

Typical diseases

The search for pharmaceutical drugs used to be rather straight forward up to the late 1990's:

A wealth of information about the disease at hand, its causes, and the clinical symptoms were readily available. Thus the starting point for the pharmacological therapy was known.

Example: inhibition of an pathogenic enzyme

Thus the target was fixed. Frequently, experience with existing medications was available. Therefore a *valid target* or at least a *druggable target* was present.

→ The *target* undergoes a change of its activity caused by the drug

Often, multiple targets can be exploited to treat the same disease. → Therapeutic Categories



Therapeutic Categories

Grouping drugs under the aspect of their pharmacological and therapeutic application results in about 200 categories:

ACE Inhibitor
Adrenocortical Suppressant
Adrenocorticotrophic Hormones
Aldose Reductase Inhibitors
Aldosterone Antagonists
 α -adrenergic Agonists
 α -adrenergic Blockers
 α -Glucosidase Inhibitors
Anabolic Steroids

Analgesic, Dental
Analgesic, Narcotic
Analgesic, Non-narcotic
Androgens
Anesthetics, Inhaled
Anesthetics, Intravenous
Anesthetics, Local
Angiotensin II Antagonists
Anorexics

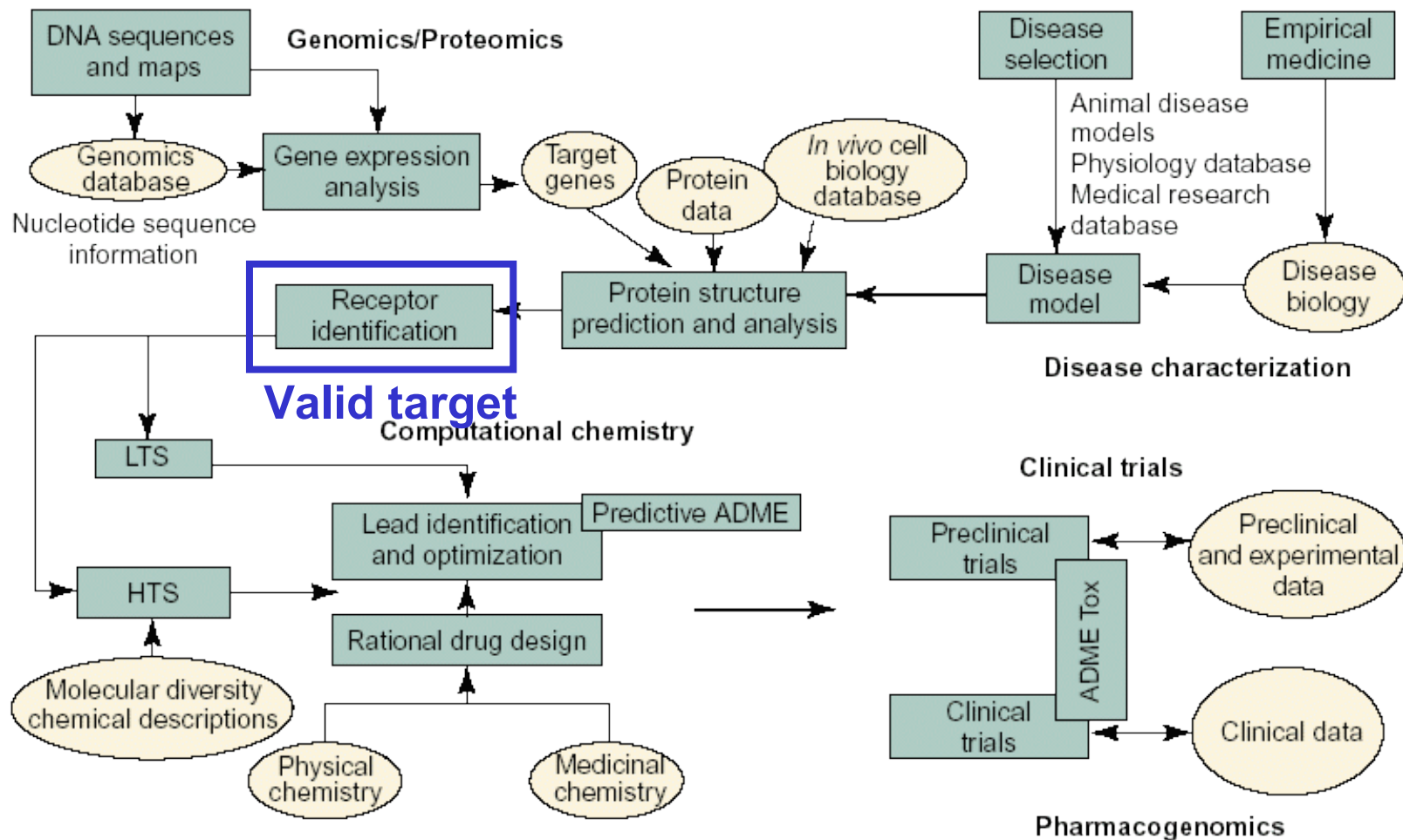


see the corresponding section in the Merck Index



In most cases it is not obvious to recognize the treated disease from a therapeutic class (at least for non-medical persons), sometimes not even the actual molecular target(s).

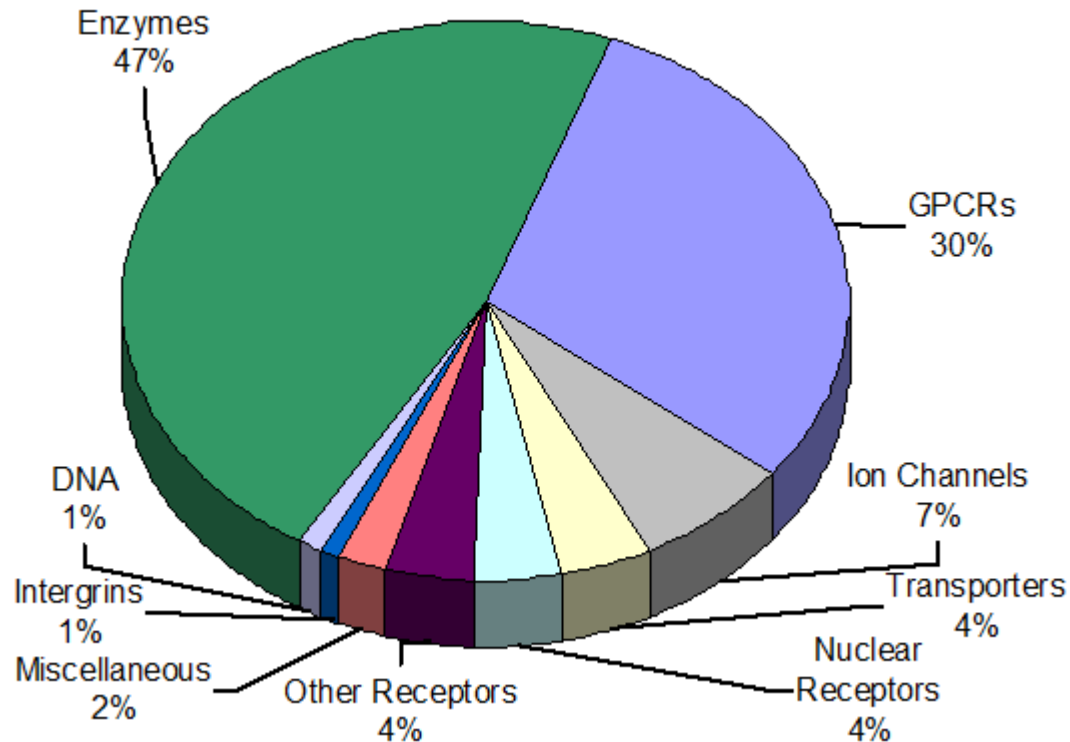
Flow of information in a drug discovery pipeline



