

Therapeutic Categories

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

ACE Inhibitor	Analgesic, Dental
Adrenocortical Suppressant	Analgesic, Narcotic
Adrenocorticotrophic Hormones	Analgesic, Non-narcotic
Aldose Reductase Inhibitors	Androgens
Aldosterone Antagonists	Anesthetics, Inhaled
α -adrenergic Agonists	Anesthetics, Intravenous
α -adrenergic Blockers	Anesthetics, Local
α -Glucosidase Inhibitors	Angiotensin II Antagonists
Anabolic Steroids	Anorexics

see the corresponding section in the Merck Index



In most cases it is not obvious to conclude the treated disease from a therapeutic class. (At least for non-medical persons)

Typical diseases

The search for pharmaceutical drugs used to be rather straight forward until recent times:

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

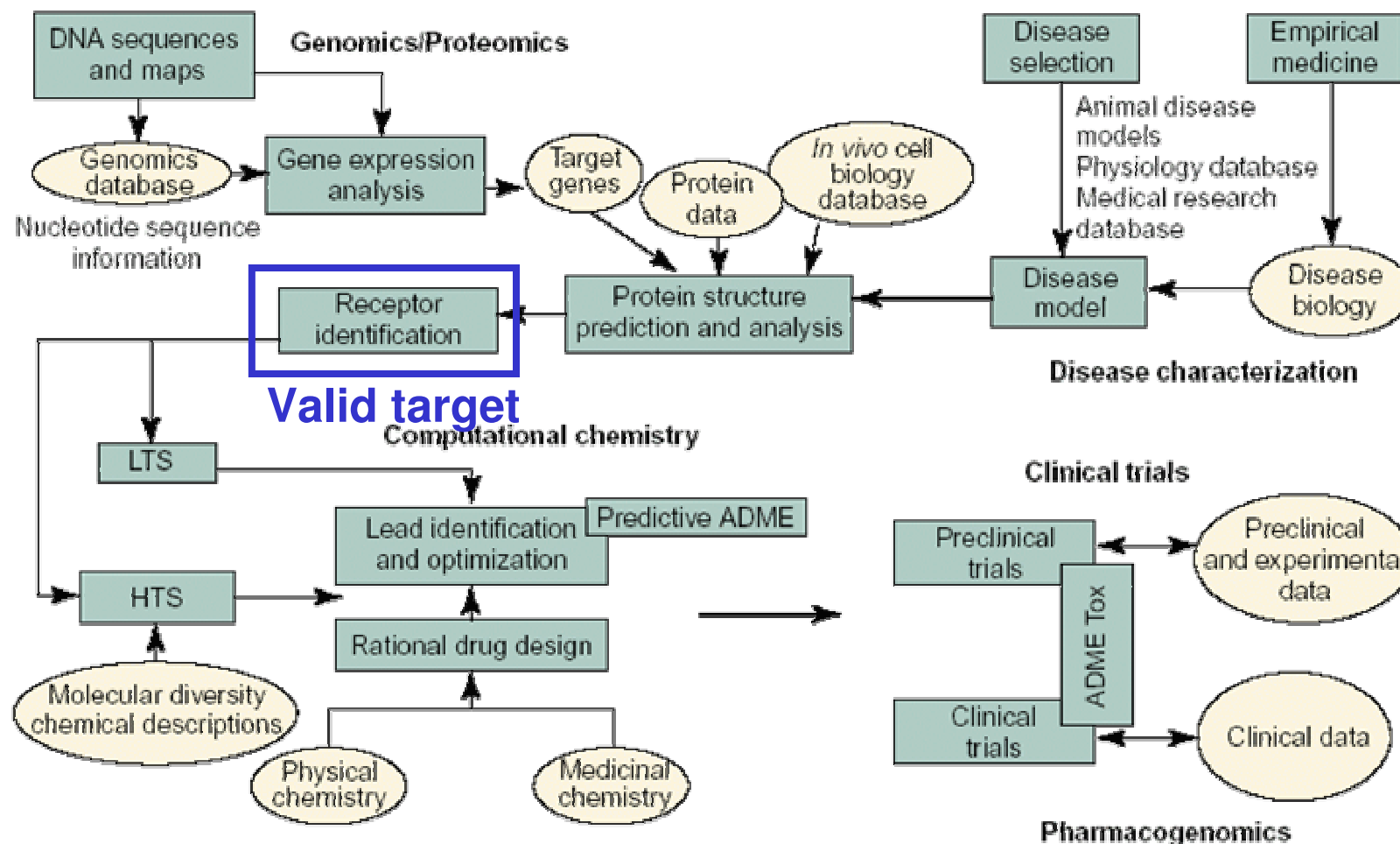
Example: inhibition of an enzyme

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

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



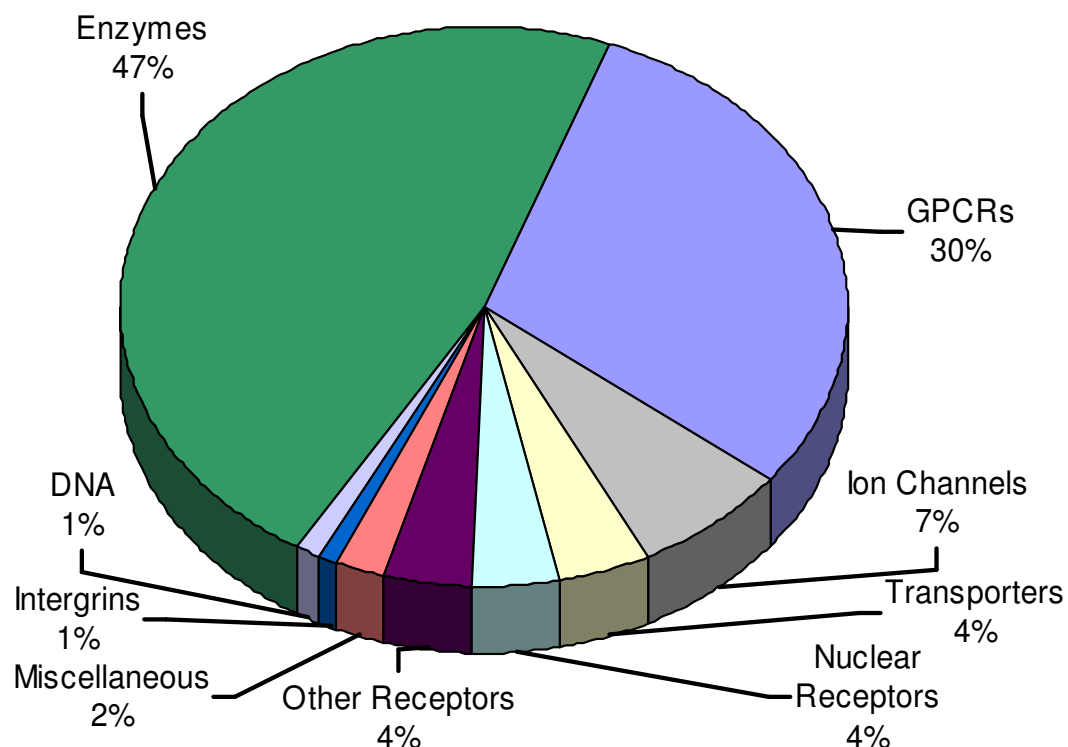
Flow of information in a drug discovery pipeline



