Semester I.
Seminar 10.

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Exam titles 19-20-21

19.

- Factors influencing the drug effect. (FORMER SEMINAR) Preclinical phase of drug development
- Pharmacology of cardiac glycosides
- Drugs promoting gastrointestinal motility. Emetics and antiemetic drugs

20.

- Drug interactions. Biologicals (biological therapy), special considerations with respect to their development.
- Positive inotropic substances except cardiac glycosides
- Pharmacotherapeutic approach to exocrine pancreatic diseases

21.

- Clinical phase of drug development.
- Adrenergic neuron blockers and reserpine. Antihypertensive mode of action of ß-blockers
- Botanical/herbal remedies

Drug interactions

Drug Interactions

- A **drug interaction:**
  - is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together.

- This action can be:
  - **synergistic** (when the drug's effect is increased) or
  - **antagonistic** (when the drug's effect is decreased) or
  - **a new effect** can be produced that neither produces on its own.

- Examples:
  - **drug-drug interaction**
  - **drug-food interactions**
  - **drug-plant interactions**

How often can we meet a drug-drug interaction?

- Statistically, if you take **six** different drugs, you have an **80 percent** chance of at least **one** drug-drug interaction.

- Elderly people - polypharmacy

Outcomes of drug interactions

- Loss of therapeutic effect
- Toxicity
- Unexpected increase in pharmacological activity
- Beneficial effects e.g additive & potentiation (intended) or antagonism (unintended).
- Chemical or physical interaction

Host factors affecting the development of adverse interactions

- Age
- Sex
- Medical conditions
- Size and fat-mass
- Exclusionary diets (e.g. vegan diets)
- Use of substances of abuse
- Medical conditions that require the care of different specialists and multiple medications
- High risk patients
  - patients that should be treated with caution due to a specific health condition
  - e.g., pregnant women, malignant cases, diabetic patients, patients with liver or kidney disorders, asthmatic patients and cardiac disorders, elderly patients using many drugs (polypharmacy)…

High risk drugs

High risk drugs: drugs that show a narrow therapeutic index

e.g.,

- corticosteroids,
- rifampin,
- oral contraceptives,
- Antiarrhytmics
- digoxin
- Anticoagulants
- Antacids
- Anticonvulsives
- Antidiabetics
- Citostatics
- Cardiac glycosides
- Theophyllin

Cardiovascular drugs are on the top of the list, because:

- Cardiac patients usually receive more than one drug (multiple drugs needed)
- Long term use
- More possible interactions with drugs used in acute conditions
- Very serious adverse reactions may occur

Mechanisms of drug interactions

- Pharmaceutical (incompatibilities)
- Pharmacodynamic, related to the effect, mechanism of effect
- Pharmacokinetic, related to:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmaceutical Interactions

- also known as **pharmacological incompatibilities**.
- Interactions that occur prior to systemic administration.
  - The reactions occur when two or more drugs are mixed outside the body of the organism for the purpose of joint administration.
  - The interaction of some drugs with the transport medium can also be included here.
    - Example: certain drugs cannot be administered in plastic bottles because they bind with the bottle's walls, reducing the drug's concentration in solution.
- These interactions can be:
  - physical (e.g. with a visible precipitate) or
  - chemical with no visible sign of a problem
- **Examples** include:
  - the mixing of penicillins and aminoglycosides in the same serum bottle, which causes the formation of an insoluble precipitate,
  - or the mixing of ciprofloxacin with furosemide also results an insoluble white precipitation