Drug Discovery Today

typical targets

drug targets by biochemical class

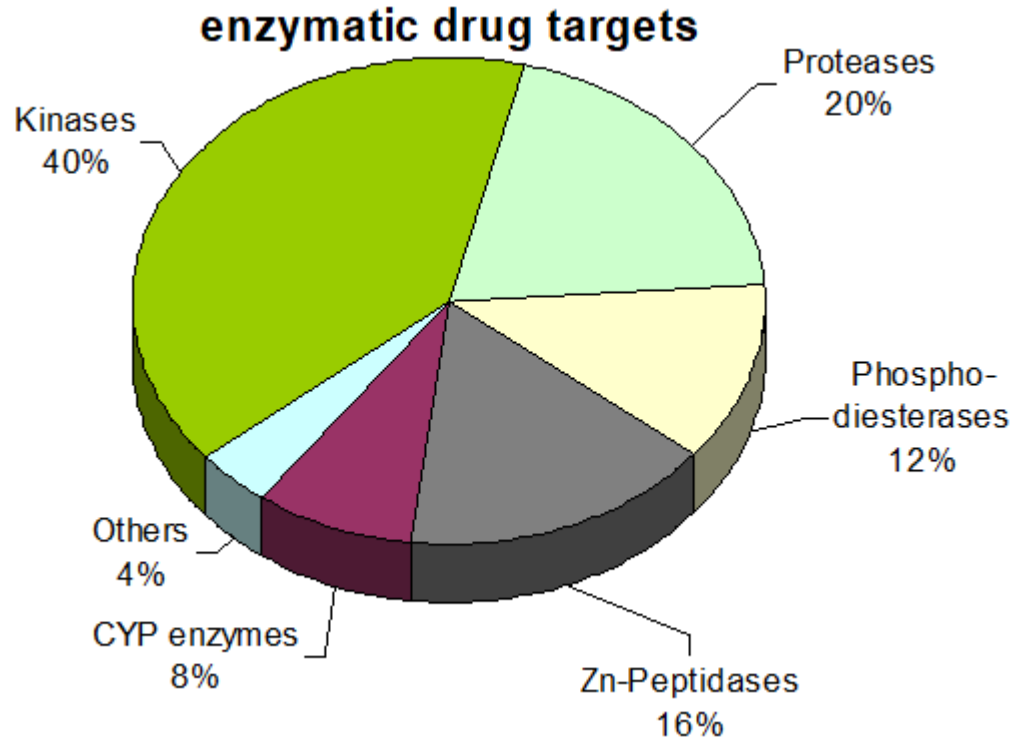


Fractional content of marketed drugs according to their biochemical targets

data: Hopkins & Groom, *Nat.Rev.Drug.Disc.* 1 (2002) 727



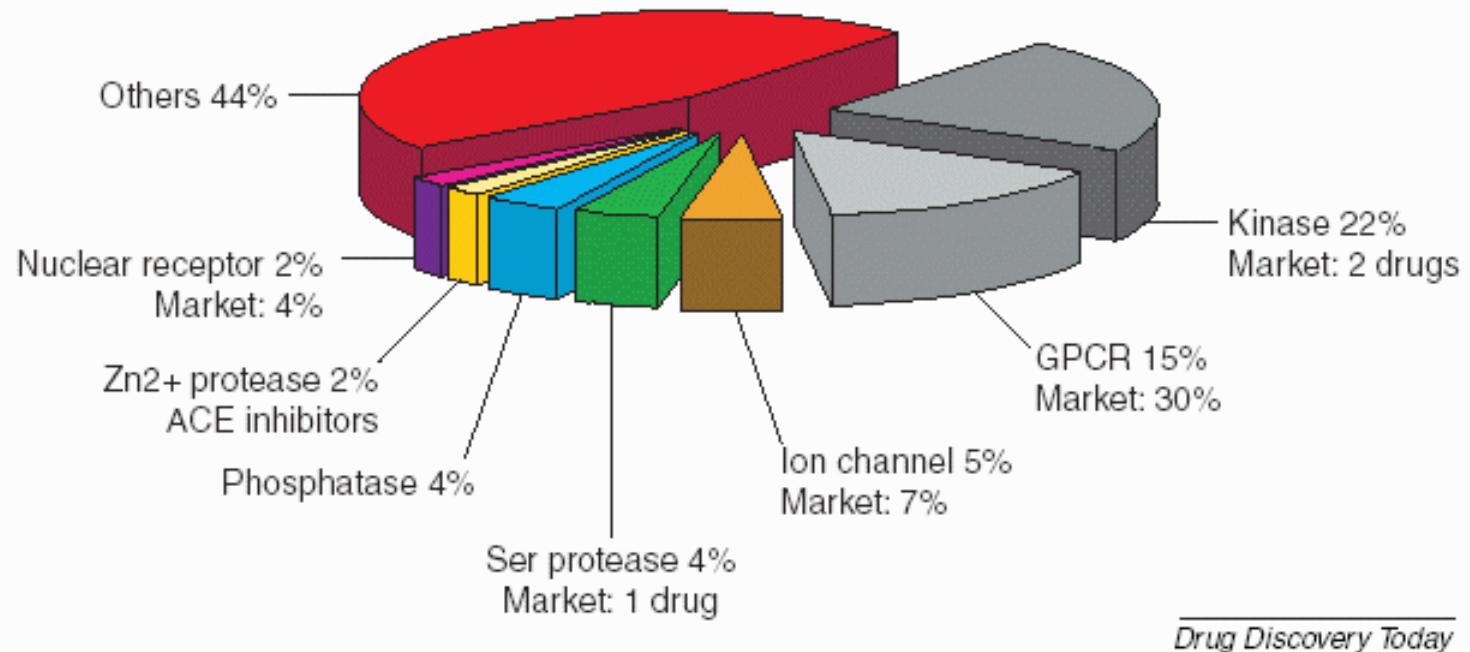
Enzymatic targets



Distribution within the class of enzymes



typical targets

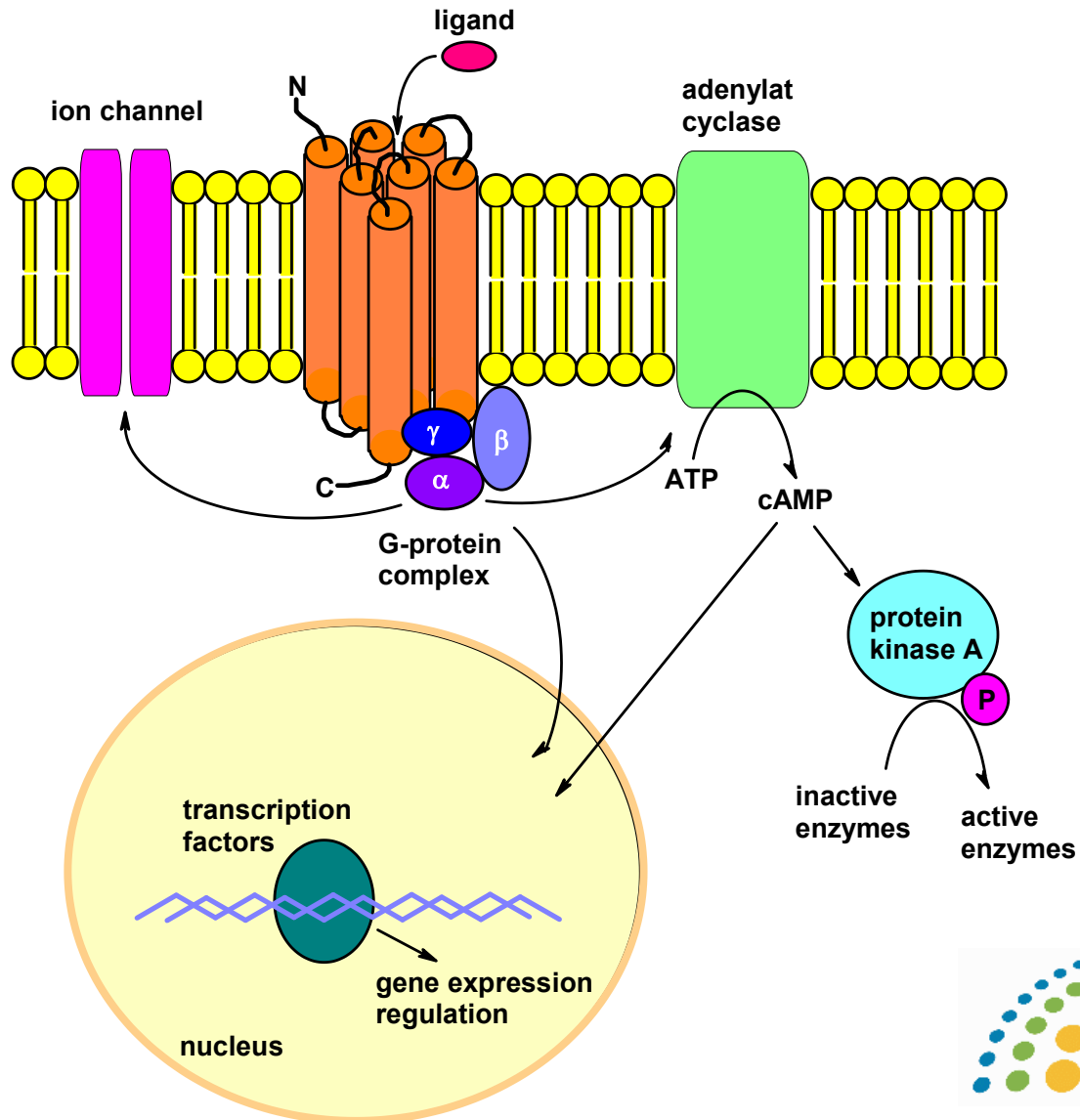


Contribution to the human genome and marketed drugs.
About 500 enzymes have been used as targets, so far.
20,000 - 100,000 estimated potential targets in the human genome.

854 proteins have been associated with FDA approved drugs (source: The Human Protein Atlas)

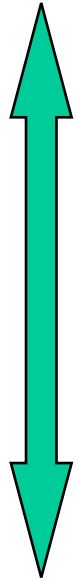


GPCRs and other targets



How do drugs interact with targets ?

proteome



genome

enzymes: substrate analogs, competitive ligands, reversible and irreversible inhibitors, allosteric modulators, protein-protein inhibitors

receptors: antagonists and agonists, orthosteric and allosteric ligands.

ion channels: openers and blockers (inhibitors)

transporters: inhibitors, e.g for (re-)uptake

nuclear receptors: binding to specific DNA-motives

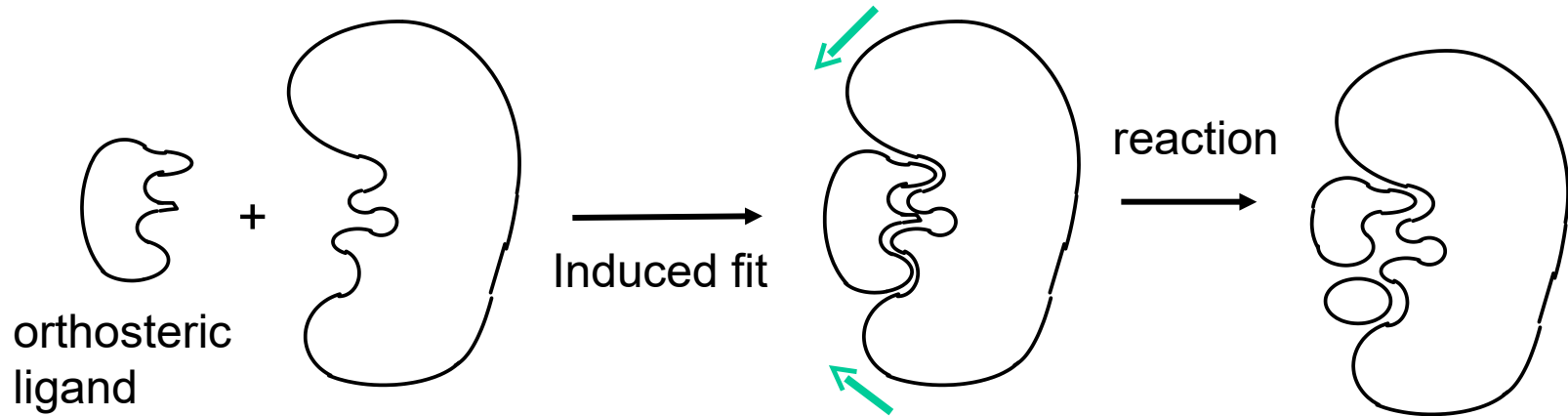
DNA: binding to grooves, intercalation, alkylation, etc.

→ Possible targets can be found in a multitude of cell compartments and at different loci.

Problems: Drug delivery and drug transport / distribution

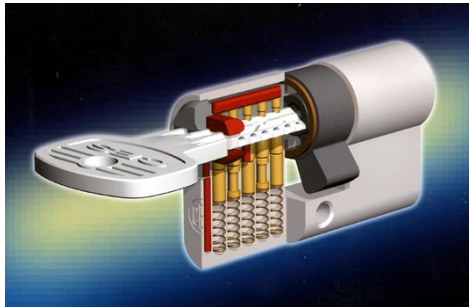
Drugs: mode of action (I)

Normal enzymatic turn-over



conformational
change

lock and key
principle



Drugs: mode of action (II)

competitive inhibitor:

higher affinity than natural substrate, directly acting at the orthosteric site



allosteric inhibitor/effector:

prevents binding by modifying the conformation, but at the allosteric site



Irreversible binding:

chemical reaction leads to inactivation of the enzyme

e.g. acetyl-salicylic acid acetylates Ser530 of Cyclooxygenase, ibrutinib reacts with Cys481 of Bruton's tyrosine kinase



Anti-metabolite:

