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INTRODUCTION TO THE STUDY OF PHARMACOLOGY

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Dept. of Pharmacology, LF MU

Lecture Content

- Definition of pharmacology and its subdivisions
- Basic pharmacological terms
- Development of new drugs, clinical trials
- Principles of correct drug use – types of pharmacotherapy and rational pharmacotherapy.

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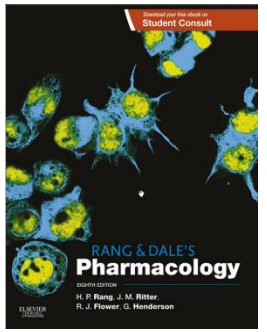
Organisation remarks, literature

- periodic lessons, weeks 2-16
- practical lessons as follow-up to lectures
- basic knowledge from the lectures
- practical tasks, worksheets, problem oriented learning
- self-study of selected topics, the interim evaluation system
- **Rang, H.P. a kol. Rang and Dale‘s pharmacology 8th ed. (2016)**



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Pharmacology as science

pharmacology ≠ pharmacy

- pharmakon (φάρμακον) = „drug“ + logos (λόγος) = „science“

- **INTERACTIONS BETWEEN SUBSTANCES..**

  introduced into the organism from the environment

..AND THE LIVING ORGANISM

on all levels of complexity:
molecular, cellular, organ and organism as a whole…

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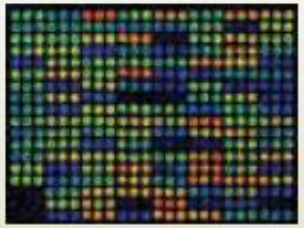
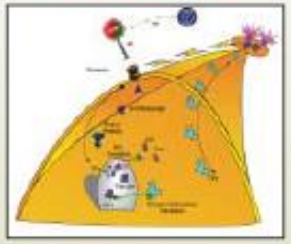
Pharmacology as science

Genetic



Gene Chip Microarray.
Courtesy of Annette Thelen, MSU Genomics Structure Facility.

Molecular

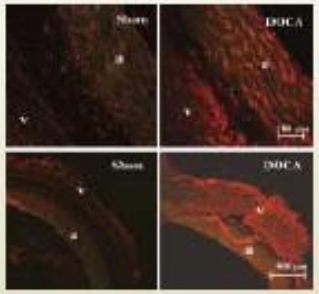


Interaction of the dopamine (D2) and dynorphin system in regulation of tuberoinfundibular neuronal function.
Courtesy of Y. Will-Murphy and K. Lookingland

Cellular

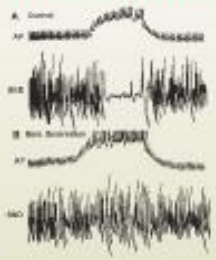
Astrocyte, labelled with Glial Fibrillary Acidic Protein
Courtesy of J. Edwards and B. Atchison.

Tissue



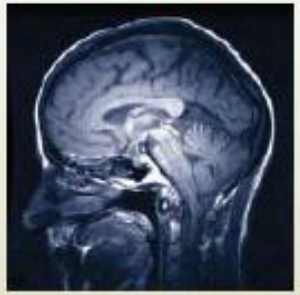
Superoxide measurement through dihydroethidium in artery (a) and vein (v) of normotensive (sham) and hypertensive (DOCA) rats.
Courtesy of H. Xu and J. Galligan

Whole Animal



Effect of sectioning baroreceptor nerves (denervation) on the inhibition of sympathetic nerve discharge during a rise in arterial pressure in an anesthetized cat.
AP = arterial pressure, SND = sympathetic nerve discharge.
Courtesy of S. Barman and G. Gebber.

Human



MRI of Human Head
Courtesy of Kevin Henley and James Potchen of the Radiology Department, MSU

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History of the Pharmacology

- Founder of specific drug effects - physiologist **Newport Langley (1852–1925)** and immunologist **Paul Ehrlich (1854 – 1915).**

- Langley – pharmacology of vegetative nervous system and hormonal regulations

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History of the Pharmacology

- Theory of specific drug effects was supported by the research of Raymond P. Ahlquist - „A study of the adrenotropic receptors“ published in 1948 in American Journal of Physiology /**α a β receptors**/

- 1964 british clinical pharmacologist James W. Black developed „**propranolol**“ – the first beta-blocker

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History of the Pharmacology

Discovery of DNA double helix, James D. Watson a Francis Crick, Nature 1953

- 1972 - recombinant DNA firstly produced (rDNA)
- 1975 - first mAb – monoclonal antibody developed (mAb)
- 1982 - first fully recombinant drug used clinically - insulinn (Genentech)

- Chemical substances
- Biotechnological drugs (monoclonal antibodies)
- Advanced Therapy Medicinal Products (ATMP)
  - Gene therapy medicinal products
  - Somatic cell therapy medicinal products
  - Tissue engineered products

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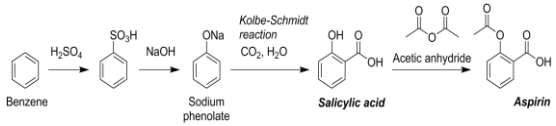
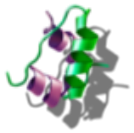
„Chemical“ versus „biotechnological“ drugs