Drug Discovery Today

typical targets

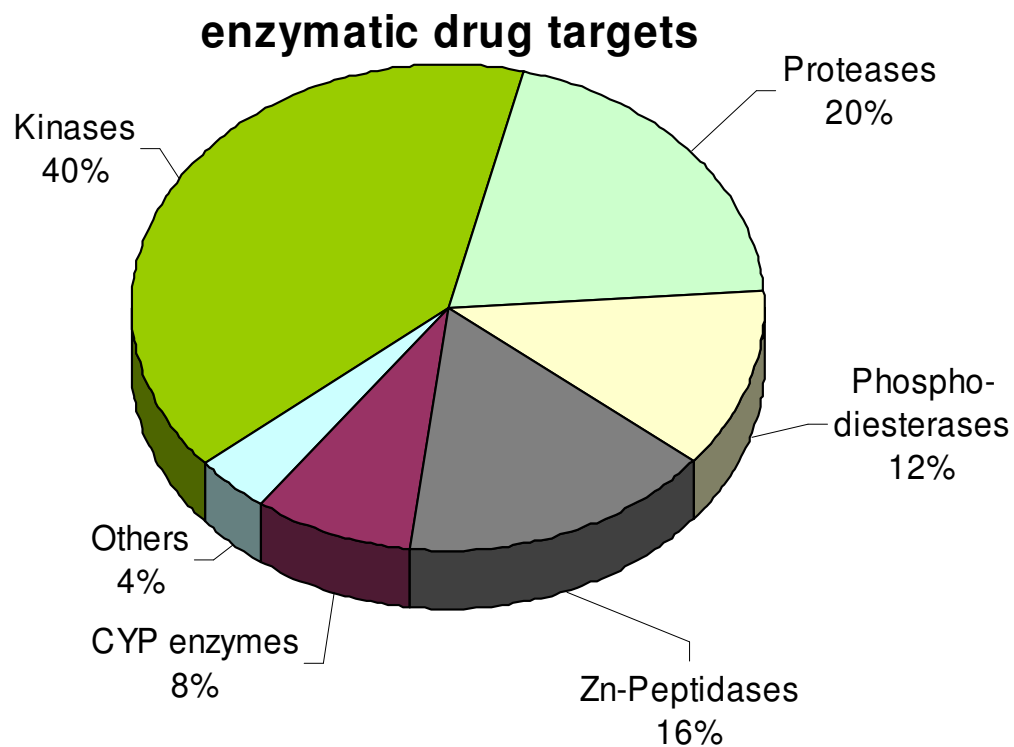
drug targets by biochemical class



Fractional content of marketed drugs according to their biochemical targets

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

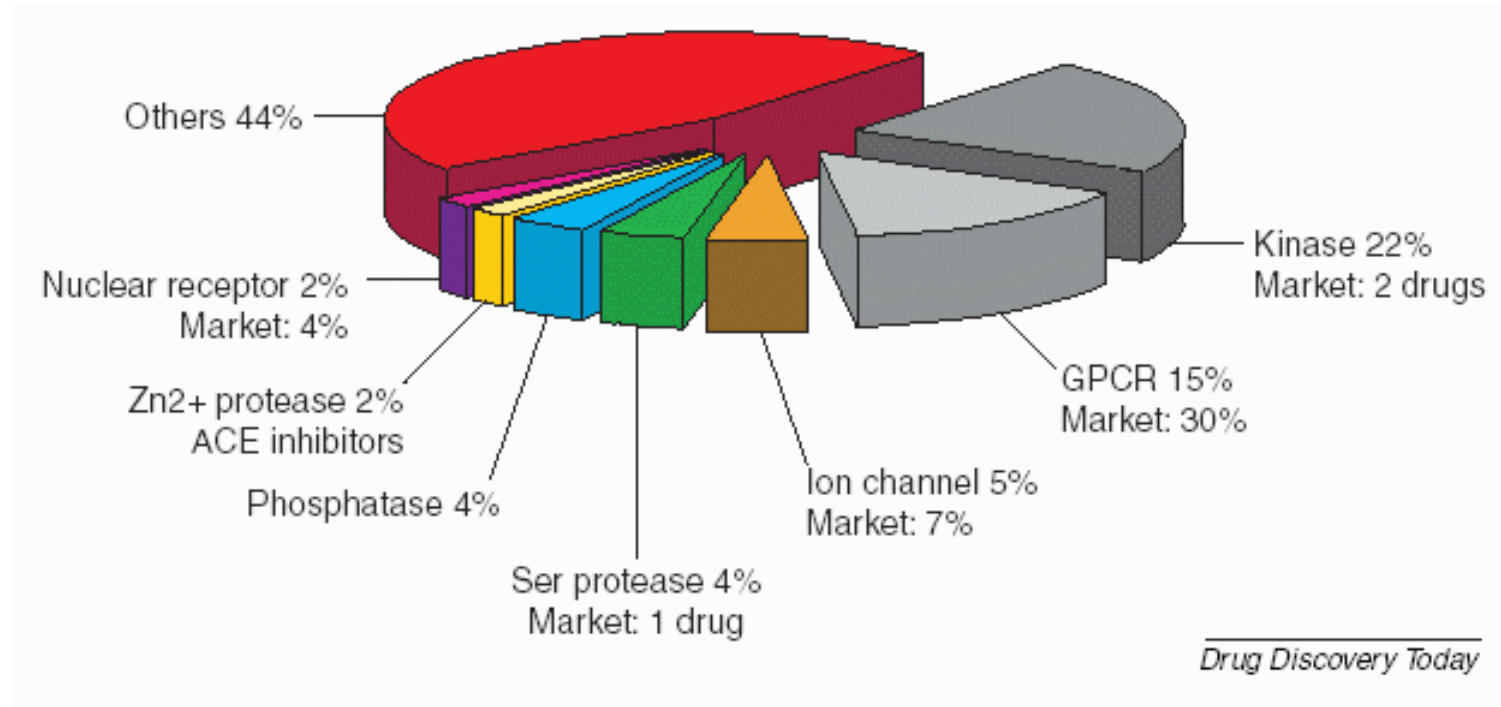
Enzymatic targets



Distribution within the class of enzymes



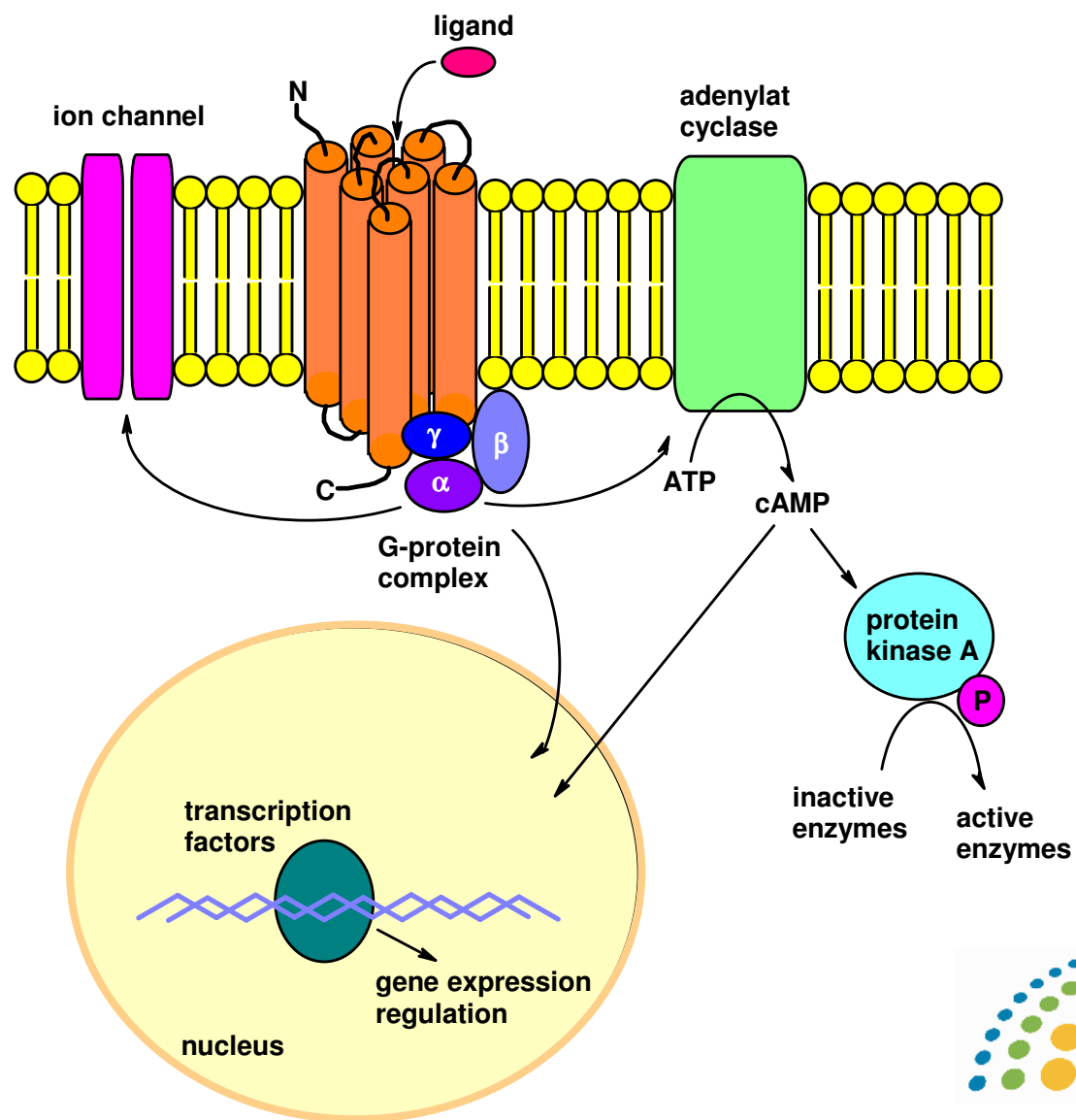
typical targets



contribution to the human genome and marketed drugs
about 500 enzymes have been used as targets
100,000 estimated potential targets in the genome

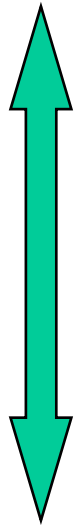


GPCRs and other targets



How do drugs interact with targets ?

proteome



enzymes: substrate analogs, competitive ligands, reversible and irreversible inhibitors

receptors: antagonists and agonists

ion channels: openers and blockers (inhibitors)

transporters: (re-)uptake inhibitors

DNA / nuclear receptors: intercalate, binding to specific DNA-motives, grooves, etc.