Pharmacodynamic Interactions

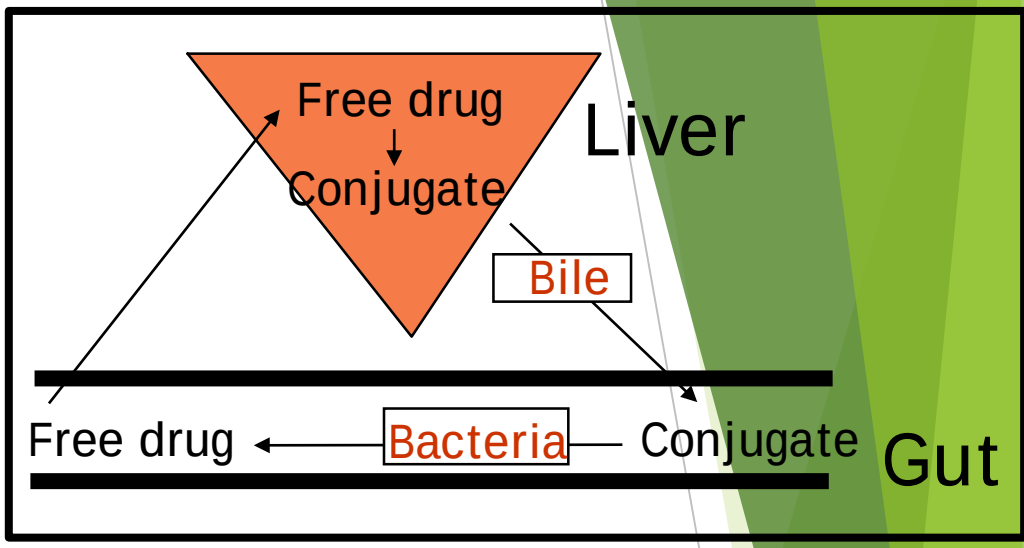
- When two drugs alter the effect of each other.
- Types:
  - Synergistic effects
    - Addition: the combined effect is the sum of the effects produced separately
    - Potentiation: the combined effect is more, than the sum of the effects produced separately
  - Antagonistic effects
    - Receptorial antagonsim
      - Reversible, competitive antagonism
      - Irreversible „non-competitive" antagonism
      - Allosteric antagonism (non-competitive)
    - Non-receptorial antagonisms
      - Inhibition of signal transduction (with site of action other than on the receptor)
      - Functional antagonsim = Opposite effect on different receptor
- In most cases it is easier to prevent pharmacodynamic interactions because we don't administer 2 drugs with well-known opposite effects.
- Synergistic effects can be utilized as well.

See also: Seminar 3 - Combinative drug-effects

Pharmacodynamic interaction examples

- Β2-agonists used in asthma (e.g. **salbutamol**) + non-selective Β-blockers (e.g. **propranolol**) used in hypertension,migraine profilaxis or arrhythmia
- **MAO inhibitors** + fermented cheese e.g. Camembert (rich in **tyramine**)/**ephedrine**
  - MAO inhibitors increase the amount of noradrenaline stored in noradrenergic nerve terminals
  - ephedrine or tyramine release stored NA
- **Warfarin/acenocoumarol** + **food** (containing high levels of vitamin K)
  - the anticoagulant action of warfarin/**acenocoumarol** is decreased
  - E.g.: kale, spinach, kohlrabi, swiss chard, cabbage, broccoli, brussels sprouts, asparagus, cucumber etc.
- **Warfarin/acenocoumarol + Aspirin**
  - Increased bleeding
  - Same anticoagulant effect, different mechanism = Aspirin is platelet aggregration inhibitor
- **Sulfonamides** + **Trimethoprim**
  - Inhibit different enzymes in the folate-cycle ➔ together they have a synergistic action

Pharmacokinetic interactions – Absorption



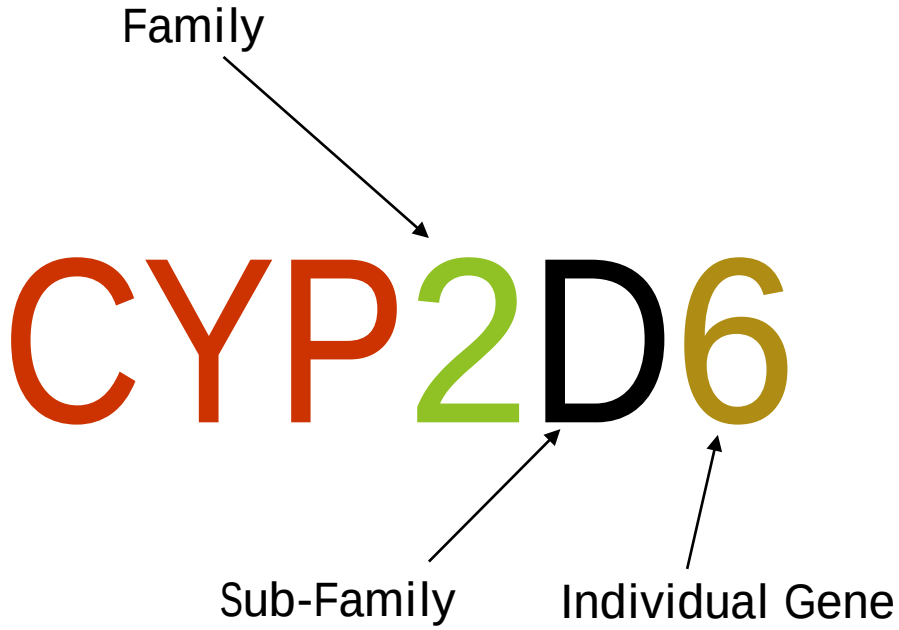
- Change in gastrointestinal pH
  - Ketoconazole needs acidic conditions in gut
- Drug binding in GI tract
  - tetracycline + calcium (milk)
  - Colestyramine + warfarin/digoxin
- Changes in gastrointestinal flora
  - oral contraceptives + antibiotics
    - Oral contraceptives take part in enterohepatic circulation
  - Warfarin/acenocoumarol + antibiotics
    - Warfarin/acenocoumarol compete with vitamin K, preventing hepatic synthesis of various coagulation factors
    - Colonic bacteria synthesize a significant portion of humans' vitamin K needs
    - Antibiotics may kill intestinal flora ➔ less vitamin K ➔ the anticoagulant action is increased.
    - newborns often receive a vitamin K shot at birth and then monthly to tide them over until their colons become colonized by vitamin K-synthetizing bacteria (at the time they get food beside their mother's milk)
- Change in gastrointestinal motility
  - Metoclopramide increases motility ➔ absorption of many drugs decreases
- Malabsorption caused by other drugs
  - Orlistat (Xenical) and fat soluble vitamins (unintended)
  - Adrenalin + local anaesthetics (intended)