Small Molecule

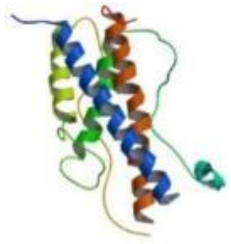
Acetylsalicylic acid[1]
~ 180 daltons



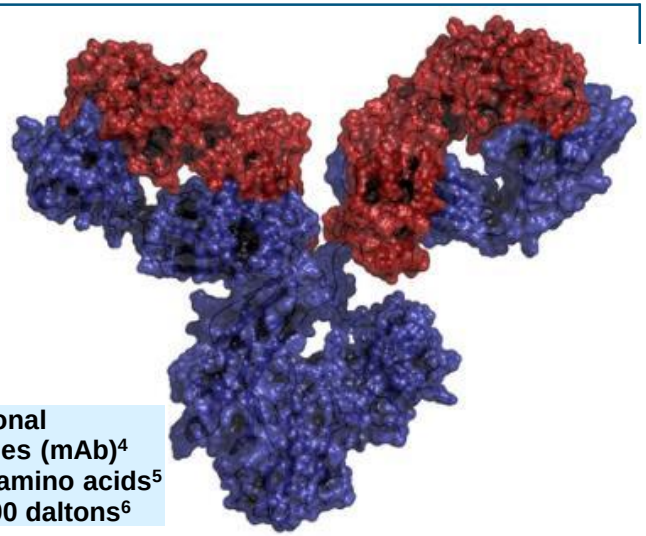
Biologics



Insulin[2]
~ 5,700 daltons



Growth hormone[3]
191 amino acids
~ 22,000 daltons



Monoclonal antibodies (mAb)[4]
~ 1,300 amino acids[5]
~ 150,000 daltons[6]

Generic	Small Biologic	Large Biologic
Same Structure	Highly Similar Structure	

Jimenez AG, et al. Presented at: ICH GCG ASEAN Training Workshop on ICH Q5C; May 30–31, 2011

Branches of Pharmacology

- Basic Pharmacology (general principles + pharmacology of the systems
- Experimental Pharmacology (preclinical pharmacology)
- Clinical Pharmacology (subbranches)
  - Clinical pharmacokinetic (TDM)
  - Pharmacogenetics / pharmacogenomics
  - Toxicology
  - Pharmacoepidemiology
  - Pharmacovigilance
  - Pharmacoeconomics

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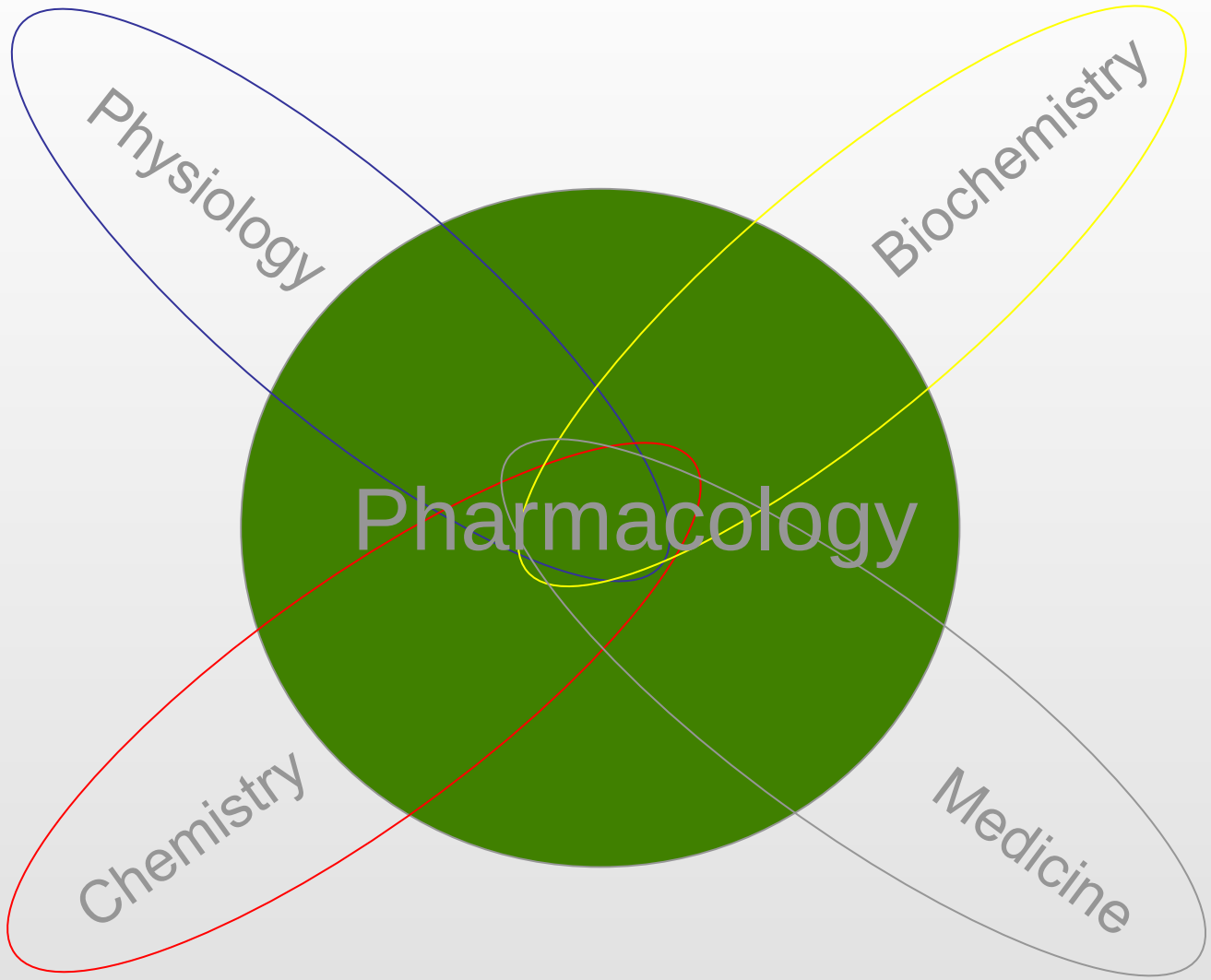
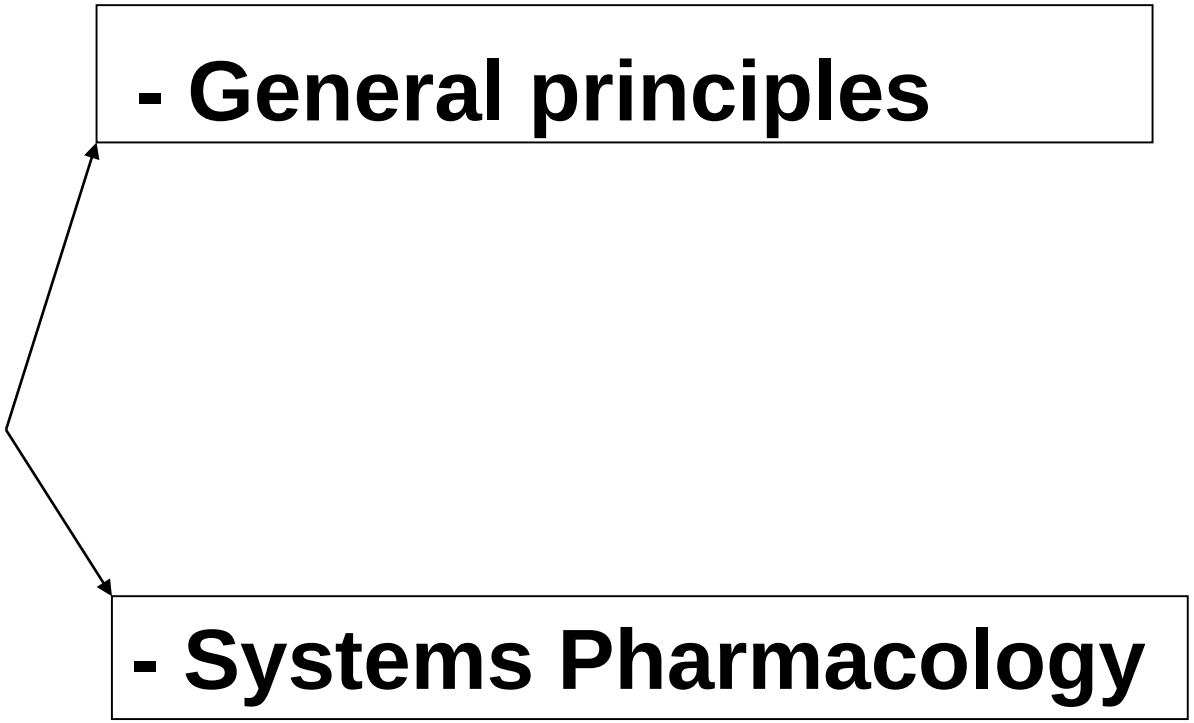
Pharmacology as the synthesis of several biomedical sciences….