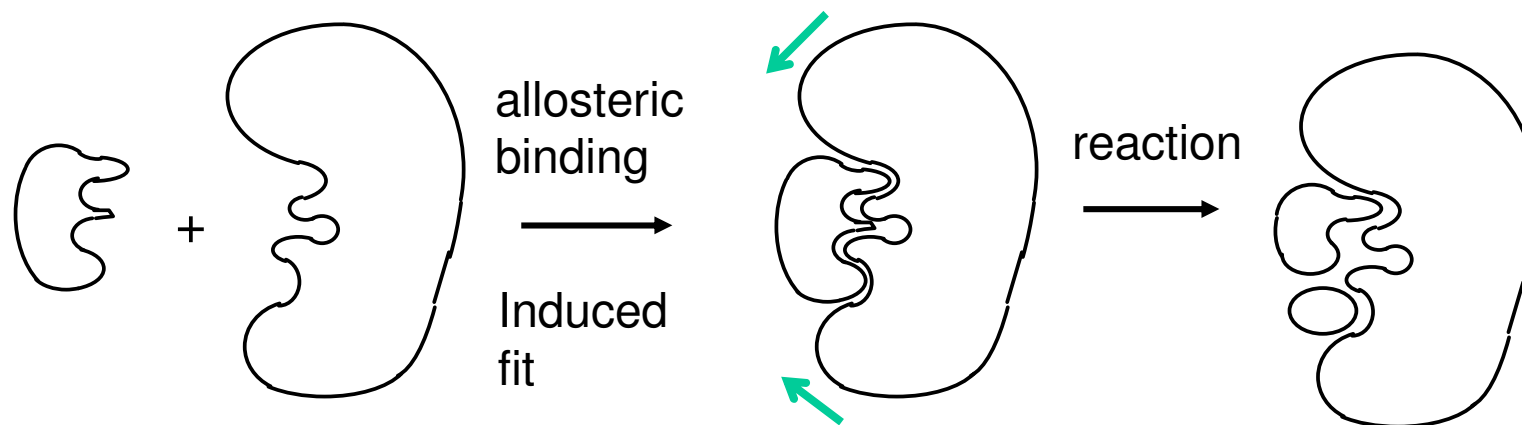
genome

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

Problems: Drug delivery and drug transport / distribution

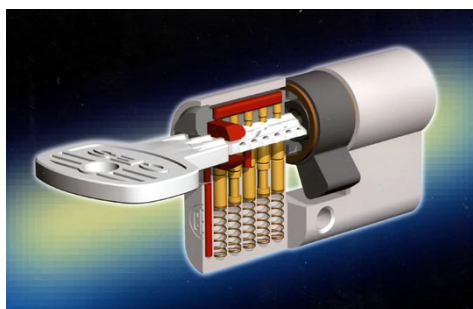
Drugs: mode of action (I)

Normal enzymatic turn-over



conformational change

lock and key principle



Drugs: mode of action (II)

competitive inhibitor:
higher affinity than
natural substrate,
directly acting



allosteric
inhibitor/effector:
prevents binding by
modifying the
conformation



Irreversible binding:
chemical reaction
leads to inactivation
of the enzyme

e.g. acetyl-salicylic
acid acetylates
Ser530 of
Cyclooxygenase



Anti-metabolite:

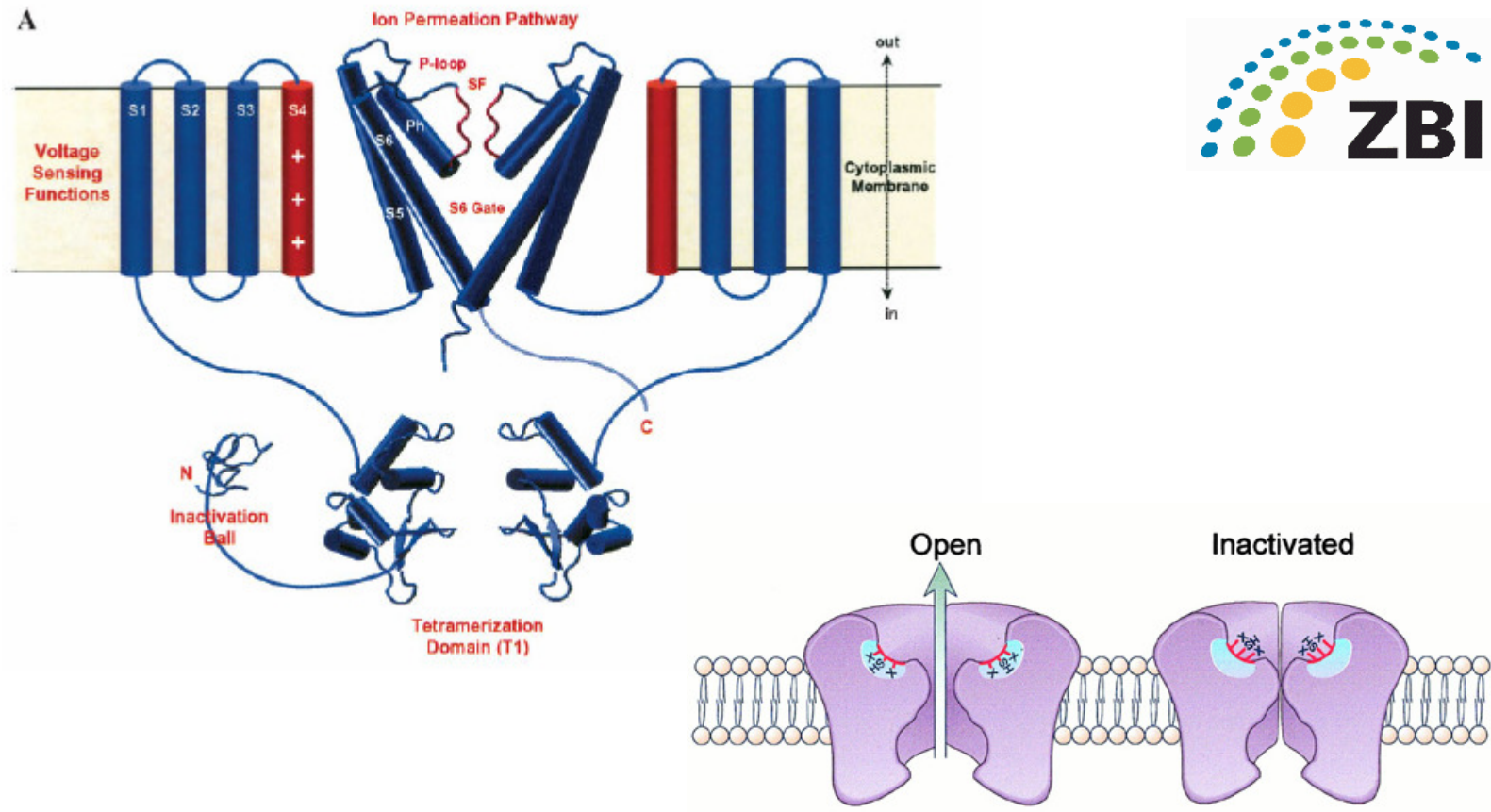
Competitive alternate („wrong“)
substrate

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

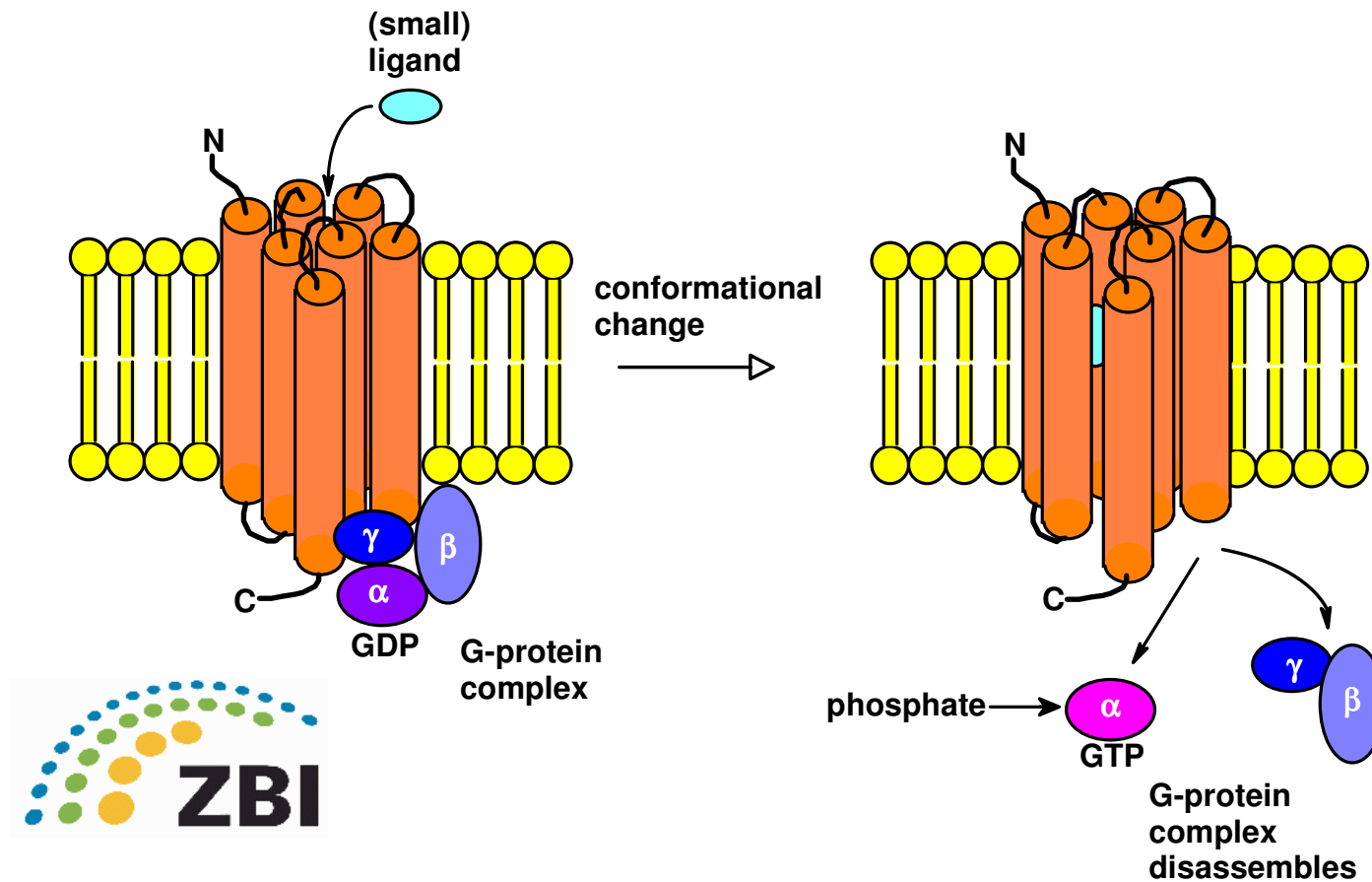


Drugs: mode of action (III)

Ion channels: Mode of action by ligand binding, indirectly through receptors, or voltage gated