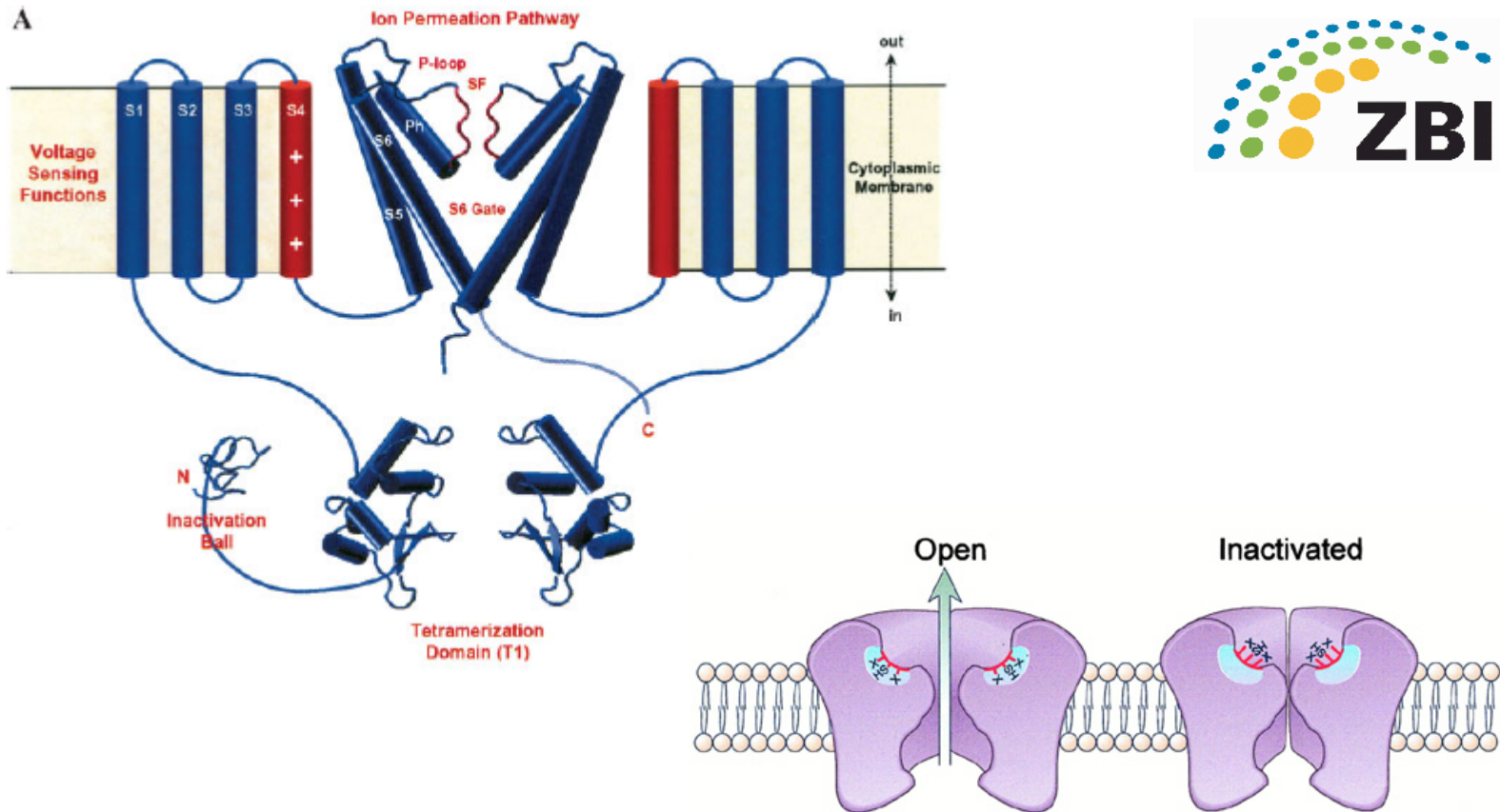
Competitive alternate („wrong“) substrate

e.g. methotrexate instead of dihydrofolate, antiviral nucleoside analogues

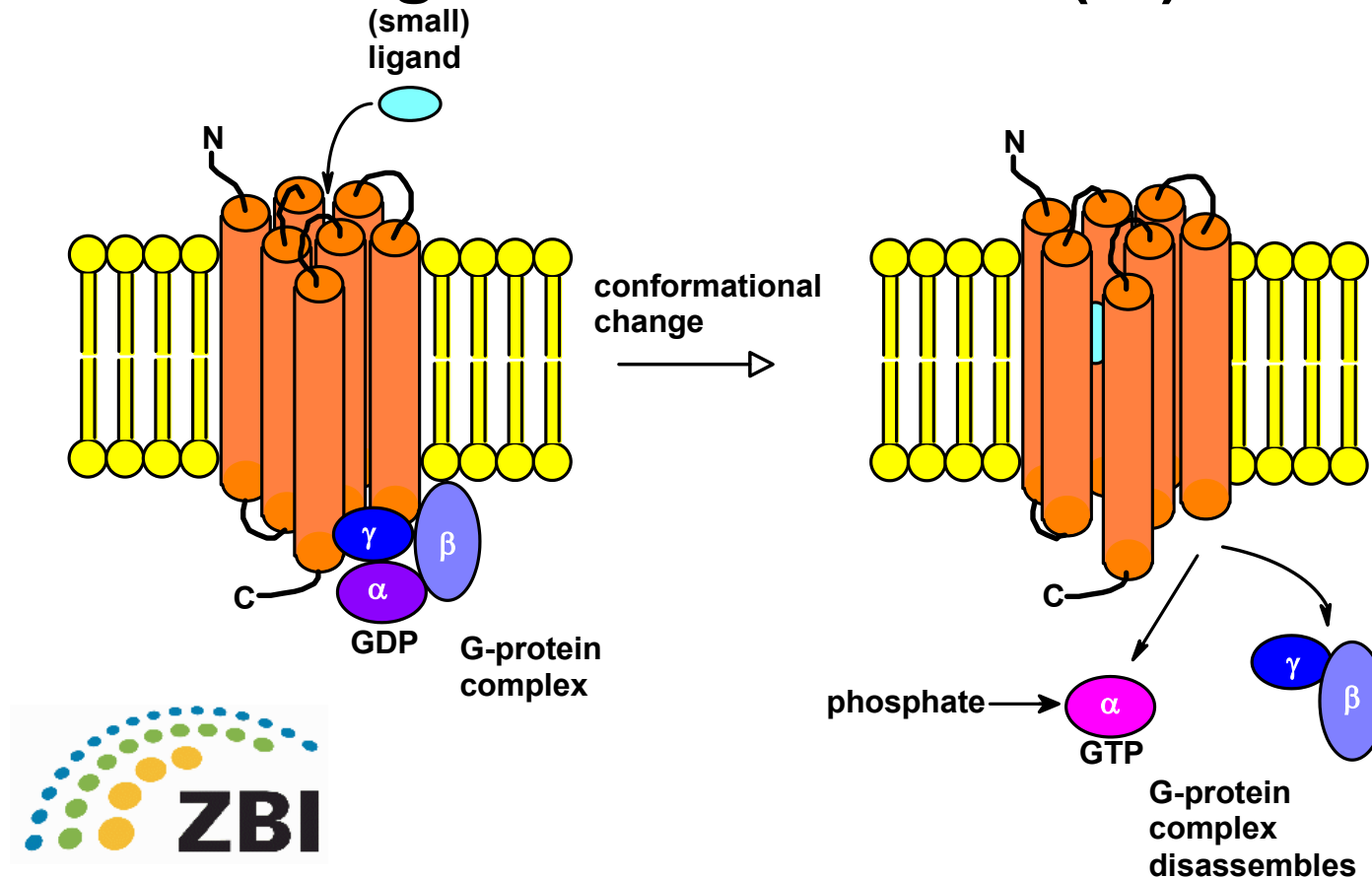


Drugs: mode of action (III)

Ion channels: Mode of action by ligand binding, and also indirectly through receptors



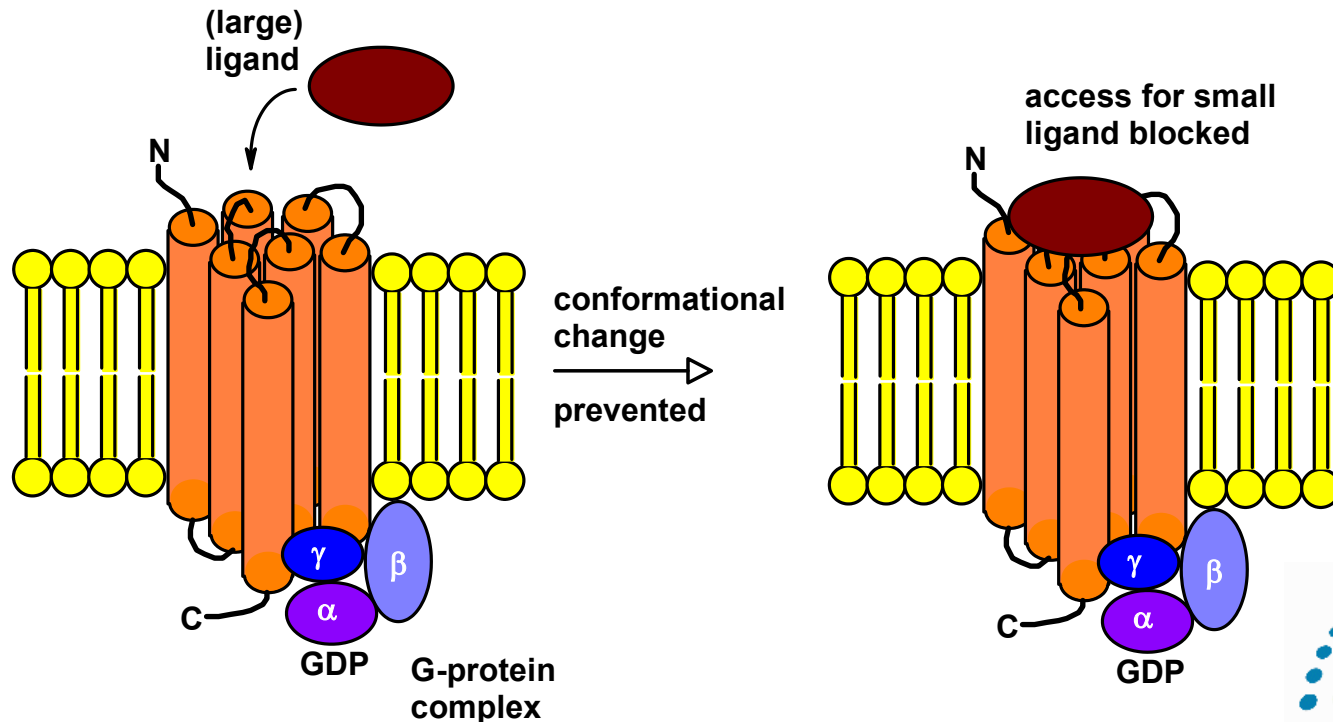
Drugs: mode of action (IV)



agonist: (orthosteric) ligand that causes an intrinsic effect (response of the receptor)

partial agonist: weakly working agonist with high binding affinity, thus also working as antagonist

Drugs: mode of action (V)