Pharmacokinetic interactions – Distribution

- Protein binding interactions are one of the most common interactions among all drug interactions!
  - Only free drug exerts effects
  - Protein binding is a dynamic process
  - most significant with drugs that are highly protein-bound (>95%) and have a low therapeutic index, such as
    - warfarin + NSAIDs / sulphonamides
    - digoxin + quinidine / amiodarone

Pharmacokinetic interactions – Metabolism (biotransformation)

- The most common drug interaction type
- More than 90% of common medications are metabolized by 7 CYP isoenzymes: 3A4 (60%), 2D6 (25%), 1A2 (15%), 2C9, 2C19, 2E1 & 3A5
- Foods or dietary supplements may induce or inhibit activity of these enzyme systems ➔ may change metabolism of other drugs



- Substrate:
  Drug is metabolised by the enzyme system
- Inducer:
  Drug that will increase the synthesis of CYP450 enzymes
- Inhibitor
  Drug that will decrease the metabolism of a substrate

Inductors of CYP enzymes

- Alcohol
- Barbiturates
- Carbamazepin
- Grizeofulvin
- Meprobamat
- Phenobarbital
- Phenylbutazon
- Phenytoin
- Rifampicin
- Sulfinpyrazon

- **Higher enzyme activity**
- **Coadministered drug metabolized quickly**

- **Loss of therapeutic effect**

Inhibitors of CYP enzymes

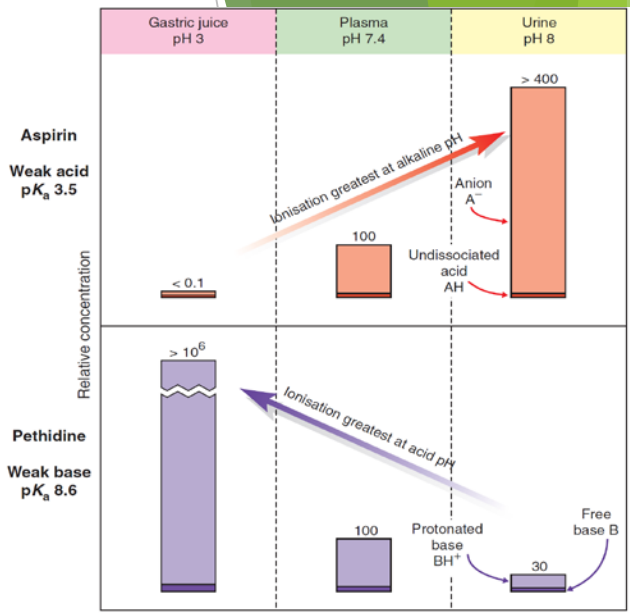
- INH
- Amiodaron
- Cimetidin
- Diltiazem
- Disulfiram
- Erythromycin
- Imipramin
- Ketoconazol
- Metronidazol
- Propranolol
- Ritonavir
- Fluoroquinolones
- Grapefruit juice

- **Lower enzyme activity**
- **Coadministered drug metabolized slower**

- **Greater effects, more side effect can occur or even toxicity**

Pharmacokinetic interactions – Excretion

- Renal excretion is the major route of elimination
- Interactions include:
  - Change in urinary pH
    - One drug forces another into the urine by changing pH
    - ➔ used in forced diuresis
  - Saturation of active secretion mechanisms
    - Active secretion mechanisms have limited capacity.
    - e.g. one acid drug may saturate the OATs
      ➔ another acid drug will then be secreted less efficiently
  - Change in renal blood flow
    - Methotrexate and NSAIDs
    - NSAIDS can decrease renal blood flow by inhibition of renal prostaglandins.
    - Reduced clearance of MTX and its active (toxic) metabolite
  - Thiazides + Lithium
    - Thiazides cause diuresis and initial sodium loss.
    - Compensatory sodium retention in proximal tubules.
    - Proximal tubules do not distinguish sodium from lithium.
    - Lithium also retained and accumulates.