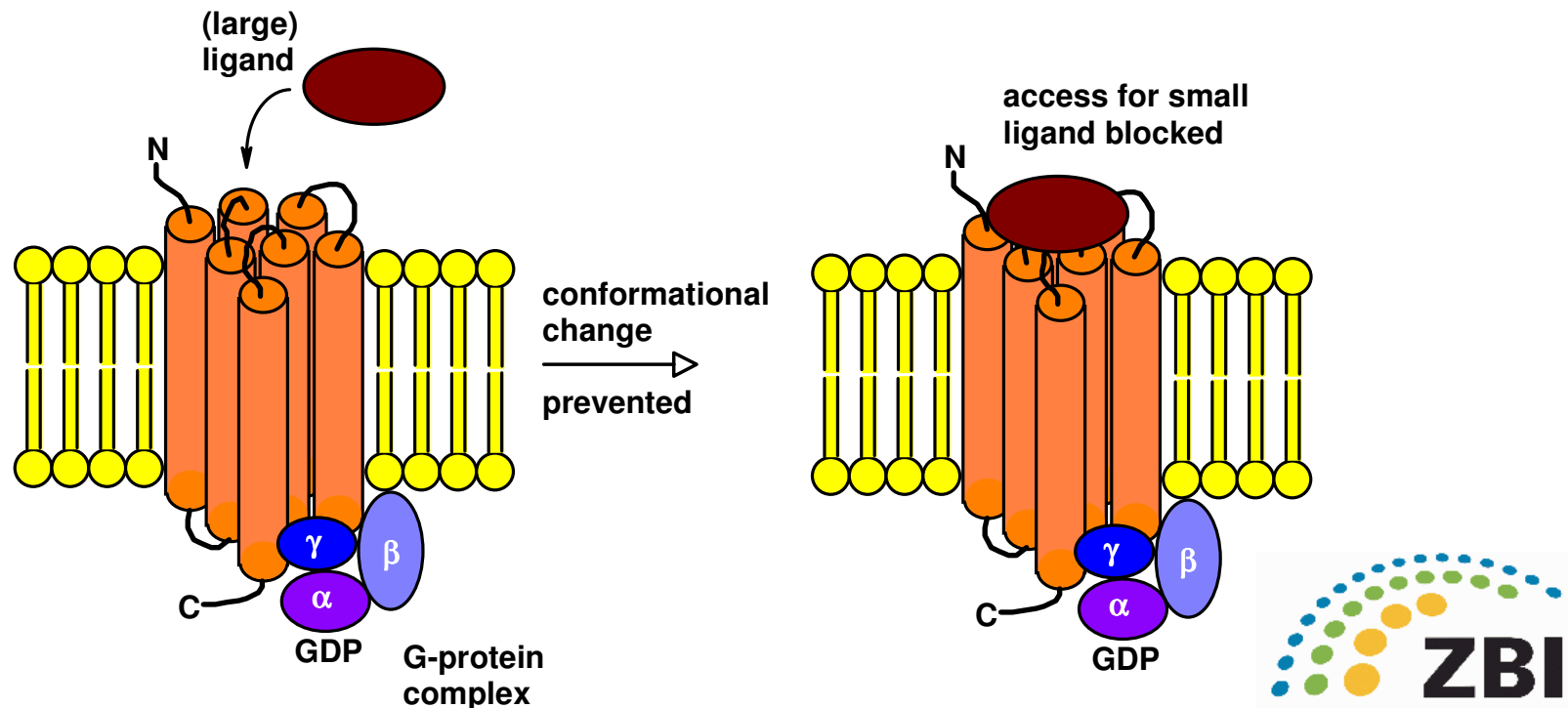
Drugs: mode of action (IV)



agonist: 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)

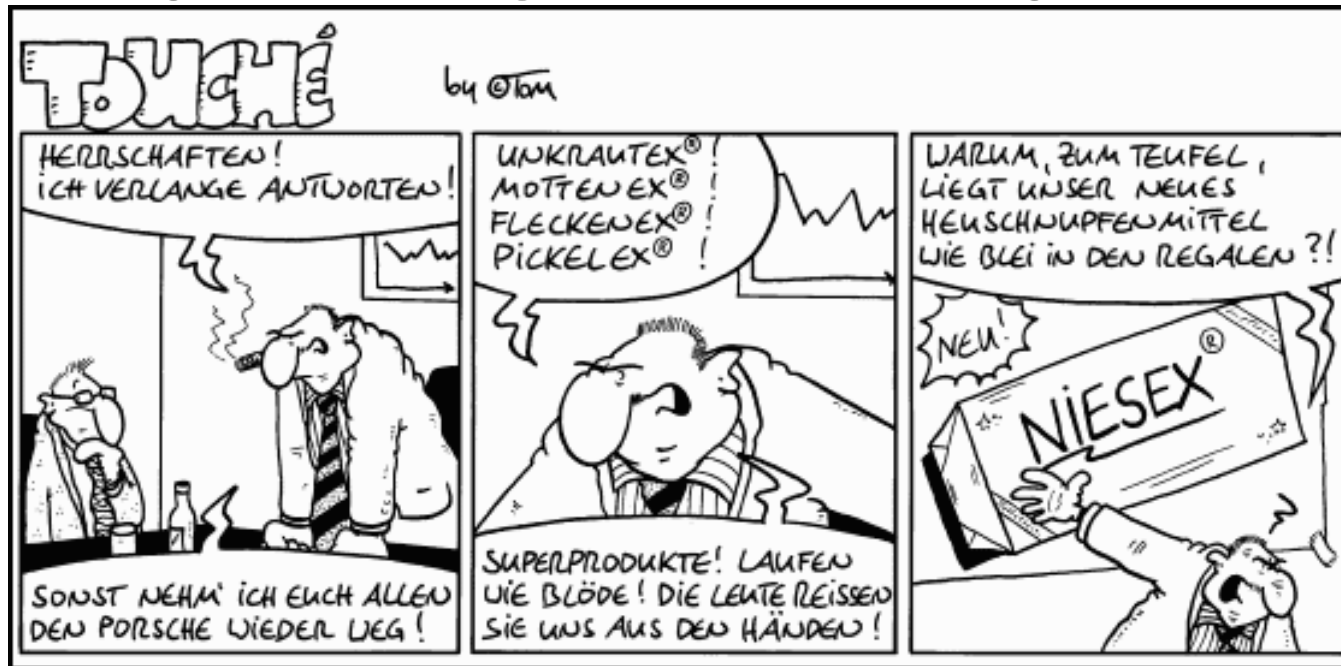


antagonist: ligand that prevents binding of the agonist, either directly (competitive binding) or indirectly (allosteric, prevents adoption of the reactive conformation)

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

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 inhibitors:

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

In such cases the drug target is obvious.



<http://www.zl.no/2L23details.htm>

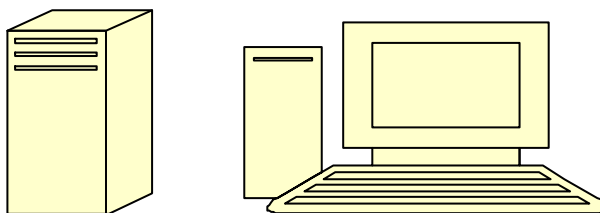


Compound Databases

existing substance libraries

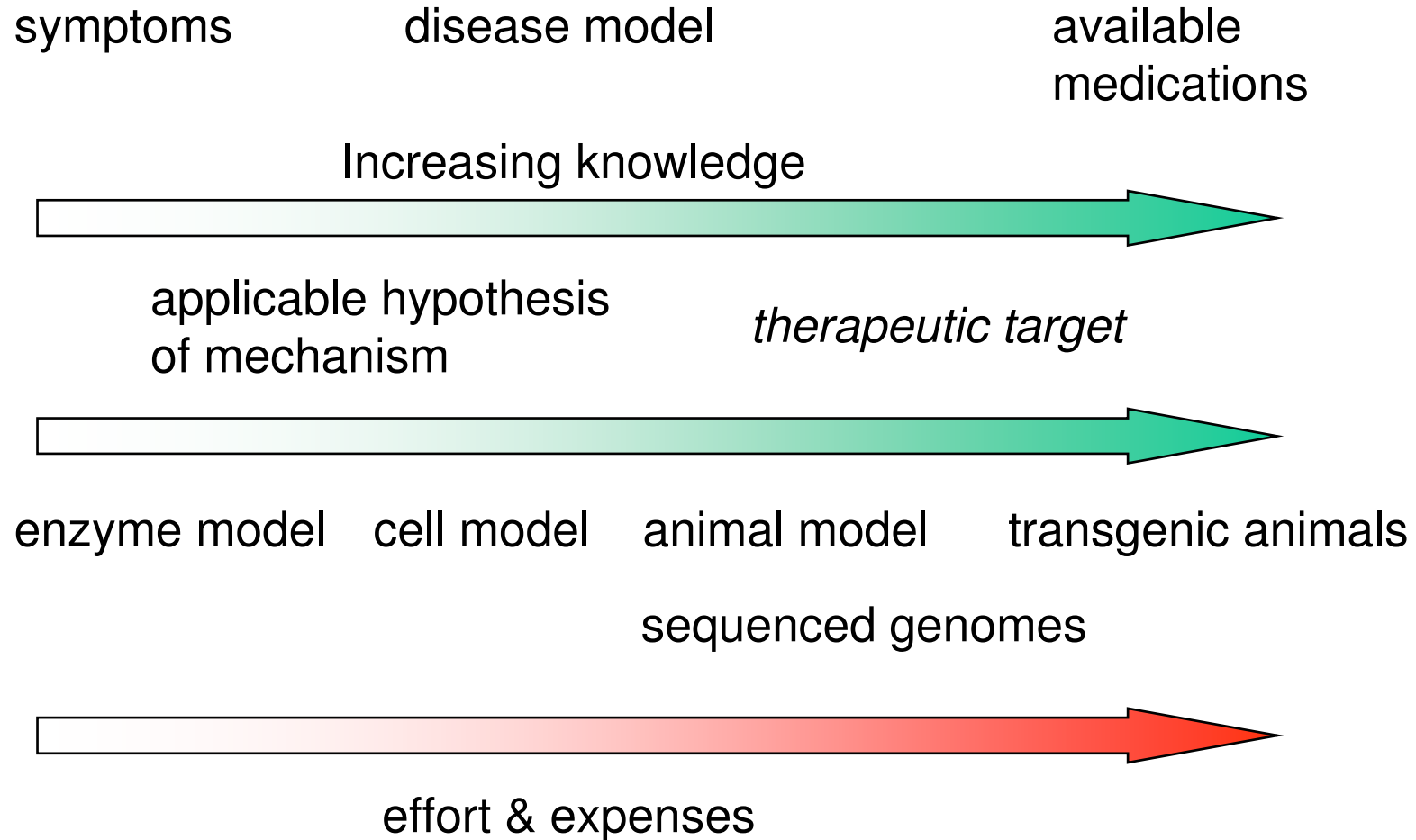
ACD	>100,000 chemicals	}	commercial
World Drug Index	58,000 compounds		
USAN	<10,000 in clinical trial		
virtual library	≈100,000 compounds		company, in house