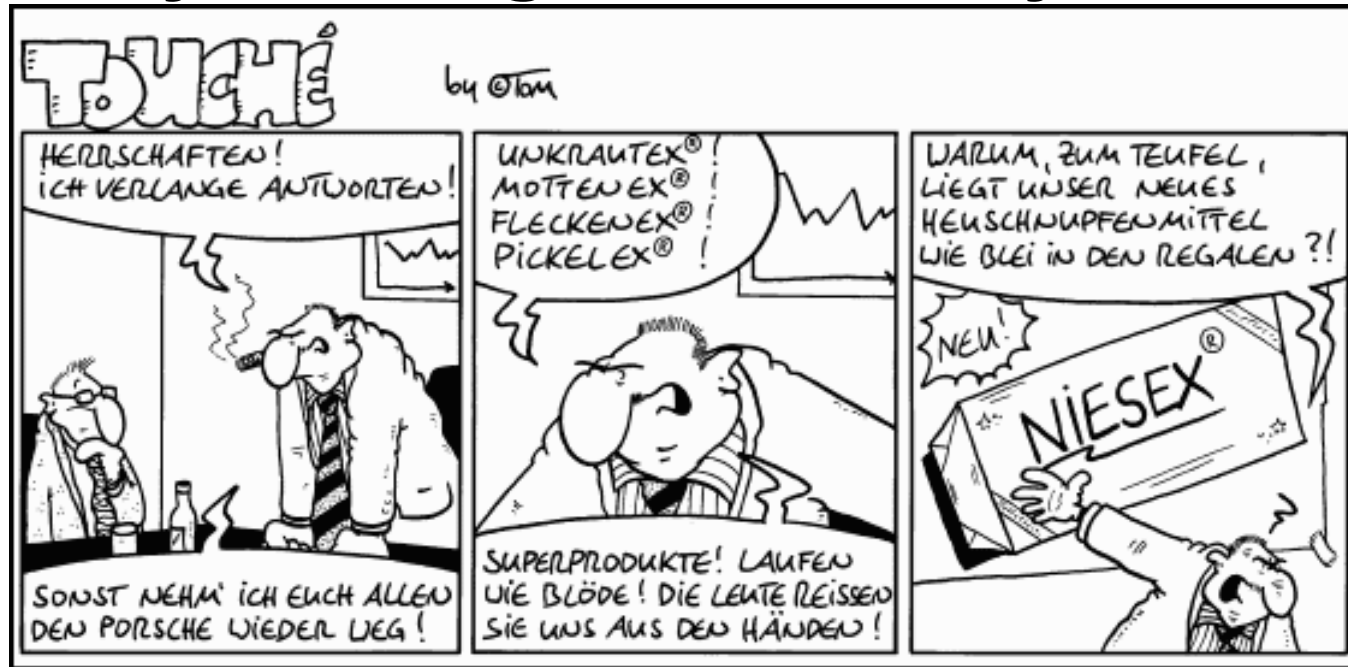


antagonist: ligand that prevents binding of the agonist, either directly (competitive binding at the orthosteric site) or indirectly (at allosteric site, prevents adoption of the reactive conformation)

inverse agonist: ligand stabilizing the inactive conformation

functional antagonist: prevents receptor response by a different mode of action

Why do drugs have funny names ?



Examples for such faults in naming products exist !



Nasonex®
(Mometasone Furoate Monohydrate
Aqueous Nasal Spray)

Naming of drugs (I)

The **trade name** of a drug is usually chosen very carefully. Associative and speech-psychological aspects are considered.

Example within the german language:

The more x and y are appearing in the name, the more toxic.

Acetylsalicylsäure → Aspirin®

Problems will occur, if a product should get the same name throughout all countries. Examples:

Twix® (earlier: Raider)



Naming of drugs (II)

Furthermore, legal aspects have to be considered:
existing words and words that imply a direct connection or
target a specific consumer group cannot be protected.

Example: „Schülerschokolade“ is not possible in Germany

Thus a lot of inspiration is required to find a
pleasant sounding name. Frequently syllables
and foreign words (latin, greek, spanish) are
used that bear associations.

c.f. names for cars



® this name is approved and protected.

™ the producer indicates his intention to have this name
protected.

Naming of drugs (III)

For the naming of the actual chemical substances there are also some (loose and empirical) guidelines.

Such names are adopted as „International Nonproprietary Name“ (INN) or „United States Adopted Name“ (USAN) at the latest upon patent application.

Most of the time, the therapeutic class can be identified solely by the name. (similar names for substances with similar function.)

Prefixes and suffixes reflect chemical modification of the root compound.

Examples: ibufenac, clofenac, diclofenac, oxidanac

→ (unselective) Cyclooxygenase inhibitors

Naming of drugs (IV)

The World Health Organization (WHO) publishes updates regarding the use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

Example: all drugs carrying the suffix (=stem) –coxib are selective Cyclooxygenase II inhibitors:

celecoxib, cimicoxib, deracoxib, etoricoxib, firocoxib,
lumiracoxib, mavacoxib, parecoxib, robenacoxib, rofecoxib,
tilmacoxib, valdecoxib

In such cases the drug target is obvious.

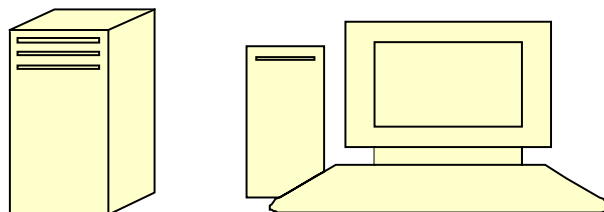


Compound Databases

Size of typical substance libraries (2026)

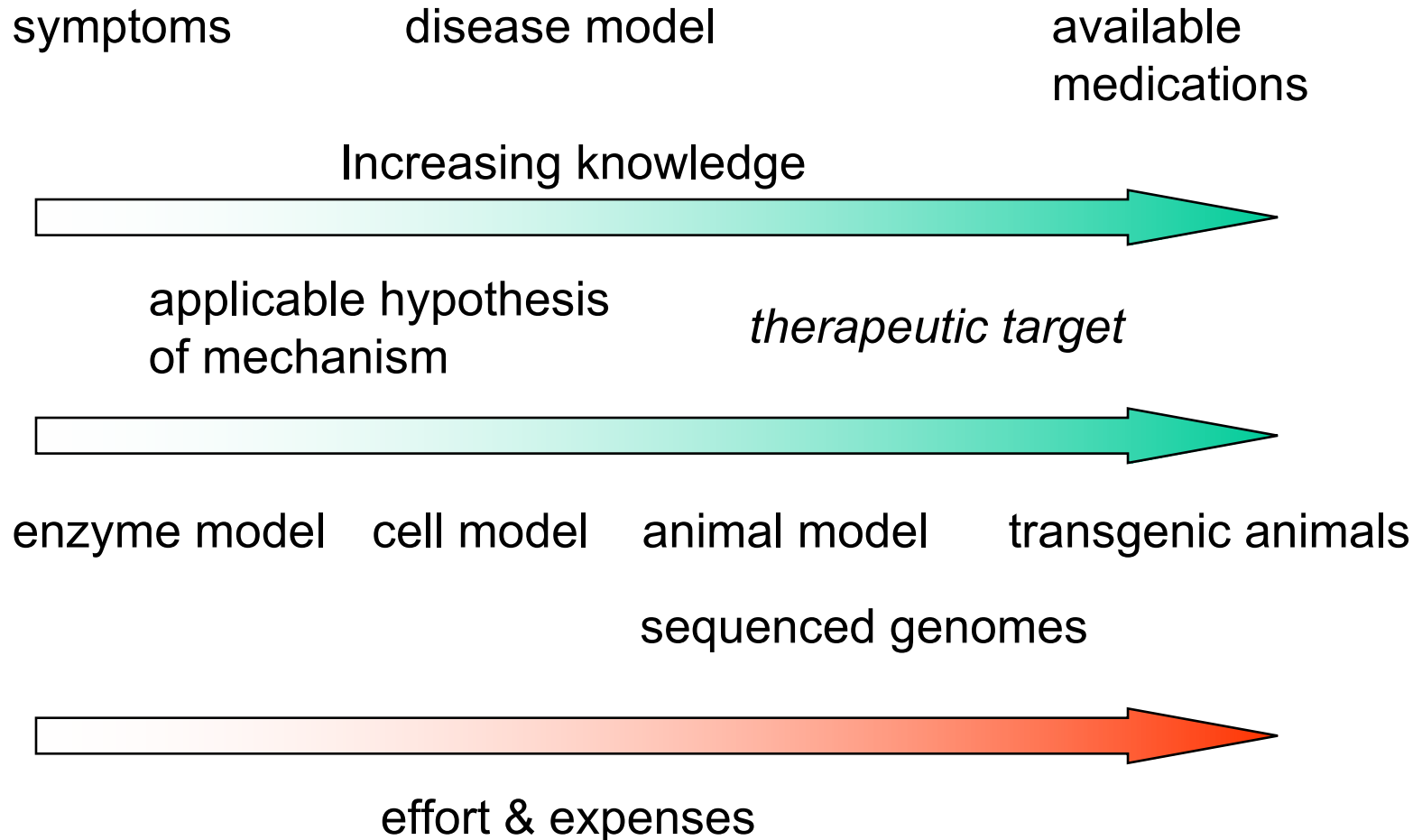
ACD	12,000,000 chemicals	}	commercial
World Drug Index	80,000 compounds		
USAN	<10,000 in clinical trials		
typical virtual library $\approx$ 100,000 compounds			company, in house

PubChem	> 123,000,000 compounds	NCBI	}	academic
ChEMBL	> 2,900,000 compounds	EMBL		
DrugBank	> 19,000 drugs	Uni. Alberta		
ZINC20	> 750,000,000 compounds	UCSF		



Investment per new chemical entity: >1,000,000 \$
New chemical entities per year: ca. 20 (strongly fluctuating)

towards the drug (I)