…but unique in its own right

Basic Pharmacology



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General Principles

- Principles which predestinate the interactions of the drug and body

Two important and interrelated areas:

- General Pharmacokinetics
- General Pharmacodynamics

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General Principles

Pharmacokinetics (PK)

Deals with the fate of the drug in the body – processes of

Absorption,
Distribution
Metabolism
Excretion

„What the body makes with the drug“

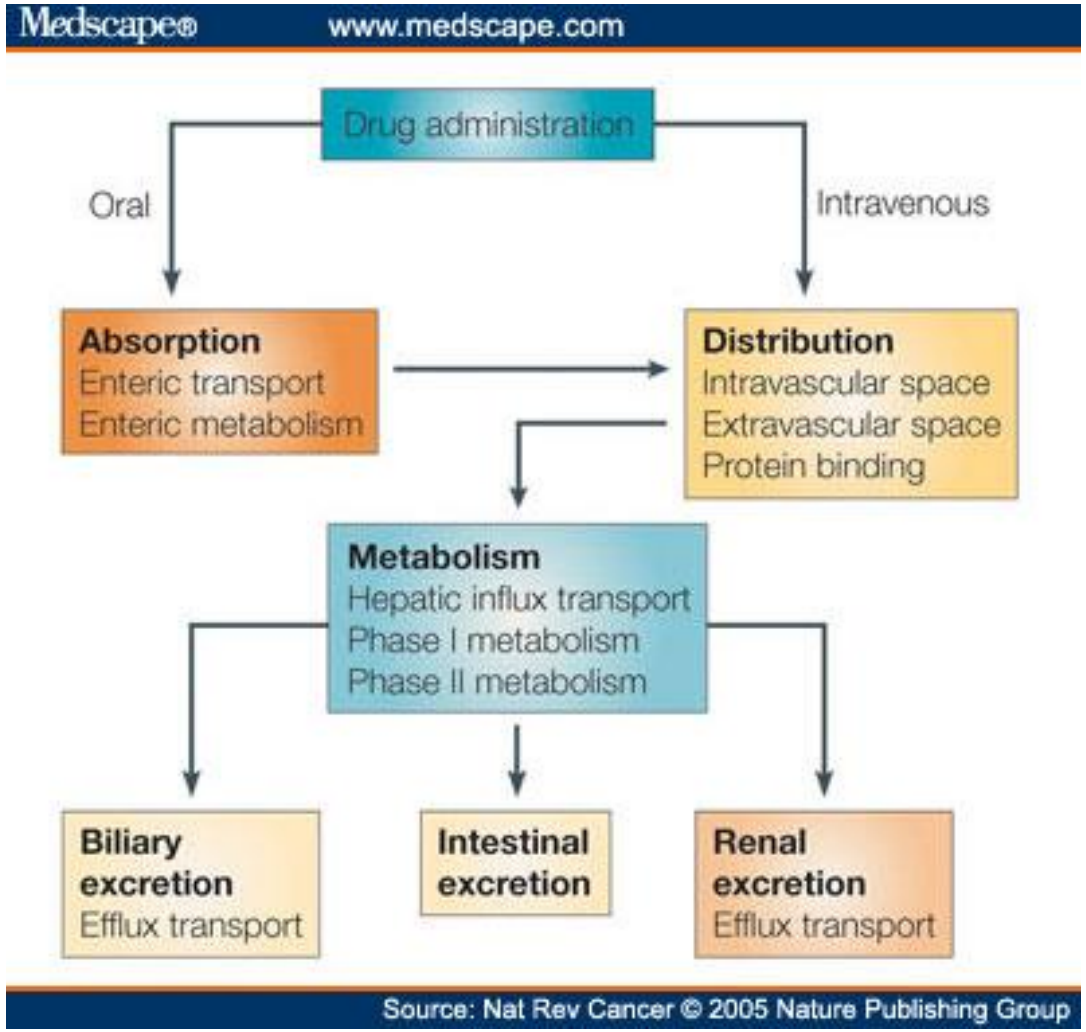
…“ADME“