PubChem	> 3,000,000 compounds	NCBI	}	academic
ChEMBL	> 1,213,000 compounds	EMBL		
ZINC	>73,126,243 compounds	UCSF		

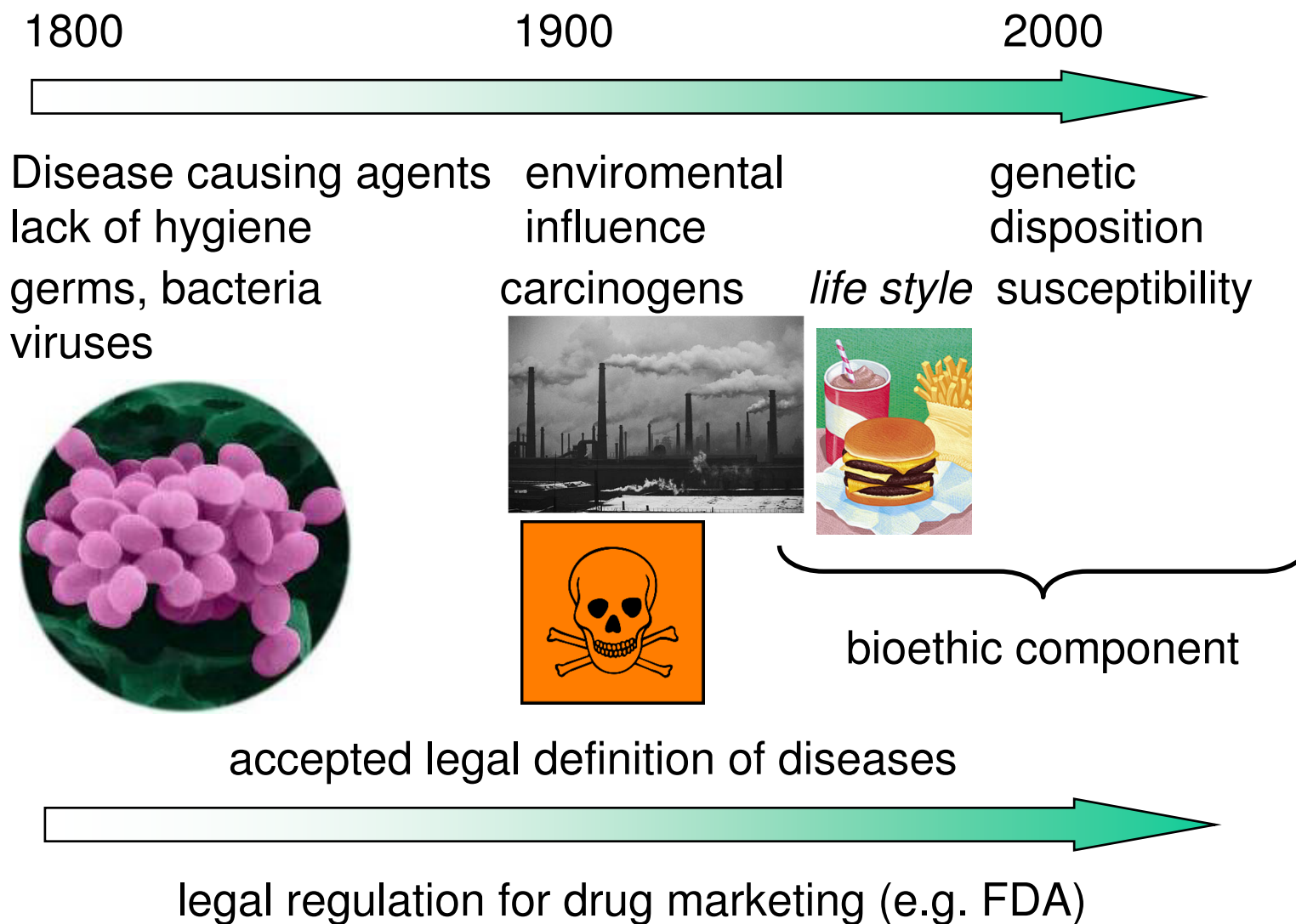


Investment per new chemical entity: >500,000 \$
New chemical entities per year: ca. 15

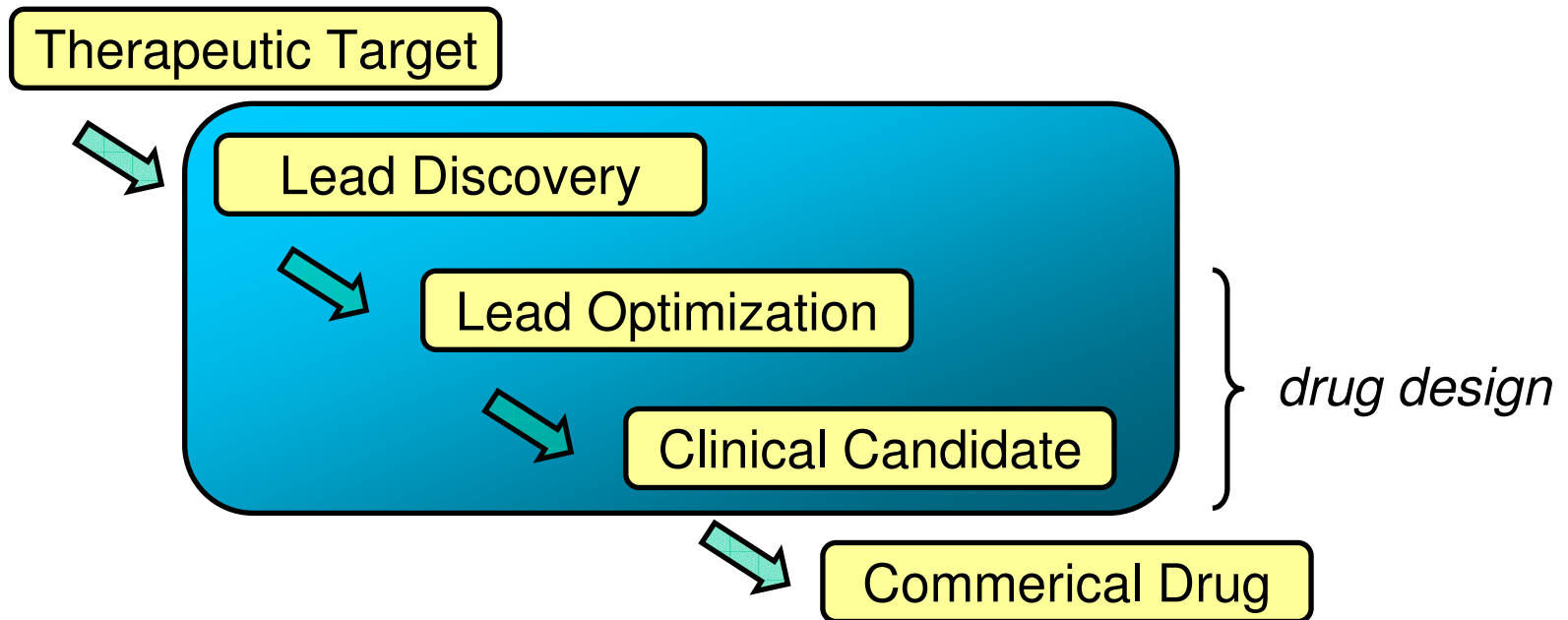
towards the drug (I)