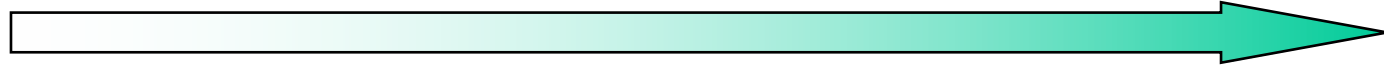


Evolution of Disease Symptoms with Time

1800

1900

2000



Disease causing agents
lack of hygiene
germs, bacteria
viruses



enviromental
influence
carcinogens



life style

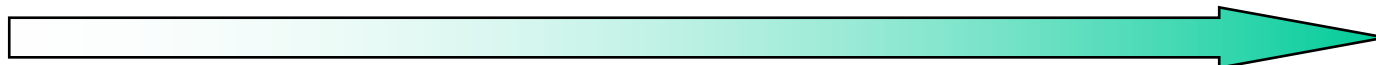


genetic
disposition
susceptibility



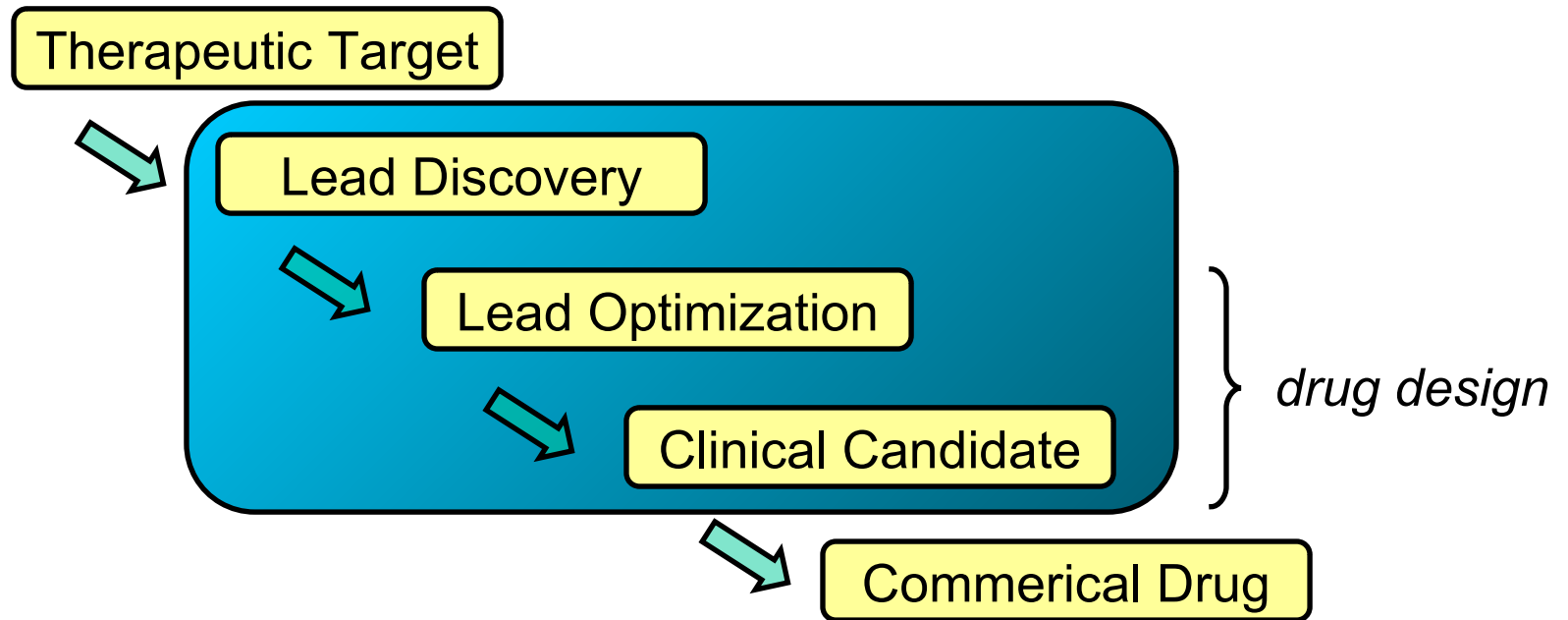
bioethic component

accepted legal definition of diseases

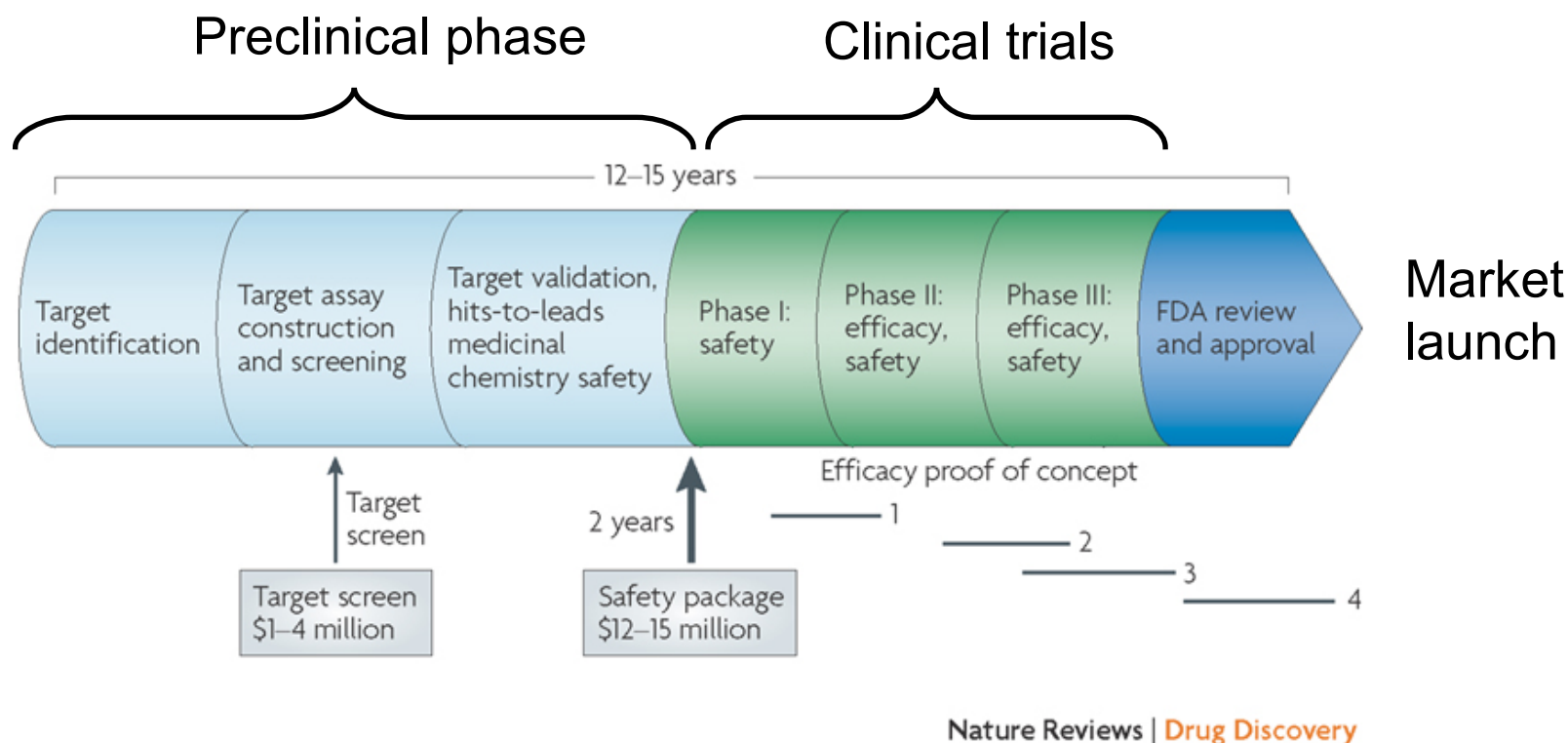


legal regulation for drug marketing (e.g. by the FDA)

The preclinical phase



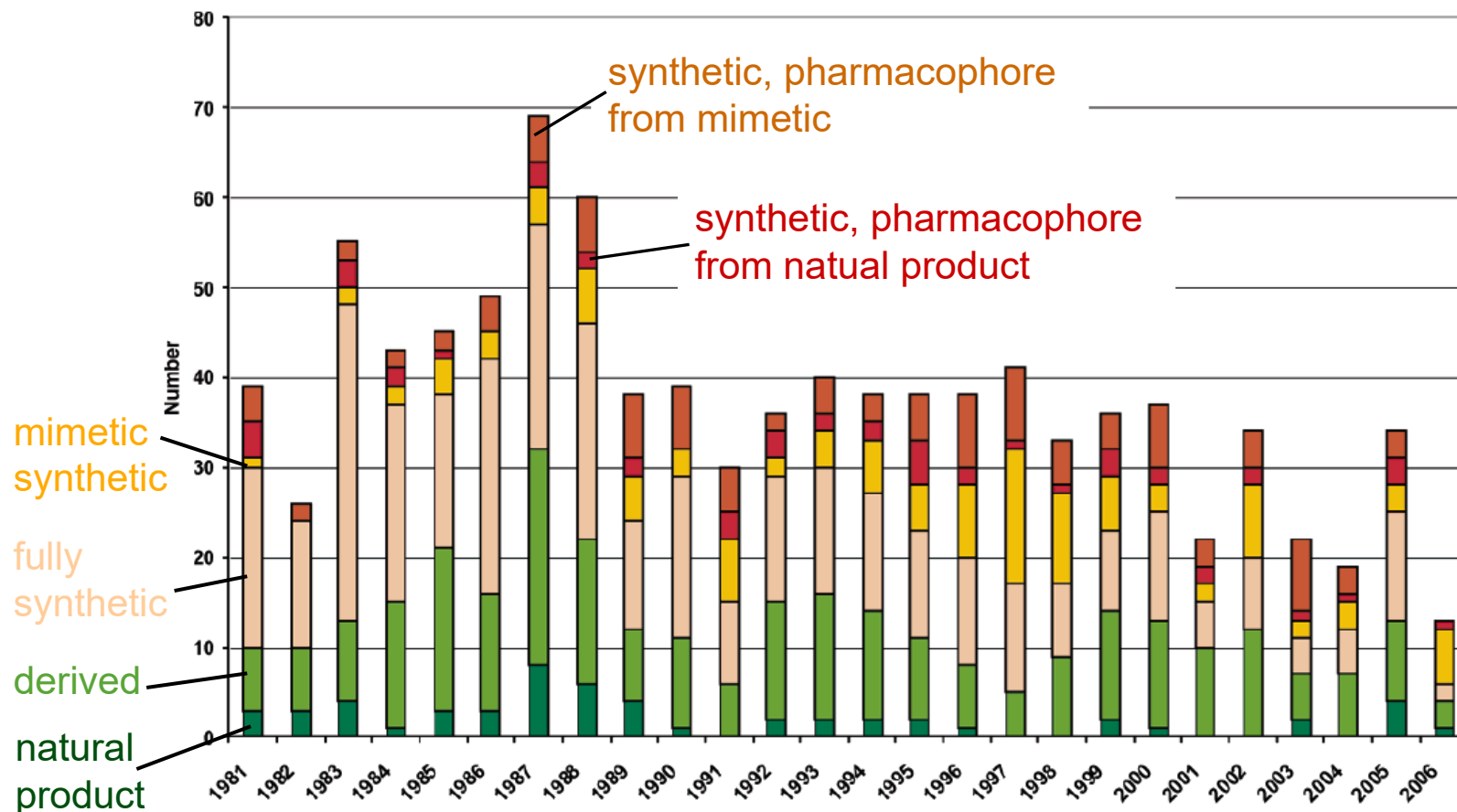
The drug discovery pipeline



A.D. Roses *Nature Reviews Drug Discovery* 7 (2008) 807.