Pharmacodynamics (PD)

deals with the mechanism of action (e.g. receptor sites, molecular level of action..)

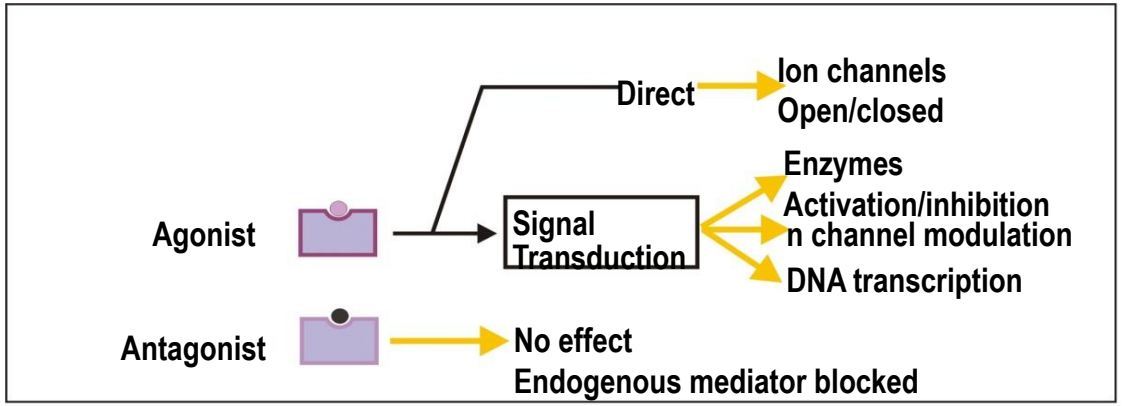
„How does it work“

Pharmacokinetics

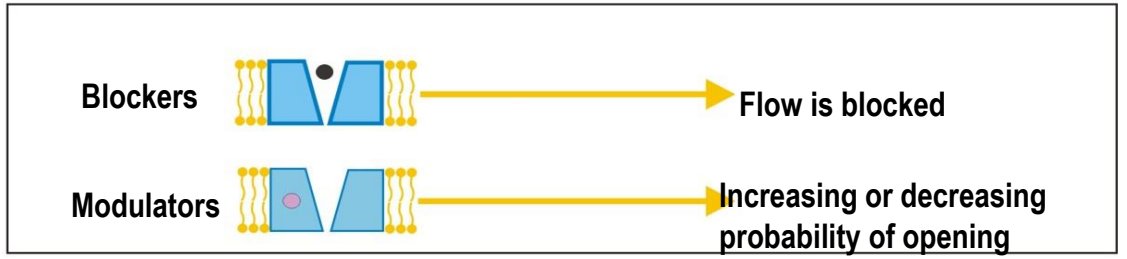


Pharmacodynamics

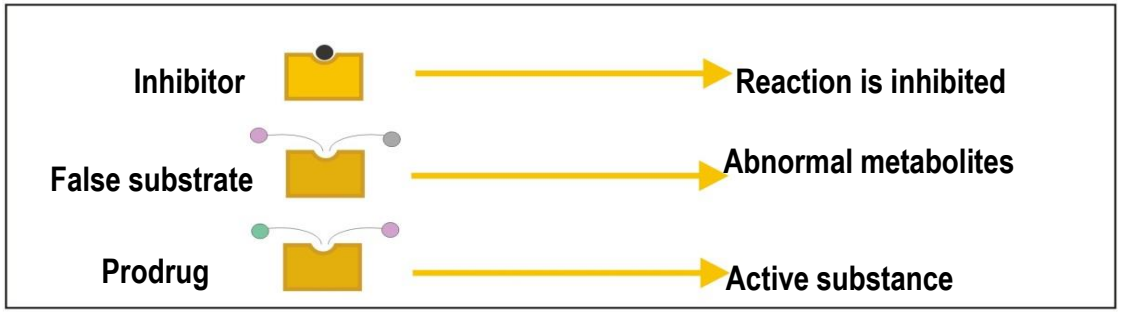
A. RECEPTORS



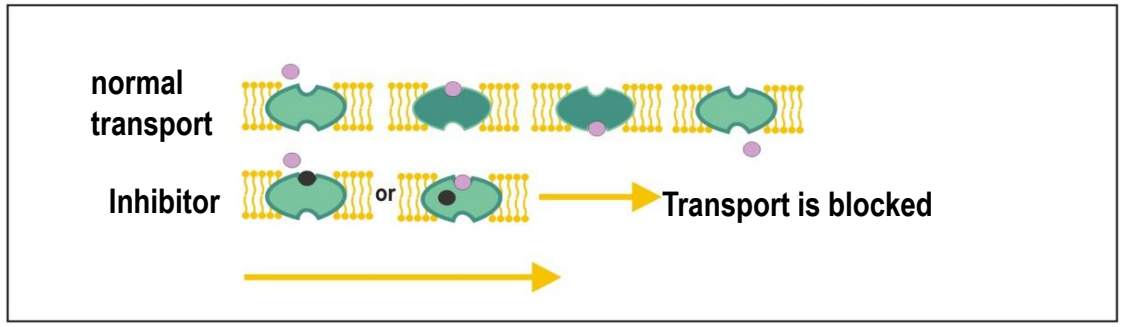
B. ION CHANNELS



C. ENZYMES



D. CARRIERS



Rang and Dale Pharmacology, 2012

Experimental pharmacology

- Experimental science
- Biological experiment
  - In silico
  - In vitro
  - In vivo
- Self-study – study material IS