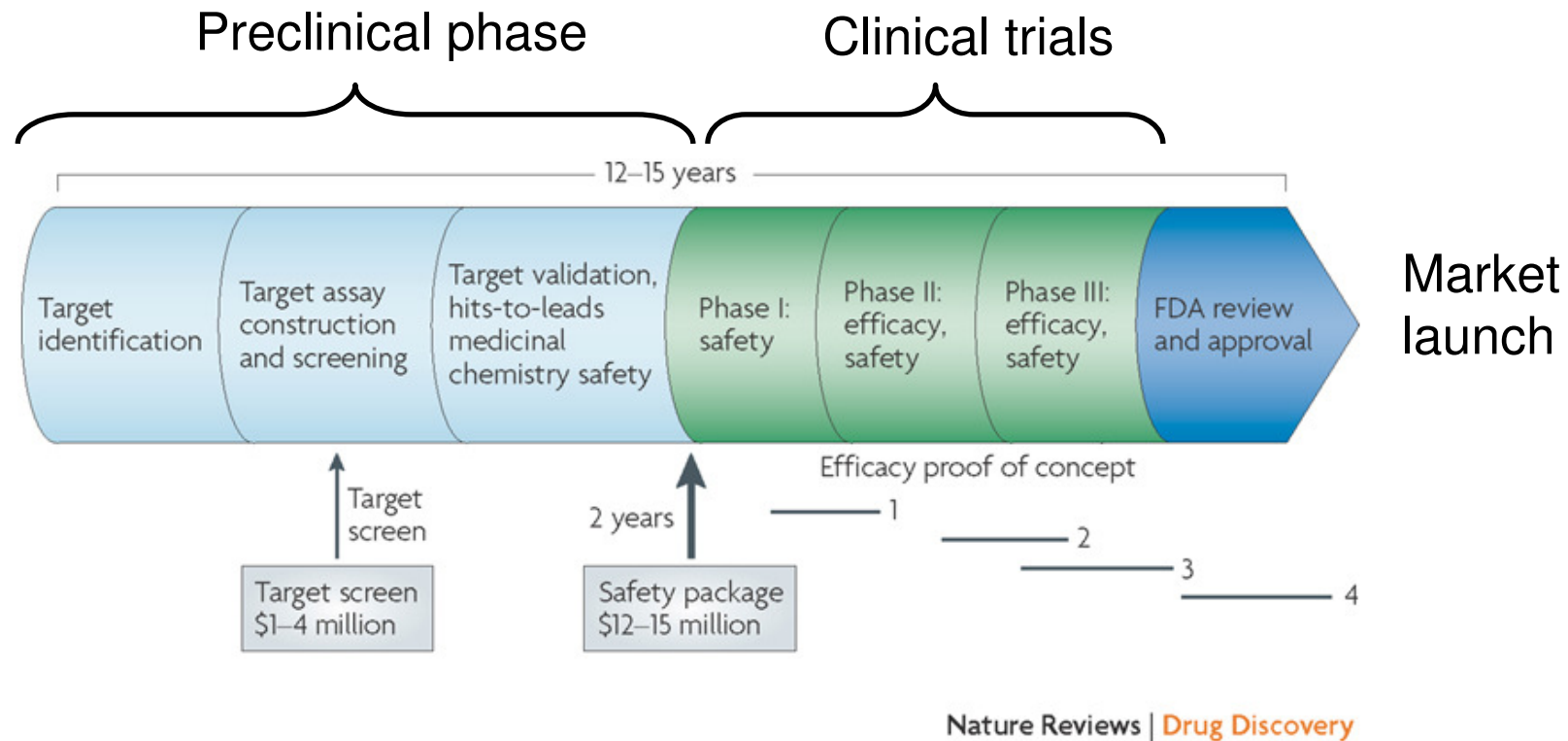
Evolution of Disease Symptoms with Time



The preclinical phase



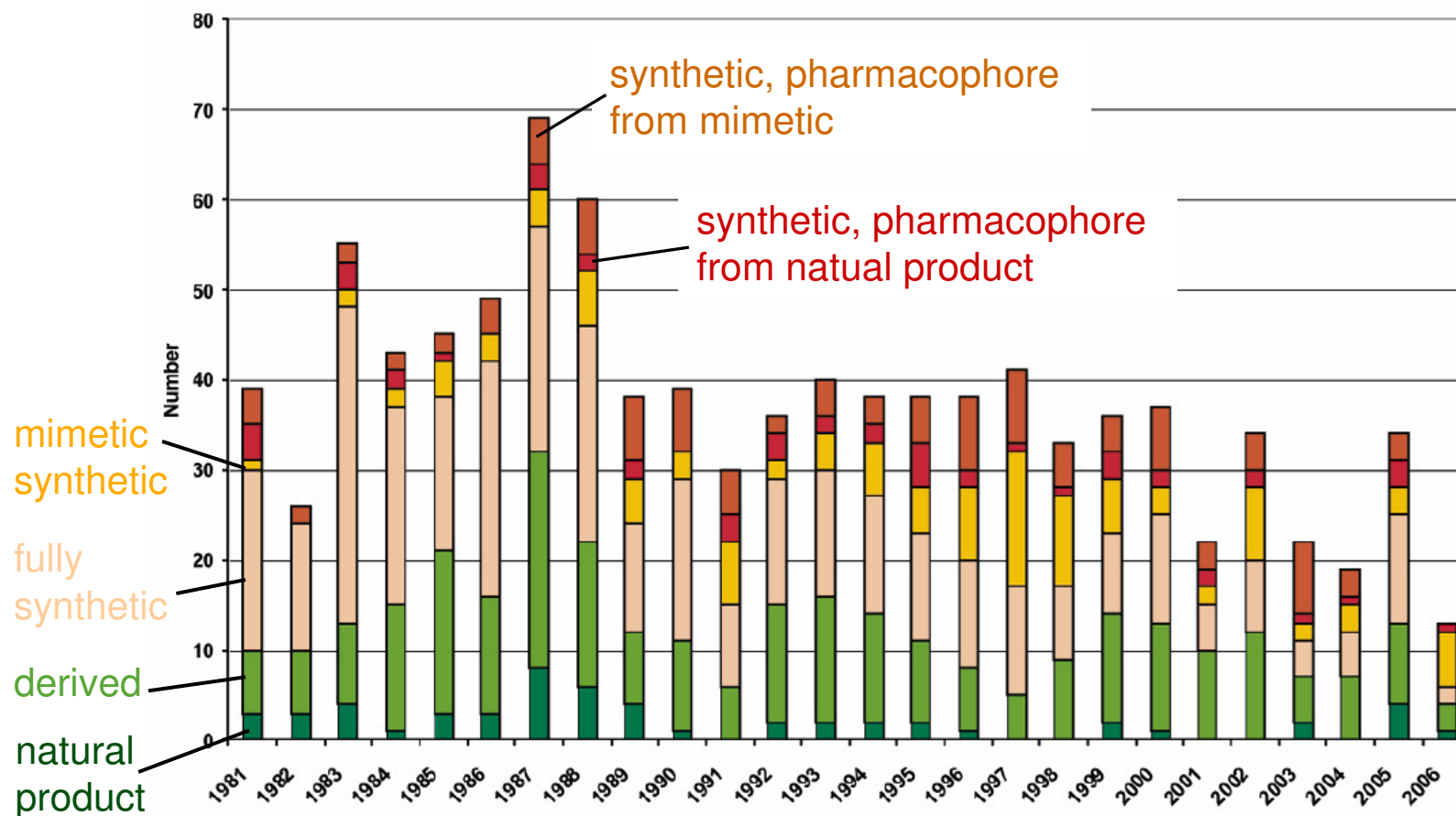
The drug discovery pipeline



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

Trend in approving new drugs

Drugs approved by the FDA within the last 25 years



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

towards the drug (II)

Example: arterial hypertension

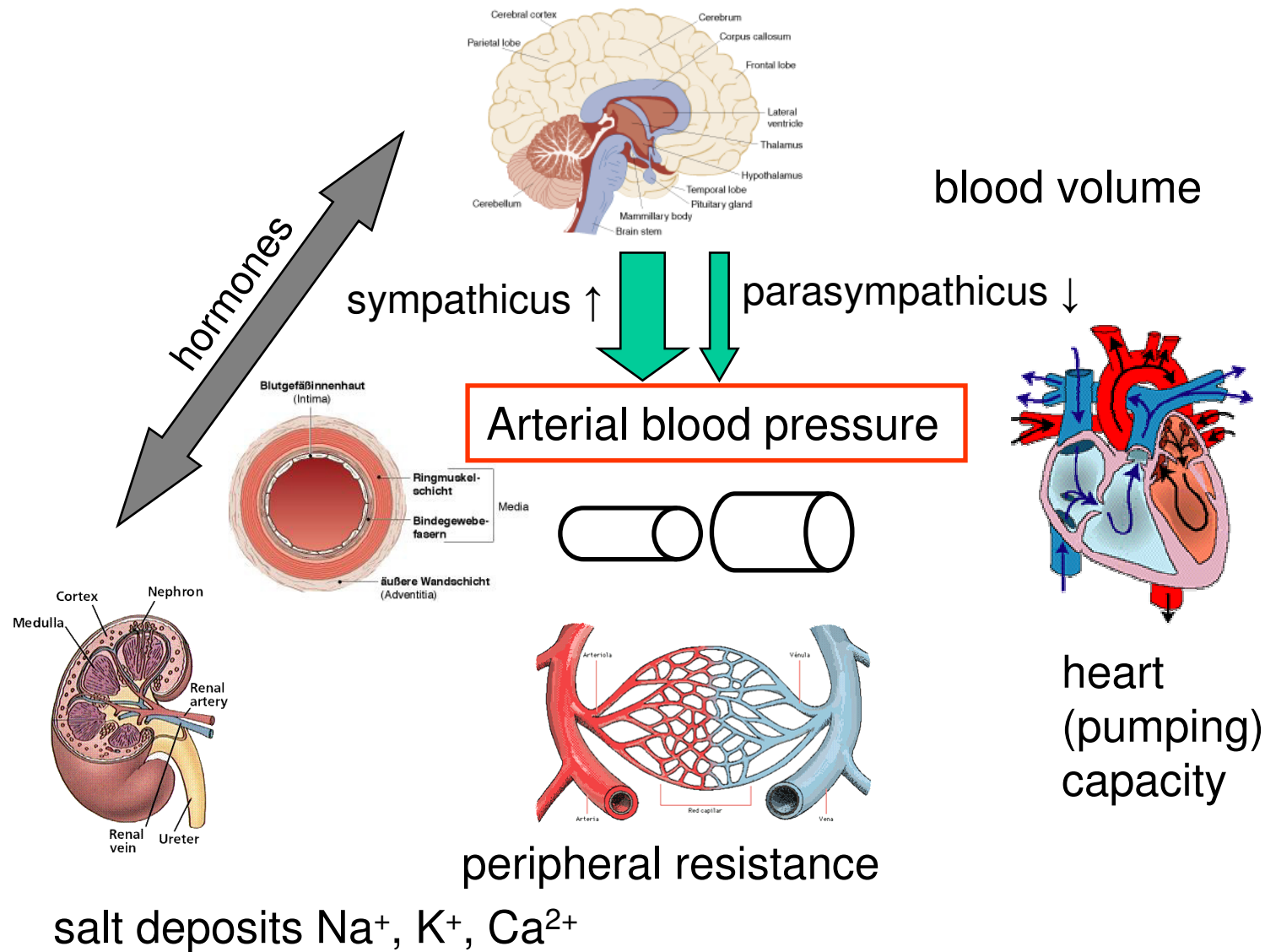
Arterial hypertension [Arterielle Hypertonie] is a frequently observed condition (about 10 - 25% of all adults are affected). Persistent hypertension can lead to damage of blood vessels, the eyes, and the kidneys. → symptoms