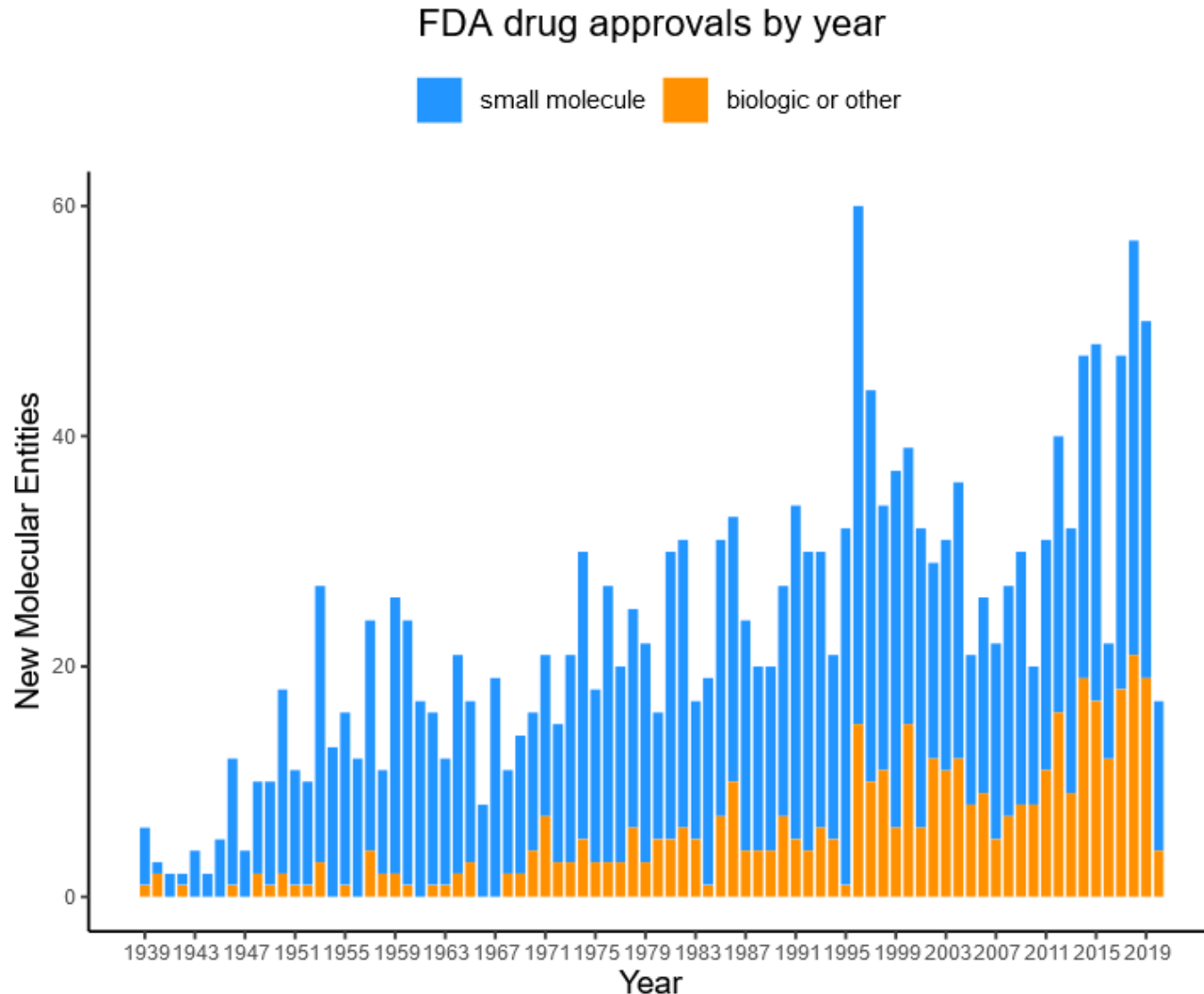
Trend in approving new drugs (I)

Drugs approved by the FDA (1981 - 2006)



Lit: D.J. Newman, G.M. Cragg *J.Nat.Prod.* **70** (2007) 461-477.

Trend in approving new drugs (II)



towards the drug (II)

Example: arterial hypertension

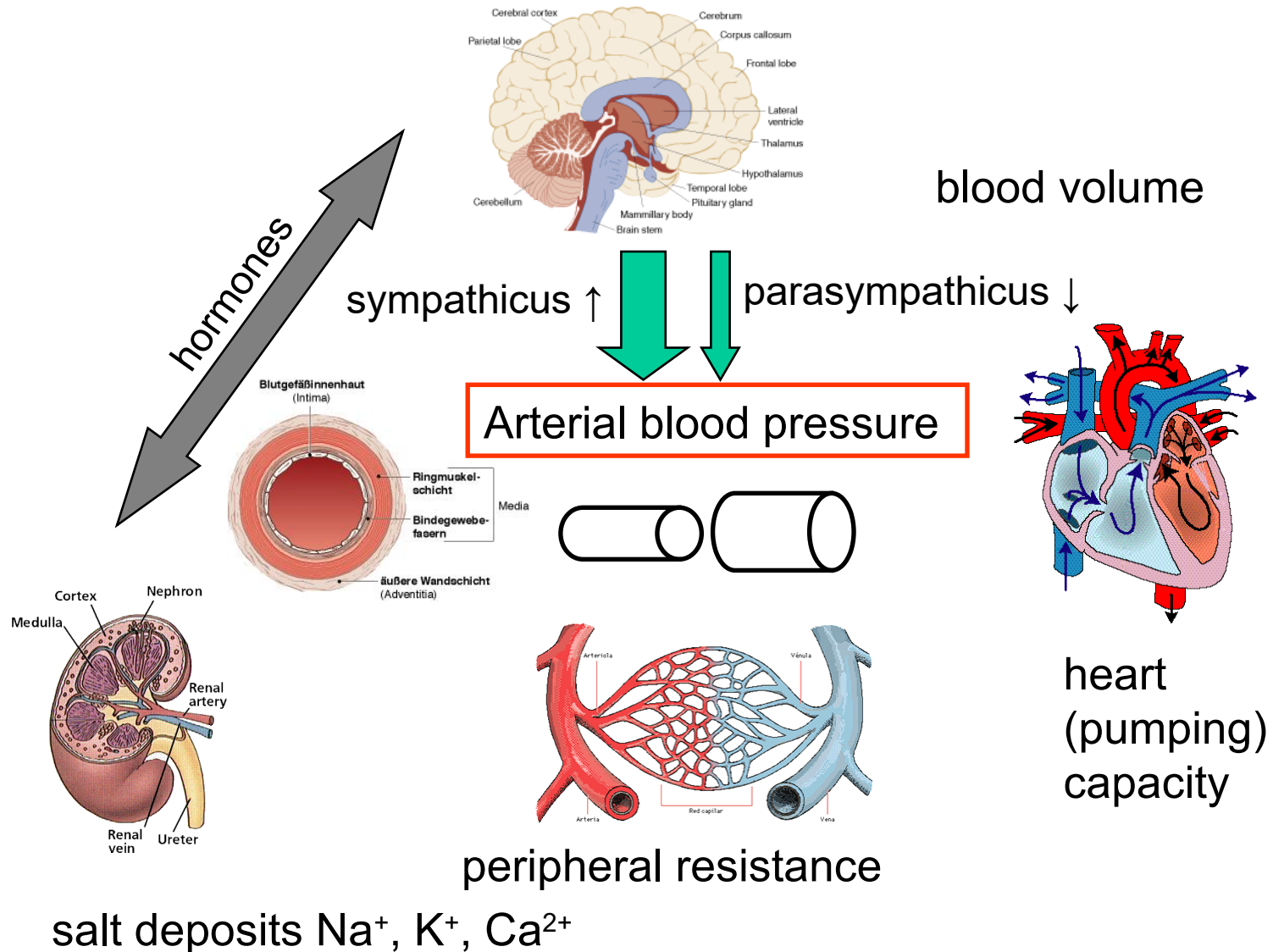
Arterial hypertension [Arterielle Hypertonie] is a frequently observed condition (about 10 - 25% of all adults are affected). Persistent hypertension can lead to damage of blood vessels, the eyes, and the kidneys. → symptoms

category	systolic		diastolic	
optimum	<120	and	<80	
normal	<130	and	<85	
normal-high	130 - 139	or	85 - 89	
mild HD	140 - 159	or	90 - 99	
moderate HD	160 - 179	or	100 - 109	
strong HD	>180	or	>110	mm (Hg)



source: *Archives Int. Med.* **157** (1997) 2413.

Regulation of the blood pressure (simplified)

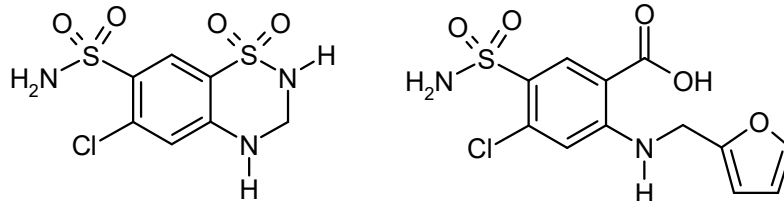


diuretica and saluertica

Ions in the blood and in other salt deposits bind water. By elimination of these ions the volume of the blood can be reduced.

This effect is caused by diuretica and saluertica:

Examples: hydrochlorothiazide, furosemide



Therapeutic administration of thiazides since 1960

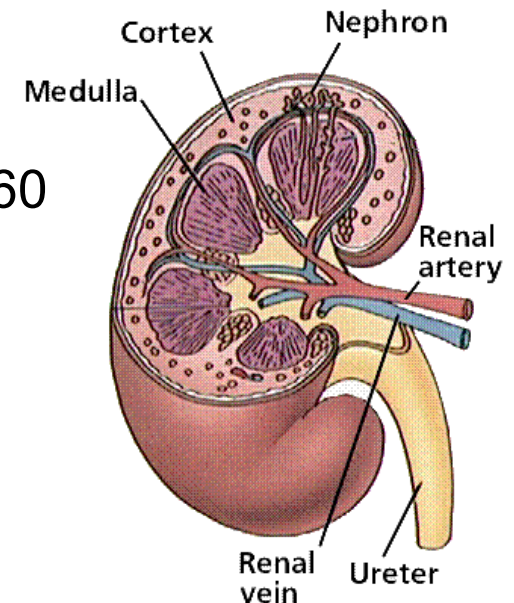
Disadvantages / side effects:

deficiency of potassium

increased level of uric acid [Harnsäure]

increased level of fatty acids in the serum

not suitable with diabetes



α and β -blocker

Act relaxing via the peripheral nervous system and reduce the pumping capacity of the heart.

Examples: prazosin, tetrazosin, doxazosin, propanolol, atenolol, labetalol, pindolol

Simultaneously, the hormonal control is affected, whereby the peripheral resistance is diminished.

Therapeutic administration since 1970

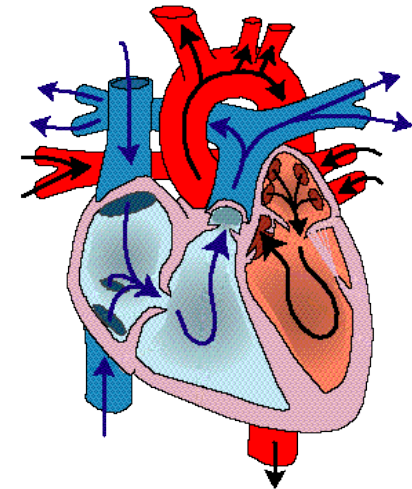
Disadvantages and side effects:

withdrawl symptoms

reduced capacity of the heart [Herzinsuffizienz]

increased levels of fatty acids in the serum

effects on the central nervous system



vasodilators and calcium antagonists

Act relaxing on the smooth muscles of the arterias and thereby reduce the resistance.

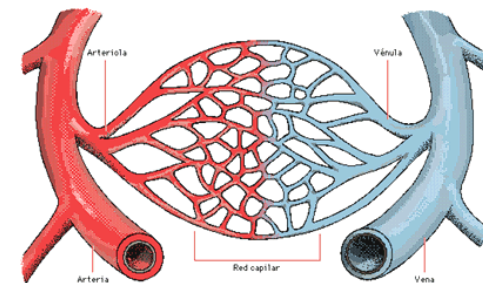
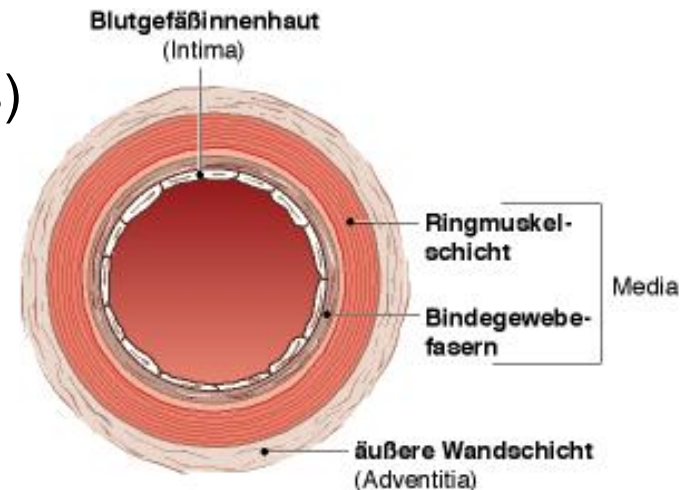
Bind to the hAT_2 -receptor (vasodilators) or inhibit the calcium pump (calcium antagonists)

Examples: hydralazine, minoxidil, diazoxide, verapamil, diltiazem, nifedipine

Therapeutic administration since 1980

Disadvantages and side effects:

Predominately on the function of the heart



Angiotensin Converting Enzyme Inhibitors

The endogenic oligopeptide Angiotensin II is one of the strongest vasoconstrictors.