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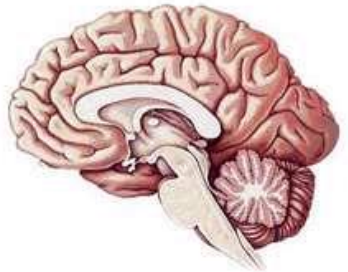
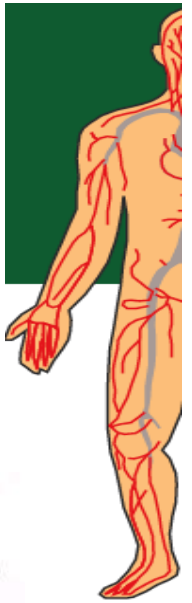
Systems pharmacology

❖ **Neuropharmacology:** study of the effect of drugs on components of the nervous system (brain, spinal cord, nerves)

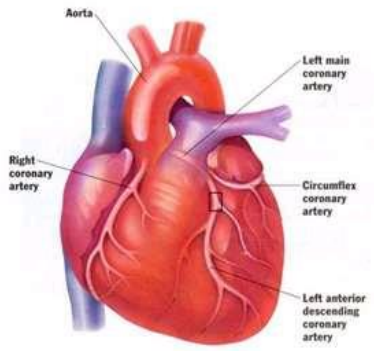
Example: treatment of Alzheimer's dissease





❖ **Cardiovascular Pharmacology:** study of the effects of drugs on heart, vasculature, kidney, nervous and endocrine systems that participate in cardiovascular function.

Example: treatment of high blood pressure (hypertension)



Clinical Pharmacology

- deals with different drugs and their varied clinical usage
- interdisciplinary branch, which integrates basic and experimental Pharmacology with the clinical and complementary branches…

AIM: to study and evaluate the effect of the drug using objective methods (EBM)

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Toxicology

- the study of the toxic effects of chemicals on living organism

- study of symptoms, mechanisms, treatments and detection of poisoning
  - ✓Experimental (in vitro, in vivo)
  - ✓Clinical - poisoning prophylaxis, diagnosis, treatment
  - ✓Forensic toxicology…

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Pharmacogenetics

- deals with the influence of genetic variation on Pharmacokinetics and Pharmacodynamics
- study of the drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity
- consequences can be either quantitative or qualitative

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- Drugs metabolized by cytochrome P450
- Glucose-6-phosphate dehydrogenase deficiency
- Succinylcholine - prolonged apnea
- Altered kinetics of butyrylcholinesterase
- Isoniazid - fast and slow acetylation
- Mutation of the N-acetyltransferase gene

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Pharmacogenetics, pharmacogenomics

- 1959 Friedrich Vogel used first time term „**pharmacogenetics**“

- 1997 First time used term “**Pharmacogenomics**“

Pharmacogenetics considers one or at most a few genes of interest, while pharmacogenomics considers the entire genome.

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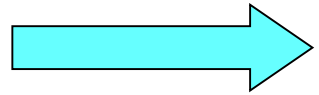
Pharmacovigilance

- Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects 
- collecting, monitoring, researching and evaluating information from healthcare providers and patients on the adverse effects of medication
- AIM: to minimize the risk of adverse effects

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Regulatory Agency_CZ and EU

Pharmacoepidemiology

- Study of the effect of drugs on populations; questions dealing with the influence of genetics are particularly important
- Risks and benefits of the therapy using epidemiological methods
- Approach of the health specialists (GP, pharmacist)
  - ✓ patient (compliance)
  - ✓ society (drug abuse, marketing, financial resources…)

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Pharmacoeconomics

- rationalize the use of sources in health care
- Compares the costs of therapeutic approaches by the pharmacoeconomical analyses
- The goal is not „to decrease total money spent in health care“ , but to use the sources effectively

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Basic Terms: Pharmacon / Drug

classical WHO definition:

- „Any substance (other than normal body components or substances necessary for normal body functions (food, water, oxygen), that, after administration into the organism evokes a change of a body function“

More precise definition according to Ph.Eur.:

- Substances or their mixtures designed to the administration in humans or animals with a purpose of treatment, prevention or diagnose of a disease or its symptoms and also to modulation of physiological substances.
  - European Pharmacopoea (Ph. Eur. 6th Ed.)
  - Pharmacopoea Bohemica 2009 (Ph. B. 2009)

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Medicinal product

- a substance or combination of substances
- presented as having therapeutic or preventive properties or as having influence over physiological functions, or administered to set the medical diagnosis.
  - Prevention
  - Diagnosis
  - Treatment of disease

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Generics

- **Original MPs** – originally conceived MPs

- **Generic MPs** – equivalents to original MPs that may enter the market:
  - once the patent protection of the original MPs expires
  - once the principle of fundamental similarity with the original MP is met
  - the price of generic MPs is usually lower than the price of original MPs

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Biosimilars

- „Legal copies” of biotechnological pharmaceuticals after the patent protection of the original biotechnological pharmaceutical expires

- Called Follow-on-Biologics, or FOBs for short, overseas.