How to avoid unwanted drug–drug interactions in clinical practice

- Ensure you have a full drug history (including OTC and herbal products)
- Pharmacodynamic drug–drug interactions can be anticipated based on pharmacological knowledge
- Pharmacokinetic drug–drug interactions are more difficult to anticipate but
- Recognise drugs producing major pharmacokinetic interactions
- Recognize drugs that have a narrow therapeutic index
- Prescribe fewer drugs and know them well.

- These will help prevent most of these interactions

Biologicals (biological therapy), special considerations with respect to their development.

Biologicals, biological therapy

- Synonym: Biopharmaceuticals
- Drugs that are not created by combinatoric chemistry (pharmaceutical chemistry) but with the use of biological knowledge:
  by manipulating genetic material
- Types:
  - Genetically engineered proteins
    - Receptors
    - Monoclonal antibodies
    - Recombinant Hormones
    - Recombinant Enzymes
  - Oligonucleotids
    - siRNA
  - DNA/RNA ← also known as Gene therapy

- first-generation biopharmaceuticals are mainly copies of endogenous proteins or antibodies, produced by recombinant DNA technology
- second-generation biopharmaceuticals have been 'engineered' to improve the performance

First generation protein pharmaceuticals

- the use of **proteins** as **therapeutic agents** is **not a novel idea**;
  - **insulin**, extracted from animal pancreas tissue, and
  - **human growth hormone**, extracted from human cadaver pituitary glands,

Early problems:

- difficulties in extraction and disappointingly low yields
- administration of animal hormones to humans could evoke an immune response
- danger of the transmission of infectious agents across species, or between people.

Second generation, engineered proteins

There are several ways in which proteins can be altered prior to expression

1. Modification of pharmacokinetic properties:

- Changes in the structure
  - E.g. a form of human insulin which does not self-associate during storage ➔ faster acting
- PEGylation
  - the addition of polyethylene glycol to the molecule
  - The half-life of proteins in the blood can often be extended by PEGylation

Second generation, engineered proteins

2. Generation of novel fusion or other proteins:

- **Fusion proteins** comprise two or more proteins
  - engineered to be expressed as one single polypeptide chain,
  - sometimes joined by a short linker.

- An example is **etanercept**, (anti-inflammatory drug used in e.g. rheumatoid arthritis)
  - This consists of the *ligand-binding domain* taken *from the TNFa receptor* AND
  - *Fc domain of* a human immunoglobulin G (*IgG*) antibody.
    - The latter moiety increases its persistence in the blood.

- Another example is **aflibercept** (Eylea®) (inhibitor of neovascularisation used in diabetic retinopathy)
  - This consists of the *ligand-binding domain* taken *from VEGF receptors* AND
  - *Fc domain of* a human immunoglobulin G (*IgG*) antibody.

Second generation, engineered proteins

3. Reducing immunogenicity of antibodies

- Use of monoclonal antibodies (instead of polyclonal)
  - polyclonal antibodies = mixtures of antibodies from all the plasma cell clones present in blood after antigen presentation
  - Monoclonal antibodies = produced by one particular lymphocytic clone;
    monoclonal antibodies are most specifically bind the antigen (and only that)
  - Monoclonal antibodies are easily produced using immortalised hybridoma cells;
    hybridoma cells = fusion of one particular lymphocytic clone with an immortalised tumour cell
- Second-generation, engineered monoclonal antibodies
  - First-generation monoclonal antibodies = essentially murine monoclonals
    - As mouse proteins, they provoked an immune response in 50–75%
    - had short half-life
    - may be inable to activate human complement system
  - Second-generation (humanisation): replacement of the entire Fc and Fab region with the human equivalent with the exception of the hypervariable regions (= the murine antibody's antigen-binding sites)
  - Example: The anticancer monoclonal trastuzumab (Herceptin®)