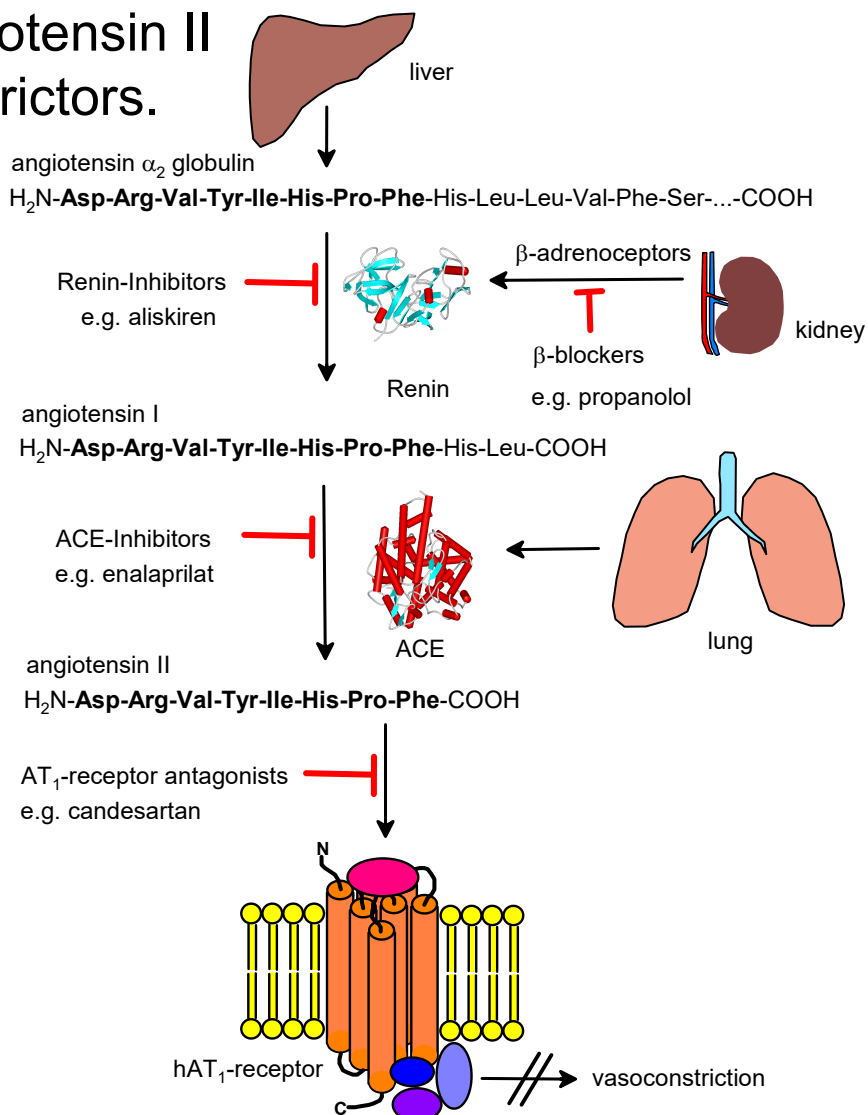
By inhibiting the angiotensin converting enzyme (ACE), the synthesis of Angiotensin II is disabled.

Examples: captopril, fosinopril, quinapril, enalapril

Therapeutic administration since 1990

disadvantages:

fetotoxic (pregnancy)



Angiotensin-II antagonists

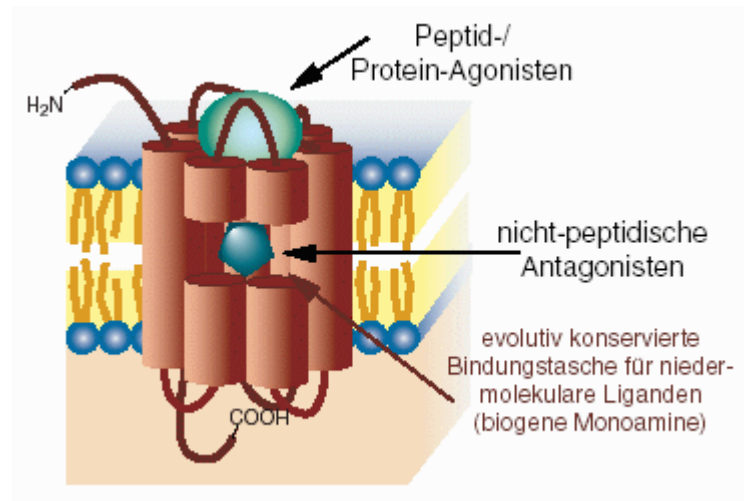
competitive binding of non-peptidic compounds to the hAT_1 -receptor (GPCR), which is the binding site of Angiotensin II.

Examples: losartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, forsartan

therapeutic administration
since 1995

disadvantages:

same as for ACE-inhibitors



Picture source: M. Gurrath *Pharm. i. u. Zeit* **288** (2001) 288.

„Evolution“ of hypertension targets over time

targets

therapeutic class

kidney

diuretica, saluretica

nervous system

α and β -blockers

calcium channels
(adrenal gland)

calcium channel blockers

hAT_2 -receptor

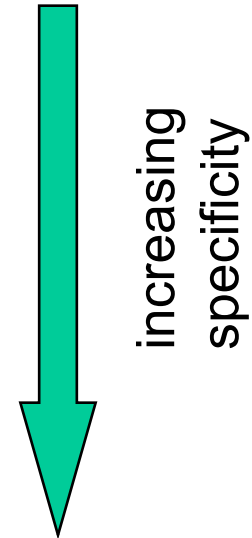
vasodilators

ACE

ACE-inhibitors

hAT_1 -receptor

Angiotensin II antagonists



Methods for Determining Atomic Structures

X-ray and electron microscopy

Diffraction and scattering of electromagnetic waves,
respectively electrons

Pro: high resolution

Con: „artificial“ conditions
solid state, crystal

NMR (nuclear magnetic resonance)

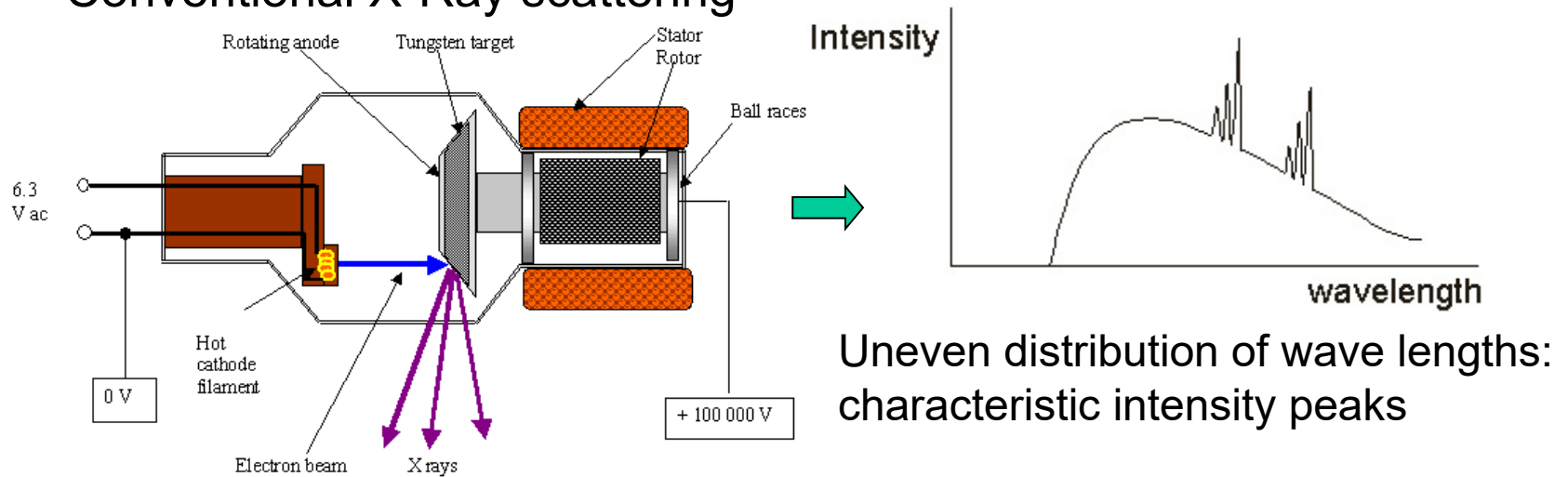
Absorption of electromagnetic waves

Pro: „natural“ conditions
aqueous solution

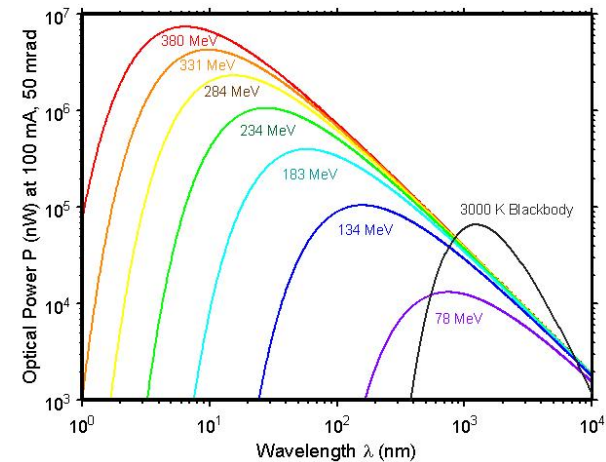
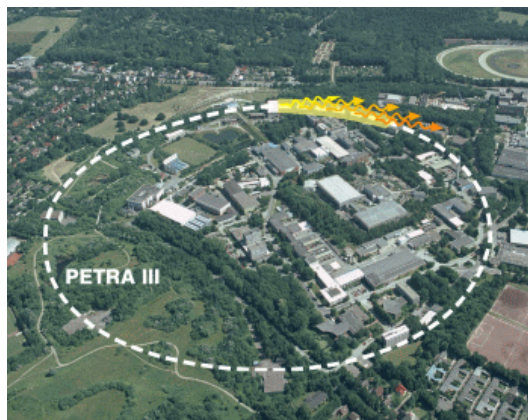
Con: only for small proteins
<100 amino acids

Obtaining X-Ray structures (I)