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Drug names

- **Chemical name** (according to chemicals structure)
- **Generic name** (non-proprietary)
  supposed to be used internationally
  has to be printed on the packing of the drug (under the registered trade name) for the universal terminological identification of the medicines

  e.g. paracetamol

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Drug names

Trade name (proprietary)

registered, patent-protected ®
e.g. Panadol, Coldrex, Paralen

Officinal name

latin name in Pharmacopoeia (e.g. Paracetamolum)
has to be prescribed on Rx formulary in case of individually prescribed medicines
Paracetamolum

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Some drug-family names…

- „-olol“ betareceptor antagonists
- „-caine“ local anaestethics
- „-tidine“ histamine 2 receptor antagonists
- „-dipine“ calcium channel blockers of dihydropyridine type
- „-statin“ inhibitors of HMG CoA transferase

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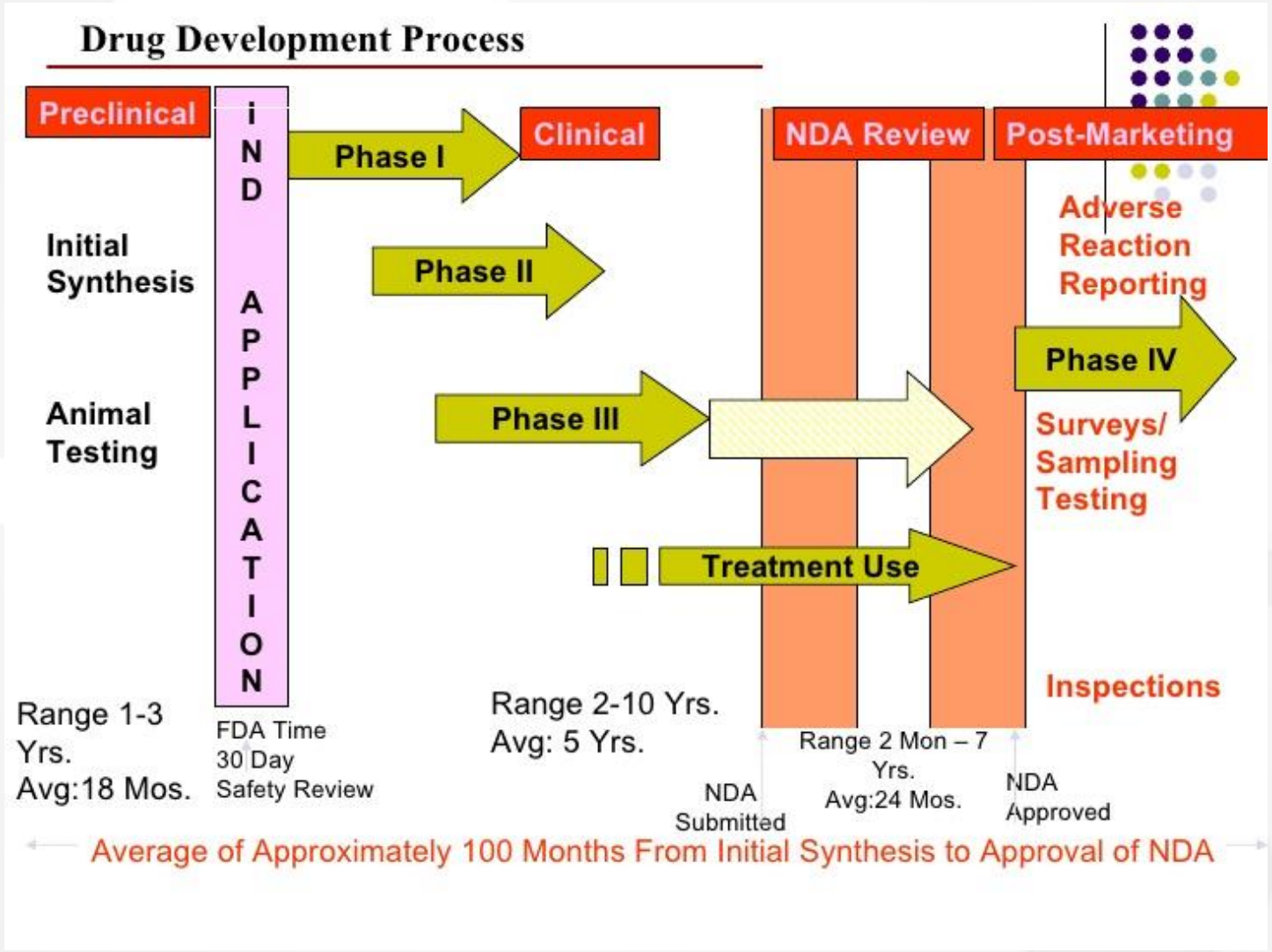
Drug Life-Cycle



Clinical Trial Phases

(Preclinical research)

Phase I trials

Phase II trials

Phase III trials

Phase IV trials

Pre-clinical Phase

Involve *in vitro* (test tube or laboratory) studies and trials on animal populations.

Wide ranging dosages of the compounds are introduced to the animal subjects or to an *in vitro* substrate.

Obtain preliminary efficacy and pharmacokinetic information.

Decisions are made during this phase regarding further development of the test compound, test item, or test article.

Phases of Clinical Trials

Category	# of Participants	Purpose
Phase I	Less than 10	Tests how to administer a new therapy, exam, or preventive option
Phase II	30-40	Test patients responses to a new therapy, exam, or preventive option
Phase III	100-1000+	Compares new therapy exam or preventive option to a standard one
Phase IV	Varies	For marketing purposes, to compare the effectiveness of two therapies already on the market or to study new uses of therapies

Phase I

First step in testing in humans.

Researchers look for safety and potentially harmful side effects.

Usually include only a limited number of human subjects (20-80).

This phase of testing usually takes several months.