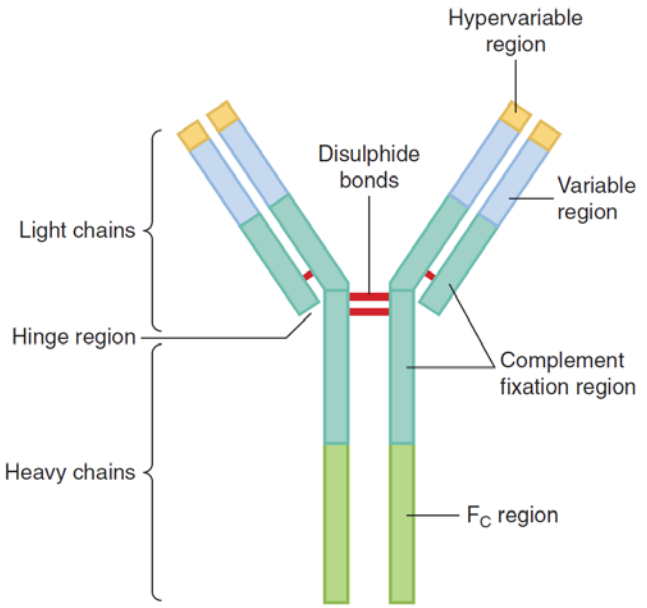


Fig. 59.1 Production of engineered 'chimeric' and 'humanised' monoclonal antibodies. The Y-shaped antibody molecule consists of two main domains: the F_c (constant) domain and the Fab (antibody-binding) domain. At the tip of the Fab regions (on the arms of the 'Y') are the hypervariable regions that actually bind the antigen. Chimeric antibodies are produced by replacing the murine F_c region with its human equivalent by altering and splicing the gene. For humanised antibodies, only the murine hypervariable regions are retained, the remainder of the molecule being human in origin. (After Walsh, 2004.)

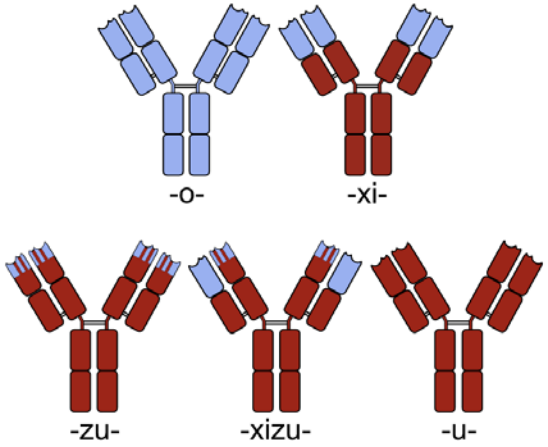
Some examples of 'second-generation' biopharmaceuticals

Type of change	Protein	Indication	Reason for change
Altered amino acid sequence	•Insulin •Tissue plasminogen activator analogues •Interferon analogue •Factor VIII analogue •Diphtheria toxin–interleukin-2 fusion protein •Tumour necrosis factor receptor–human-immunoglobulin G Fc fusion protein	Diabetes Thrombolysis Antiviral Haemophilia T-cell lymphoma Rheaumatoid disease	Faster-acting hormon Longer circulating half-life Superior antiviral action Smaller molecule, better activity Targets toxin to appropriate cells Prolongs half-life
Altered carbohydrate residues	•Glucocerebrosidase enzyme •Erythropoietin analogue	Gaucher's disease Anaemia	Promotes phagocyte uptake Prolongs half-life
Covalent attachment to polyethylene glycol (PEG)	•Interferon •Human growth hormone	Hepatitis C Acromegaly	Prolongs half-life Prolongs half-life

Some more examples of ‘second-generation’ biopharmaceuticals

Antibody	Type	Target	Use
Infliximab	Chimeric Mab	Tumour necrosis factor	Crohn’s disease, rheumatoid disease
Adalimumab	Humanised Mab	Tumour necrosis factor	Rheumatoid disease
Etanercept	Fusion protein	Tumour necrosis factor	Rheumatoid disease
Trastuzumab	Humanised Mab	HER2 epidermal growth factor receptor	Breast cancer
Palivizumab	Humanised Mab	Respiratory syncytial virus	Respiratory infections in young children
Omalizumab	Humanised Mab	Immunoglobulin E	Immunoglobulin E-mediated asthma
Abatacept	Fusion protein	B7 epitope on antigen presenting cells	Rheumatoid disease

Mab, monoclonal antibody. Therapeutic monoclonal antibody names all end in ‘-mab’, prefixed by an indication of their species -umab (human), -omab (mouse), -ximab (chimera), -zumab (humanised).



Gene therapy

Gene therapy = a treatment using genes

The transfer of recombinant nucleic acid into target cells

Aim:

- Insertion of new gene into the cell
  - Sensitizing tumor cells to cancer therapy
  - Prevention/treatment of diseases
  - Immunisation
- Repair, exchange or substitution of faulty genes
  (Genetic (metabolic)-diseases, autoimmune diseases)

Gene therapy

- The transfer of recombinant nucleic acid into target cells
- *Transfer:*
  - ***In vivo strategy***,
    - the vector containing the therapeutic gene is injected into the patient,
      - either intravenously (in which case some form of organ/tissue-targeting is required) ➔ use of Vectors (see next slide)
      - or directly into the target tissue (e.g. a malignant tumour).
  - **The *ex vivo strategy*** is to
    - remove cells from the patient (e.g. stem cells from bone marrow or circulating blood, or myoblasts from a biopsy of striated muscle),
    - treat them with the vector
    - and inject the genetically altered cells back into the patient.

