-6 years for completion.

• Results analysed statistically in the end.
• Phase IV:
  • Drug is placed on the market and patients are monitored for side effects
  • Post-marketing surveillance for safety, efficacy & pharmaco-economic studies.
Drug Regulation

• **Food & Drug Administration (FDA)**
• It is the administrative body that oversees the drug evaluation process in USA and grants approval for marketing of new drug products.
• **IND** - Investigational New Drug (if judged ready to be studied in human)
• **NDA** - New Drug Application
• If Phase 3 results meet expectations, application is made for permission to market the new agent)
• Filing of a patent
Ethics Of research in Human

- Ethical Principles of research –
- **Autonomy** – Right to self determination, informed consent
- **Beneficence** – Desire to help patients
- **Non-maleficence** – No harm
- **Justice** – should not be continued if no benefit
Drug discovery/development process

Discovery = find new active structure; Development = convert it to a useful drug.