Early stopping of clinical trials-iFAAH, sildenafil

Medical research

French drug trial leaves one brain dead and five critically ill

Ninety people took some dosage of experimental drug being tested for Portuguese pharmaceutical company Bial

Angelique Chrisafis in Paris
@achrisafis
Fri 15 Jan 2016 16.49 GMT

This article is over 2 years old

French health minister Marisol Touraine discusses the 'very serious accident'

One person is brain dead and five others are seriously ill after taking part in a drug trial for Portuguese pharmaceutical firm Bial at a clinic in north-west France.

The French health ministry said the six male patients aged 28 to 49 had been in good health until taking the oral medication. They started taking the drug on 7 January. One person started feeling ill on Sunday and the other five afterwards. The brain dead volunteer was admitted to hospital in Rennes on Monday. Other patients went in on Wednesday and Thursday.

Pierre-Gilles Edan, head of the hospital's neurology department, said one man was brain dead, three others were suffering a "handicap that could be irreversible" and another had neurological problems. The sixth volunteer had no symptoms but was being monitored.

French health minister confirms one brain dead and five seriously ill in Rennes – video

The French health minister, Marisol Touraine, said 90 people in total had taken part in the trial and received some dosage of the drug; others had taken a placebo. All trials on the drug have been suspended and all

Leading microbiome-based therapeutic falters in Phase II trial

Seres's SER-109 will miss the primary end point in its Phase II trial in patients with *Clostridium difficile* infection, showed an interim analysis of the trial last month. The setback highlights the uncertainty ahead for a burgeoning field of microbiome-based drugs.

Faecal microbiota transplantations are effective for the treatment of *C. difficile* infections, but they require the transfer of minimally processed and uncharacterized faecal matter from healthy donors to recipients (*N. Engl. J. Med.* **368**, 407–415; 2013). By fractionating and processing the stool of healthy volunteers to purify for approximately 50 species of Firmicute spores, Seres hopes that its SER-109 will provide a safer, more palatable, alternative to faecal microbiota transplantation. Seres's orally delivered drug is the first-ever clinically studied synthetic microbiome therapeutic, and it received breakthrough therapy designation from the US FDA in 2015 after producing promising Phase I/II data (*J. Infect Dis.* **214**, 173–181; 2016).

An interim analysis of the 89-subject Phase II trial of the drug recently found, however, that SER-109 is not on track to reduce the relative risk of recurrence of *C. difficile* infection at 8 weeks. Seres's CEO Roger Pomerantz noted that recurrence rates in both the treatment arm and the placebo arm were inconsistent with the company's expectations. Seres did not observe any difference in the adverse event frequency between treatment and placebo. The trial is ongoing, while Seres re-evaluates its development plan for SER-109.

Although there is great excitement over the role of the microbiome in health and disease, the disappointing results show how hard it will be to distil treatment strategies from complex bacterial imbalances.

Asher Mullard

mRNA-based drug approaches Phase I milestone

Moderna and partner AstraZeneca have filed paperwork to advance the first 'secreted protein' mRNA drug into Phase I trials.

cells, AZD8601 might provide a regenerative treatment option for patients with heart failure, diabetic wound healing and other ischaemic vascular diseases.

Earlier this year Moderna also advanced mRNA 1440 and mRNA 1851, two infectious disease mRNA vaccines against undisclosed

Asher Mullard

EMA rewrites Phase I guidelines in aftermath of FAAH tragedy

The European Medicines Agency (EMA) is proposing a set of changes to its guidelines on how to reduce the risks of first-in-human trials. The agency says a rewrite is needed in part to incorporate lessons learnt from the tragic Phase I first-in-human trial of Bial's BIA 1-2474 earlier this year. One volunteer died and four volunteers were hospitalized owing to adverse effects of the fatty acid amide hydrolase (FAAH) inhibitor. A report by French drug safety regulators found that poor study design likely contributed, noting that doses were escalated too quickly and without taking into account pharmacokinetic data from previously dosed patients.

The EMA also notes that the current guidelines, written in 2007, focus on non-clinical aspects of drug development and single-ascending-dose trials. The EMA plans to update the guidelines to reflect increased use of 'integrated' trial designs that combine multiple substudies (analysing single and multiple ascending doses, food interactions, different age groups and early proof-of-concept end points) into a single first-in-human trial.

Comments on the proposal are due by 30 September 2016. A revised draft guideline is expected by the end of the year.

Separately, the US FDA concluded last month that BIA 1-2474 "exhibits a unique

Phase II

Once a drug has shown to be safe, then it must be tested for efficacy.

This phase may last from several months to two years.

Usually involves several hundred patients

Only about 1/3 of these studies successfully complete both phase I and phase II due to poor patient activity or toxic effects.

Phase III

Randomized control trials on large patient groups (300-3000).

Compare the results of the patients on the experimental trial to those patients utilizing standard diagnostic studies or treatment.

Studies move into this phase only after a diagnostic agent, modality, or treatments have shown promise in phase I and II trials.

These trials are typically *multi-center* trials.

Many phase III trials are *randomized* and *blinded.*

Phase IV

Involve safety surveillance and ongoing technical support of a drug.

Sometimes mandated by the Regulatory authorities for additional testing including interactions with other drugs and testing on certain populations.

Adverse effects detected by Phase IV trials may result in withdrawal or restriction of a drug -recent examples include Vioxx.