Gene therapy vectors

Table 59.3 Characteristics of some delivery systems for gene therapy

Vector	Advantages	Disadvantages
Liposomes	Virus-free, cheap to produce	Low efficiency, sometimes cytotoxic
DNA cassettes	Virus-free	Low efficiency, expression temporary
Herpes simplex virus type I	Highly infective, persistent expression	No integration with host DNA, cytotoxic, difficult to handle
Adenovirus	Highly infective in epithelia	Immunogenic and transient, requires readministration
Adeno-associated virus	Stable	Low capacity
Retrovirus	Efficient, permanent	Low capacity, unstable, must integrate into host DNA, requires dividing cells

After Wolf & Jenkins, 2002.

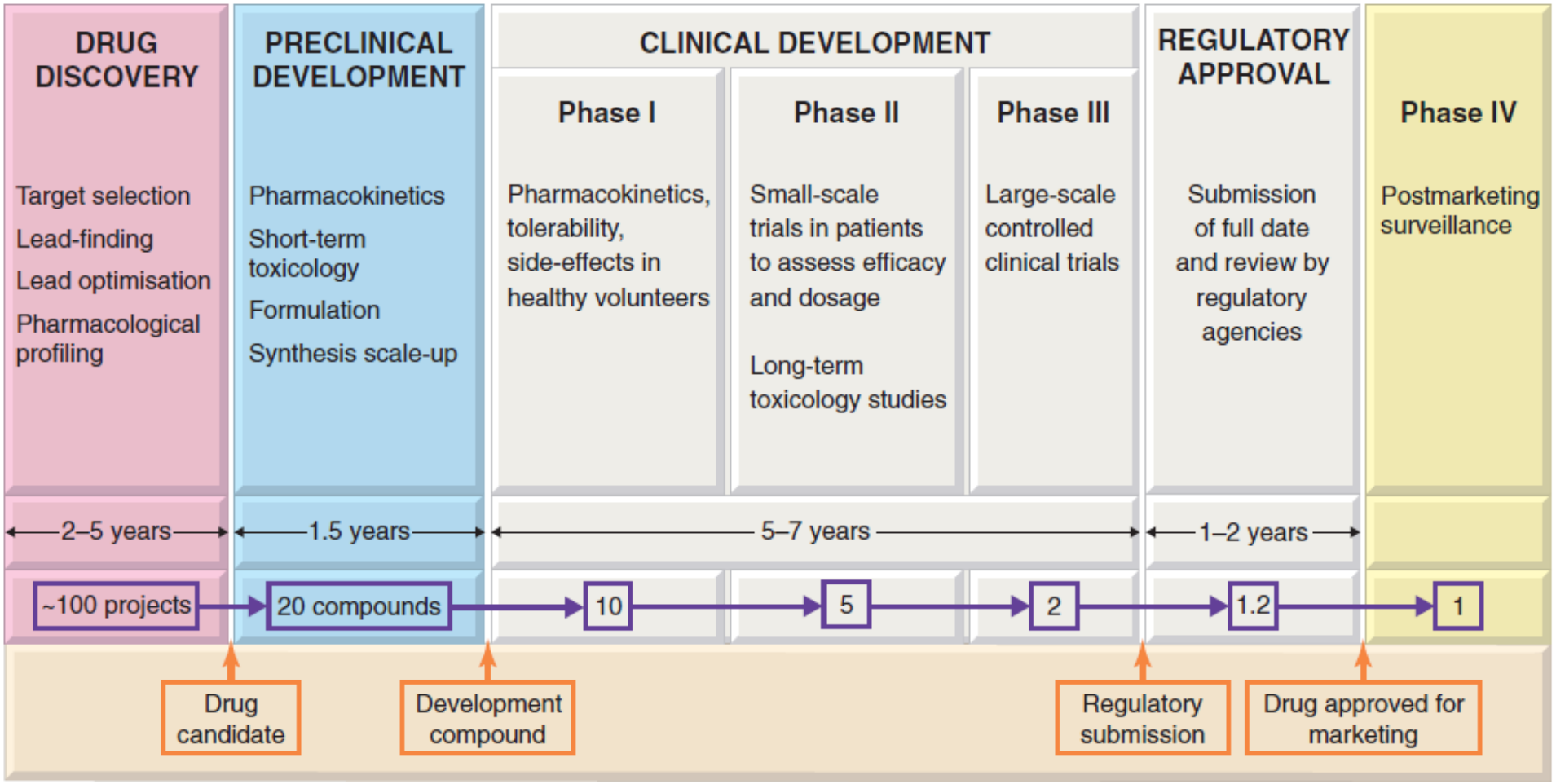
further reading: Rang & Dale 7th Edition

Preclinical and clinical phases of drug development

Drug discovery & development

- Producing a marketable drug can be divided into three main processes:
  - **1. Drug discovery,**
    during which candidate molecules are chosen on the basis of their pharmacological properties.
  - **2. Preclinical development,**
    during which a wide range of non-human studies (e.g. toxicity testing, pharmacokinetic analysis and formulation) are performed.
  - **3. Clinical development,**
    during which the selected compound is tested for efficacy, side effects and potential dangers in volunteers and patients.
- These phases do not necessarily follow in strict succession, but generally overlap.