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)

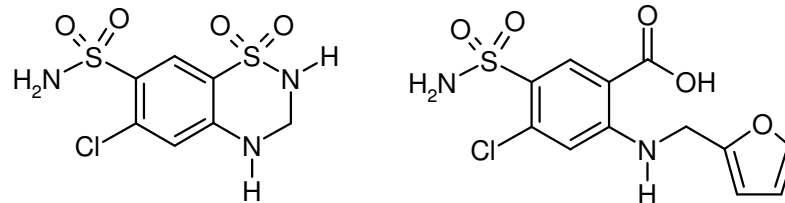


diuretica and saluertica

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:

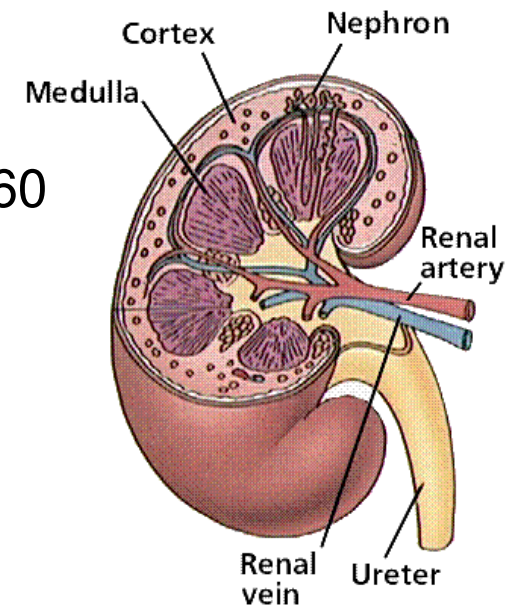
Examples: hydrochlorothiazide, furosemide



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, propranolol, atenolol, labetalol, pindolol

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

Therapeutic administration since 1970

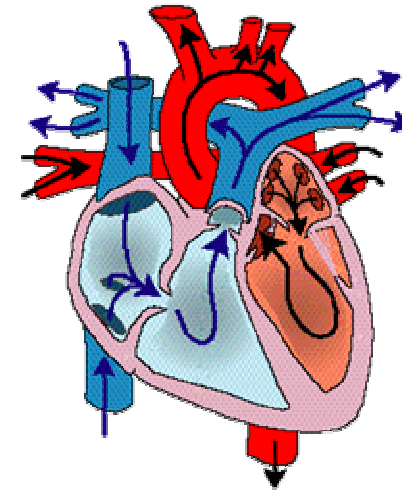
Disadvantages and side effects:

withdrawal 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.

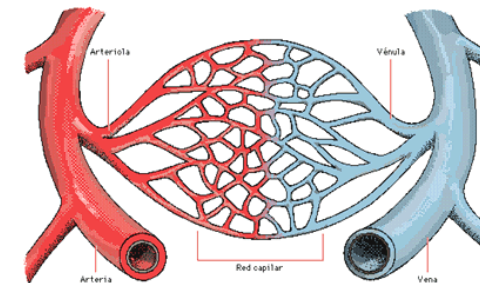
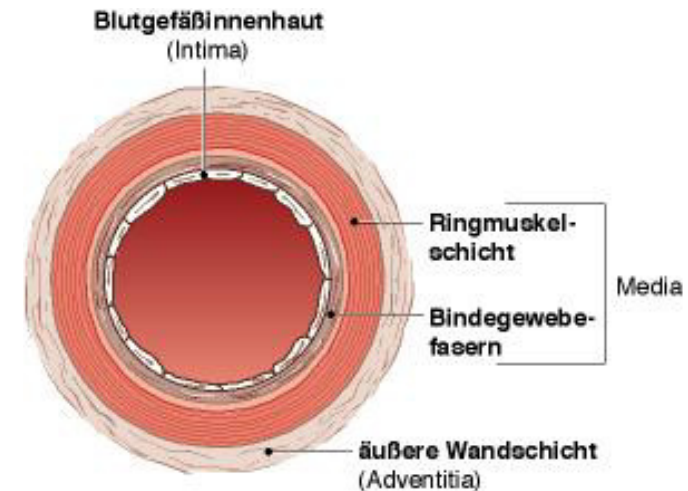
Bind to the hAT_2 -receptor or inhibit the calcium pump

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 endogenous oligopeptide Angiotensin II is one of the strongest vasoconstrictors. By inhibiting the angiotensin converting enzyme (ACE) the synthesis of Angiotensin II is disabled.

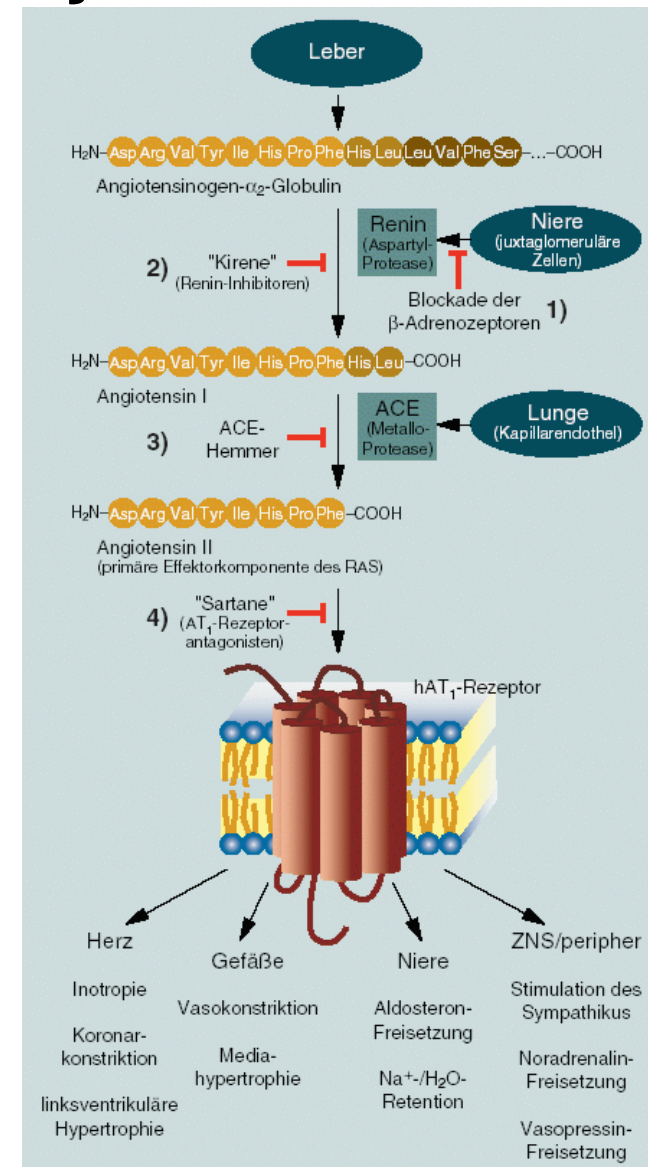
Examples: captopril, fosinopril, quinapril

Therapeutic administration since 1990

disadvantages:

fetotoxic (pregnancy)

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



Angiotensin-II antagonists

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

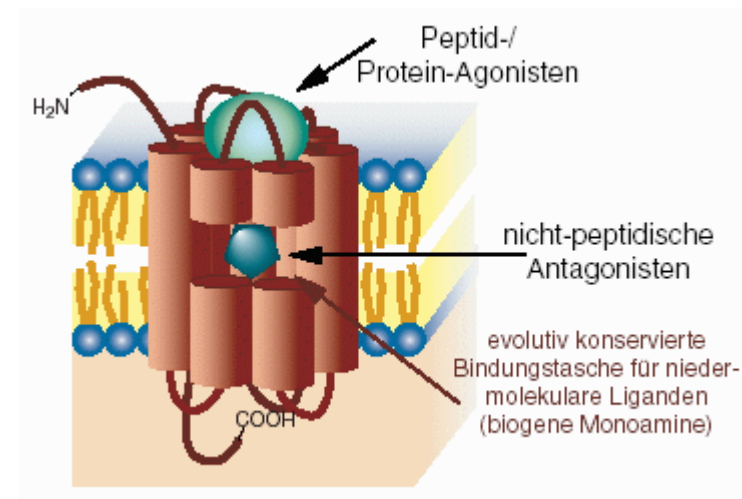
Examples: losartan, valsartan, irbesartan, candesartan, telmisartan