Examples of drug withdrawals

- **rofecoxib (HVLP Vioxx)**
- CVS AE, - AMI
- **clobutinol** (HVLP *Silomat*)
- Heart dysrhytmias
- **rosiglitazon**
- CVS risk

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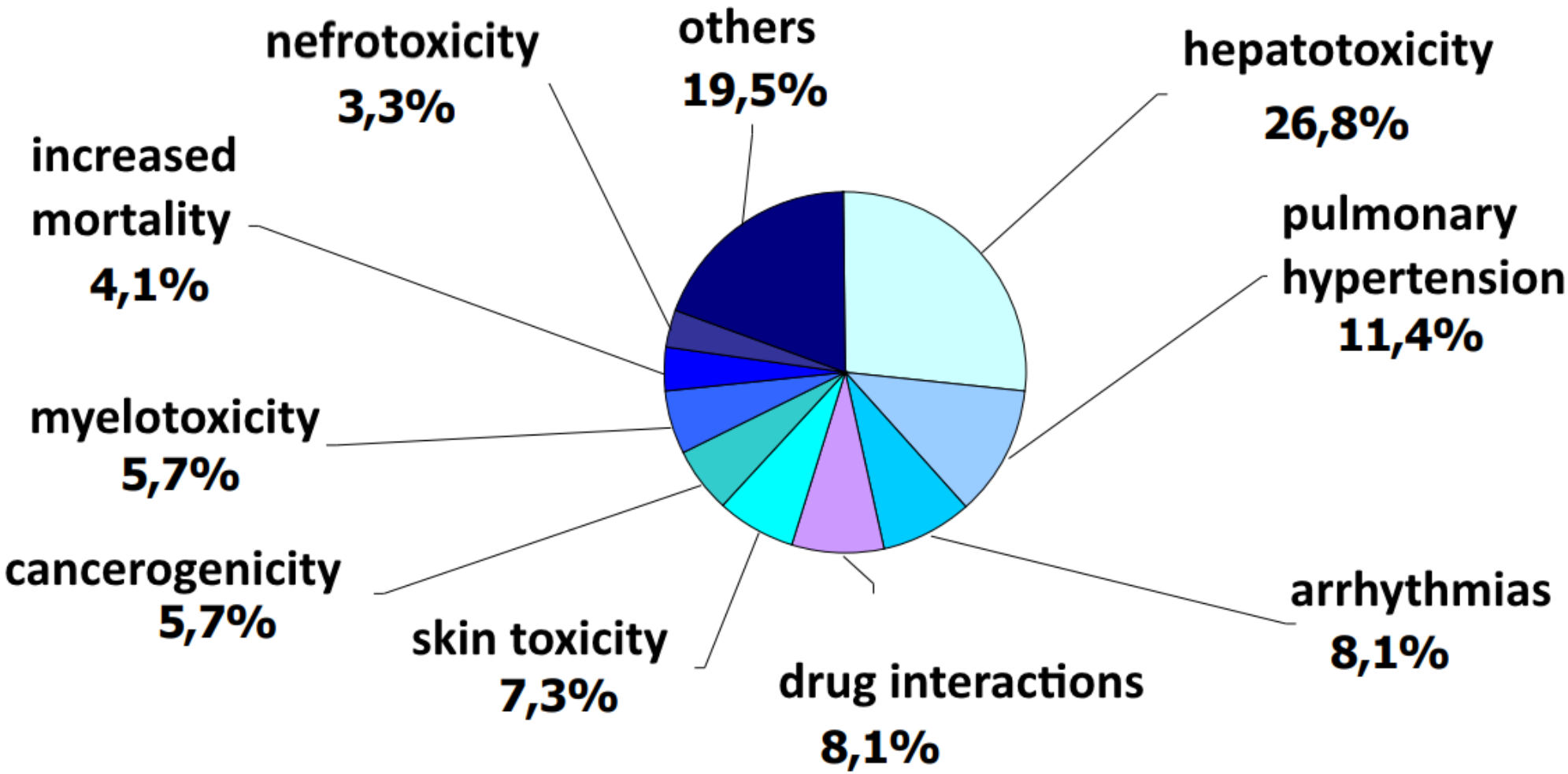
Reasons for drug withdrawal



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Clinical Trials Benefits & Risks

Possible Benefits of Trials	Possible Risks of Trials
• Having access to potentially more effective therapies than those currently available • Receiving quality medical care from leading physicians • Being closely monitored for possible negative effects • Sometimes receiving treatment at a reduced rate or free of charge • Helping to further new research that may result in significant medical advances • For patients in cancer therapy trials assigned to control groups, they still receive the top standard therapy available today	• Patients may not receive the therapy under investigation (may receive a placebo – inactive pill – instead) • The new therapy may not be more effective than the standard, thoroughly tested therapy • In Phase I trails, not knowing the safety consequences of the new therapy (risk is less in Phase III trials) • New therapy may have unexpected, possibly severe side effects or may be less effective than standard of care • Insurance companies may not cover all costs of clinical trials

Drug information sources

- **SÚKL** www.sukl.cz
- **EMA: http://www.ema.europa.eu/ema/**
- **AISLP** www.aislp.cz
- **Drugs.com**
- **Medicines.org.uk**
- **Up-To-Date**
- **Micromedex**
- **Pharmindex**

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Legal Regulations

- Research and Development
- Preclinical and clinical testing
- Registration – market access
- Pricing and reimbursement from health insuarance companies
- Tracking the safety of the marketed drug (pharmacovigilance)
- Production and distribution
- Drug dispensation (pharmacists)
- Advertisement and marketing

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KINDS OF PHARMACOTHERAPY

- CAUSAL / ETHIOLOGICAL – targeting the cause of the disease
- SUBSTITUTIONAL – administration of lacking hormone, peptide, enzyme…
- SYMPTOMATIC – treat only symptoms, not the root cause (because we usually do not know it)

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The rational use of drugs

- patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.

- correct drug
- appropriate indication
- appropriate drug considering efficacy, safety, suitability for the patient, and cost
- appropriate dosage, administration, duration
- no contraindications
- correct dispensing, including appropriate information for patients
- patient adherence to treatment

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Thank you for your attention !

- Next lecture: drug dosage forms

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