The stages of development of a ‘typical’ new drug



Drug discovery - Target selection

- in the past, drug discovery programmes were often based — successfully— on measuring a complex response in vivo
  - (e.g. prevention of experimentally induced seizures,
  - lowering of blood sugar or
  - suppression of an inflammatory response),
  - ➔ there was no need for prior identification of a drug target,
  - but **nowadays** it is rare to start without a defined protein target, so the **first step is target identification**

- Assuming that we are looking for a novel drug rather than developing a slightly improved 'me too' version of a drug already in use, we first need to **choose a new molecular target**.
- drug targets are - with few exceptions - functional proteins (e.g. receptors, enzymes, transport proteins)

- To choose wisely we need basic knowledge, biological intelligence (e.g. knowledge of disease mechanisms and chemical signalling pathways)
  Selecting *valid* and '*druggable*' targets from the plethora of potential drug targets is a major challenge

Drug discovery - Lead-finding

- When the biochemical target has been decided and the feasibility of the project has been assessed, the next step is to find *lead compounds („leads")*.
- The steps of lead-finding process are:
  - 1. Cloning of the target protein
  - 2. Development of an assay for measuring target protein functional activity (preferably „high-throughput screening" e.g. miniaturised multiwell plate format)
  - 3. Production of large compound-libraries to test on the former mentioned assays
    - For compound libraries nowadays combinatorial chemistry is used to produce hundreds of related compounds simultaneously. („high-speed chemistry")
  - 4. high-throughput random screening (mindless, but even successful)

Several cycles

Also produces many molecules that have features undesirable in a drug

- The **hit**s identified from the primary screen are used as the basis for preparing sets of homologues by combinatorial chemistry so as to establish the critical structural features necessary for binding selectively to the target.

Lead molecules

Drug discovery - Lead-optimisation

- The aim is
  - to increase the potency of the compound on its target and
  - to optimise it with respect to other properties, such as selectivity and metabolic stability
  - broader range of assays are used on different test systems
    - E.g.: animal models mimicking aspects of the clinical condition; checking for unwanted effects in animals; checking evidence of genotoxicity
  - Drug candidates
    (only 1 project in 5 succeeds in generating a drug candidate)
  - Preclinical development

Pre-clinical development

- The work falls into four main categories:
- 1. *Safety pharmacology*
  Pharmacological testing to check that the drug does not produce any obviously hazardous acute effects (such as bronchoconstriction, cardiac dysrhythmias, blood pressure changes and ataxia.)
- 2. *Preliminary toxicological testing („acute toxicology")*
  - to eliminate genotoxicity and
  - to determine the maximum non-toxic dose of the drug (usually when given daily for 28 days, and tested in two species).
  - to check regularly for weight loss and other gross changes,
  - postmortem examination at the end of the experiment to look for histological and biochemical evidence of tissue damage.
- 3. *Pharmacokinetic testing* (ADME studies) in laboratory animals.
- 4. *Chemical and pharmaceutical development*
  - to assess the feasibility of large-scale synthesis
  - to assess the feasibility of purification,
  - to assess the stability of the compound under various conditions and
  - to develop a formulation suitable for clinical studies.

Half of the drug candidates fails during pre-clinical phase

- For the succeeders a detailed dossier is prepared for submission to the regulatory authority such as the European Medicines Evaluation Agency (EMEA) or the US Food and Drugs Administration (FDA), whose permission is required to proceed with studies in humans.

„chronic/long-term toxicology" (2-3 years) continues throughout the clinical trials period (teratogenicity, mutagenicity, carcinogenicity, fertility testings)

Used techniques include: in silico studies, in vitro experiments (molecular methods, cell membrane-assays, studies on cell cultures), animal studies (healthy/diseased modells) etc. **in this order**.

GLP

- Much of the work of preclinical development, especially that relating to safety issues, is done under a **formal operating code**, known as *Good Laboratory Practice* (GLP),

  which covers such aspects as

  - record-keeping procedures,
  - data analysis,
  - instrument calibration and
  - staff training.