Conventional X-Ray scattering



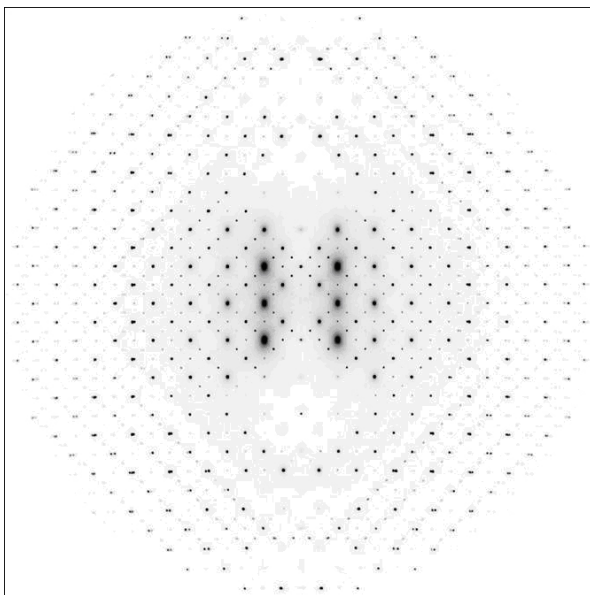
Synchrotron scattering



Continuous distribution of wave lengths

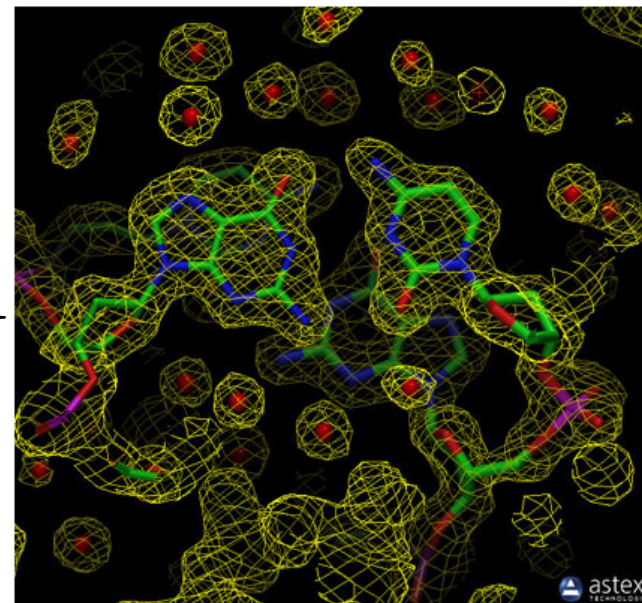
Obtaining X-Ray structures (II)

The arrangement of atoms in the crystal gives rise to a diffraction pattern



Mathematical
transformation &

Idea how the actual
structure looks like



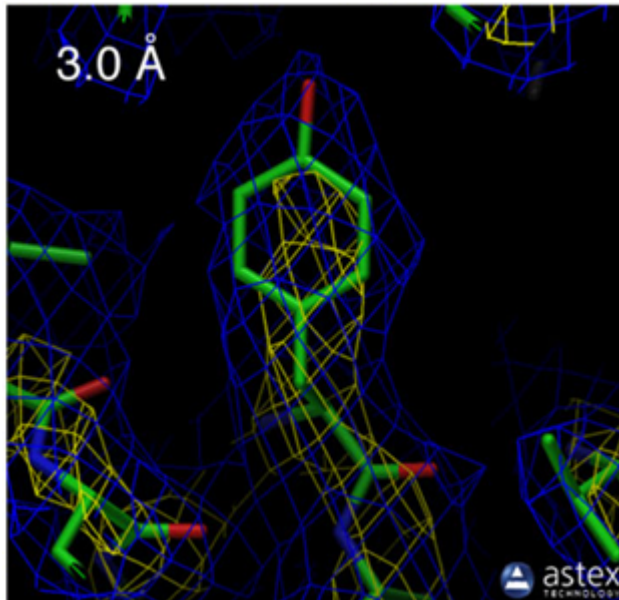
Electron density map

3D coordinates can be obtained from www.rcsb.org (Protein Data Bank)
and electron density maps from <http://www.ebi.ac.uk/pdbe/>

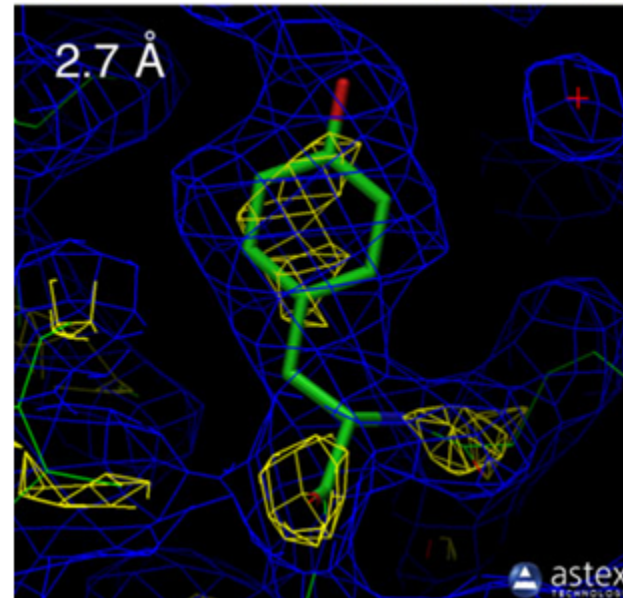
Accuracy of X-Ray structures (I)

The resolution given in .pdb files tells us the smallest wavelength (in Å) the crystal was able to diffract.

→ We “see” objects of that size



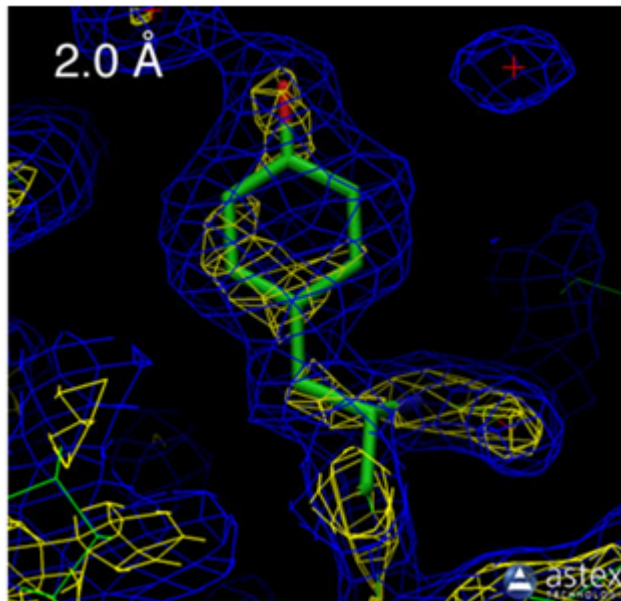
Backbone and putative positions of side chains



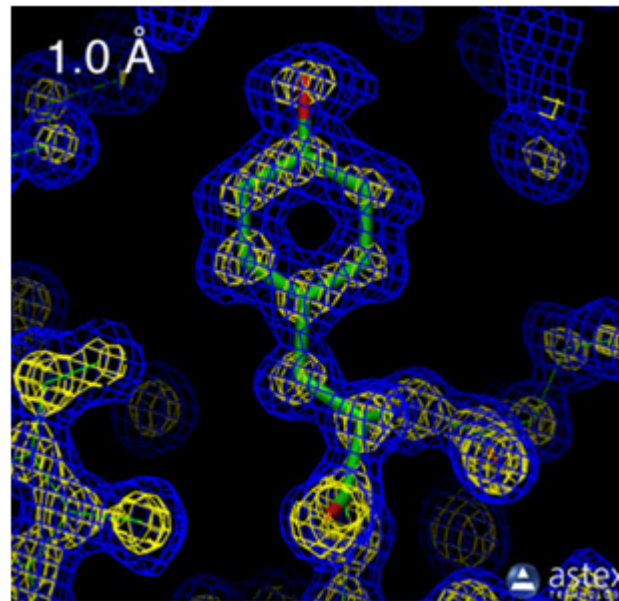
Distinguishing large and small side chains

Accuracy of X-Ray structures (II)

The atomic coordinates are fitted into the electron density grid using a force field. **yellow**: 1σ (standard deviation), **blue**: 3σ



Different rotamers of the side chains can be assigned

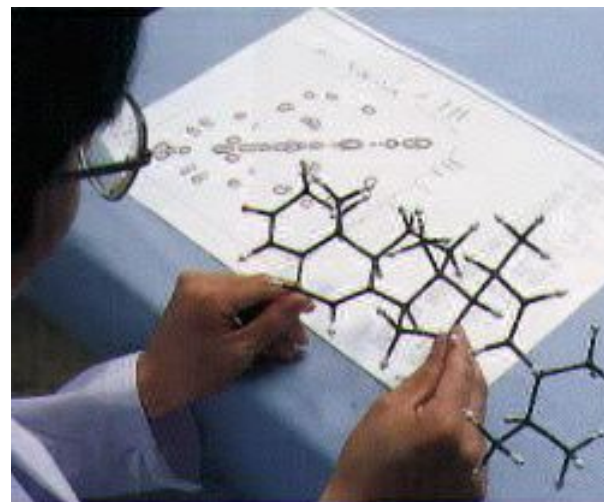
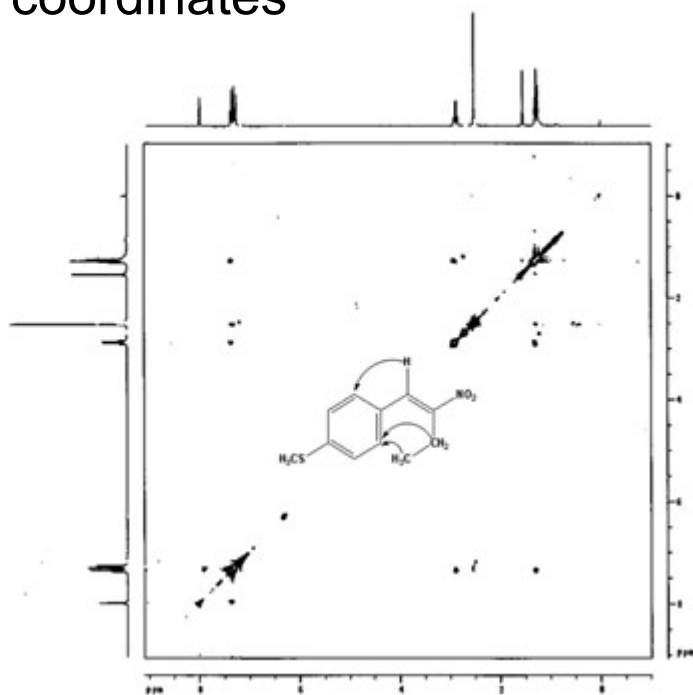


Atomic coordinates can be assigned unambiguously

NMR Structures (I)

The distance between atoms can be derived from the intensities of the cross-peaks in the 2D-NMR spectrum. Like in X-ray scattering an idea how the actual structure looks like is required.

→ constraint force field optimization of the atomic coordinates



NMR Structures (II)

Due to the dynamic behavior in solution and limited time resolution of the NMR, an „averaged“ structure is obtained.



Such .pdb files usually contain 10 individual solutions (models) and the resulting averaged structure.