- The aim of GLP is
  - to eliminate human error as far as possible, and
  - to ensure the reliability of the data submitted to the regulatory authority, and

- laboratories are regularly monitored for compliance to GLP standards.

- The strict discipline involved in working to this code is generally ***ill-suited to the creative research*** needed in the earlier stages of drug discovery, so GLP standards are not usually adopted until projects get beyond the discovery phase,
  i.e. GLP is used only in pre-clinical phase, not before.

Clinical development

- Clinical development comprises 3+1 distinct stages/phases

Phase I

- *Phase I studies* are performed on *a* ***small group*** (normally 20–80) of normal ***healthy volunteers***, and
- their aim is
  - to check for signs of any potentially *dangerous effects*, (for example on cardiovascular, respiratory, hepatic or renal function)
  - *tolerability* (does the drug produce any unpleasant symptoms, for example headache, nausea, drowsiness?); and
  - *pharmacokinetic properties* (is the drug well absorbed? What is the time-course of the plasma concentration? Is there evidence of cumulation or non-linear kinetics?).
  - Phase I studies ***may*** also test for *pharmacodynamic effects* in volunteers (e.g. does a novel analgesic compound block experimentally induced pain in humans? How does the effect vary with dose?).

Clinical development

Phase II

- *Phase II studies* are performed on ***medium-sized*** groups of ***patients*** (normally 100–300)
- and are designed
  - to *test for efficacy* in the clinical situation, and if this is confirmed,
  - to *establish the dose* to be used in the definitive phase III study.
  - to *identify the possible therapeutic indications* for the new compound and the dose required for these indications

- When new drug targets are being studied, it is not until these phase II trials are completed that the team finds out whether or not its initial hypothesis was correct…
  …and lack of the expected efficacy is a common reason for failure.
- During phase II, long-term toxicology (animal)studies also get to the finish line.

Clinical development

Phase III

- *Phase III studies* are the definitive ***double-blind, randomised*** trials, commonly performed as ***multicentre trials*** on ***thousands of patients***,
- aimed at
  - *comparing* the new drug with commonly used alternatives.
  - identifying *possible side-effects*
  - conducting *pharmaco-economic analysis*
    such that not only clinical but also economic benefits of the new treatment are assessed.

- These studies are extremely costly, difficult to organise and often take years to complete, particularly if the treatment is designed to retard the progression of a chronic disease.
- It is not uncommon for a drug that seemed highly effective in the limited patient groups tested in phase II to look much less impressive under the more rigorous conditions of phase III trials.

GCP

- Similarly to GLP, the conduct of trials has to comply with an elaborate code known as Good Clinical Practice (GCP),
- covering
  - every detail of the patient group,
  - data collection methods,
  - recording of information,
  - statistical analysis and
  - documentation.

After Phase III – Regulatory Approval

- At the end of phase III, the drug will be submitted to the relevant regulatory authority for licensing.
- The dossier required for this is a massive and detailed compilation of preclinical and clinical data.
- Evaluation by the regulatory authority ***normally takes a year*** or more, and **further delays** often arise when aspects of the submission have to be clarified or more data are required.
- Eventually, about two-thirds of submissions gain marketing approval. Overall, only 11.5% of compounds entering Phase I are eventually approved.
- Increasing this proportion by better compound-selection at the laboratory stage is one of the main challenges for the pharmaceutical industry.

After Phase III - Phase IV

- *Phase IV studies* comprise the **obligatory postmarketing surveillance**
- designed
  - to detect any *rare or long-term adverse effects* resulting from the use of the drug in a clinical setting *in many thousands of patients*.
  - Such events may necessitate limiting the use of the drug to particular patient groups, or even withdrawal of the drug.
  - Sometimes a side-effect can be favorable and may result in producing a new *therapeutic indication* for the drug

Commercial Aspects of drug Research and Development (R&D)

- The key messages are
  - (1) that it is a high-risk business, with only about one drug discovery project in 50 reaching its goal of putting a new drug on the market,
  - (2) that it takes a long time—about 12 years on average, and
  - (3) that it costs a lot of money to develop one drug (currently a mind-boggling $5.5 billion in 2013)
    For any one project, the costs escalate rapidly as development proceeds, phase III trials and long-term toxicology studies being particularly expensive.

- The time factor is crucial, because the new drug has to be **patented, usually at the end of the discovery phase**, and the period of exclusivity (**20 years** in most countries) during which the company is free from competition in the market starts on that date.
- After 20 years, the patent expires, and other companies, which have not supported the development costs, are free to make and sell the drug much more cheaply, so the revenues for the original company decrease rapidly thereafter.
- In practice, only about one drug in three that goes on the market brings in enough revenue to cover its development costs. Success for the company relies on this one drug generating enough profit to pay for the rest