Furthermore in clinical testing: olmesartan, forsartan

therapeutic administration
since 1995

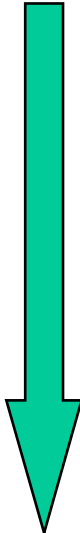
disadvantages:

same as for ACE-inhibitors



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

Evolution of targets over time

targets	therapeutic class	 increasing specificity
kidney	diuretica, saluretica	
nervous system	α and β -blocker	
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: resolution

Con: „artificial“ conditions

NMR (nuclear magnetic resonance)

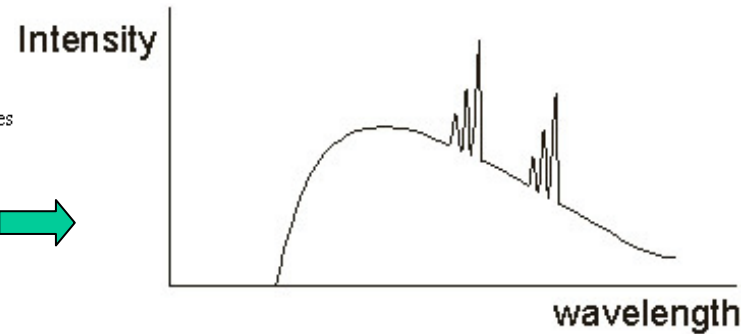
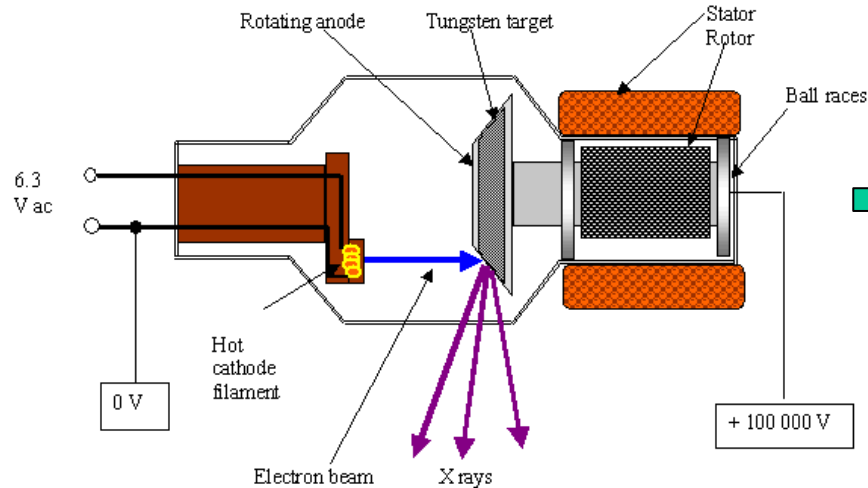
Absorption of electromagnetic waves

Pro: „natural“ conditions

Con: only for small proteins

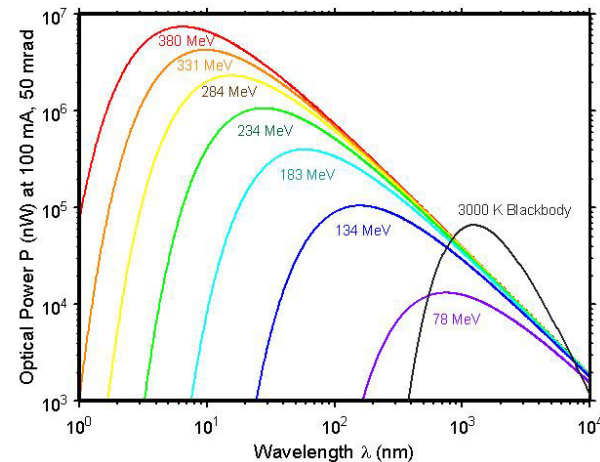
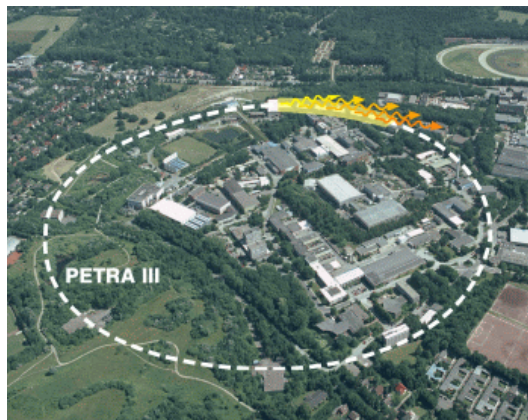
Obtaining X-Ray structures (I)

Conventional X-Ray scattering



Uneven distribution of wave lengths:
characteristic intensity peaks

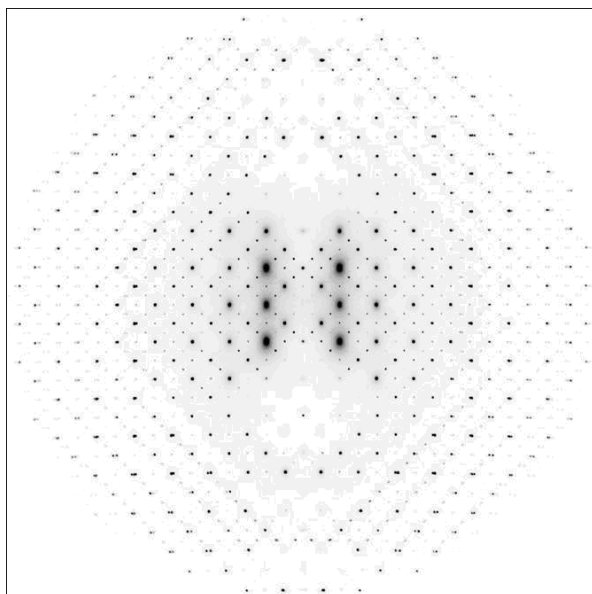
Synchrotron scattering



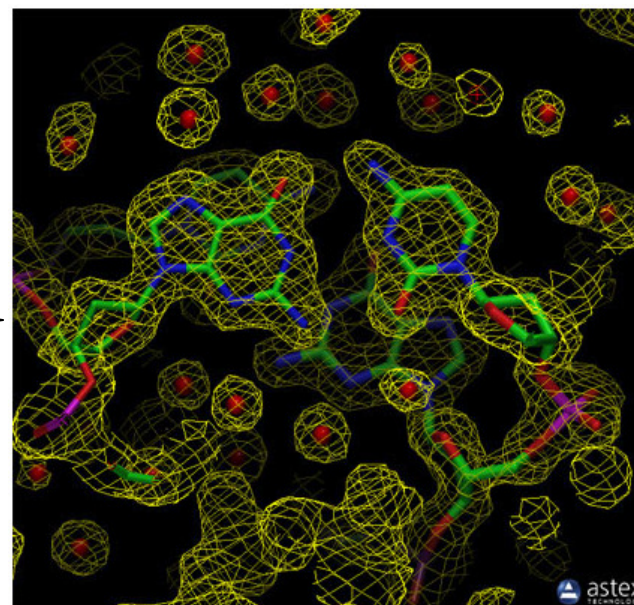
Continuous distribution of wave lengths

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



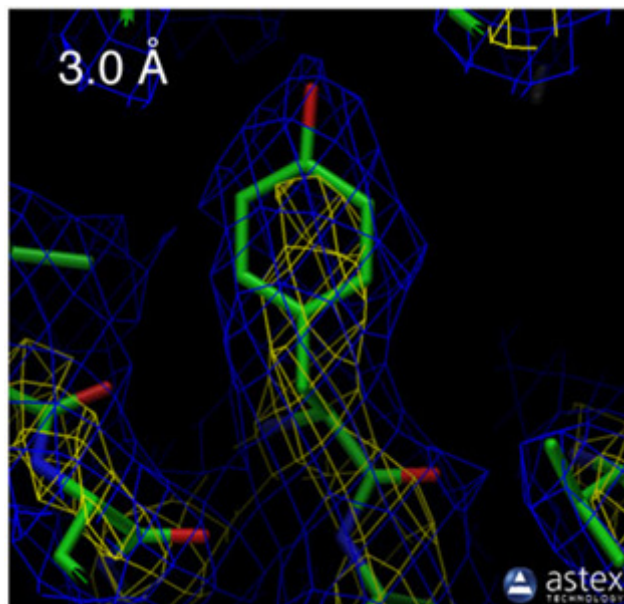
Electron density map

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

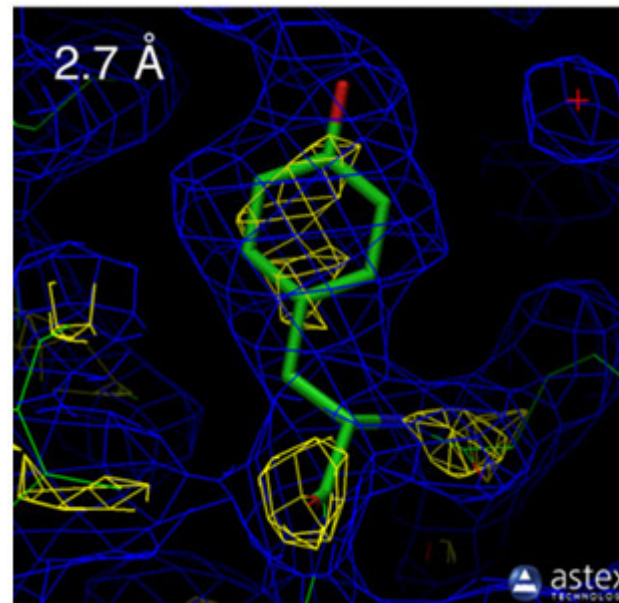
Accuracy of X-Ray structures (I)

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



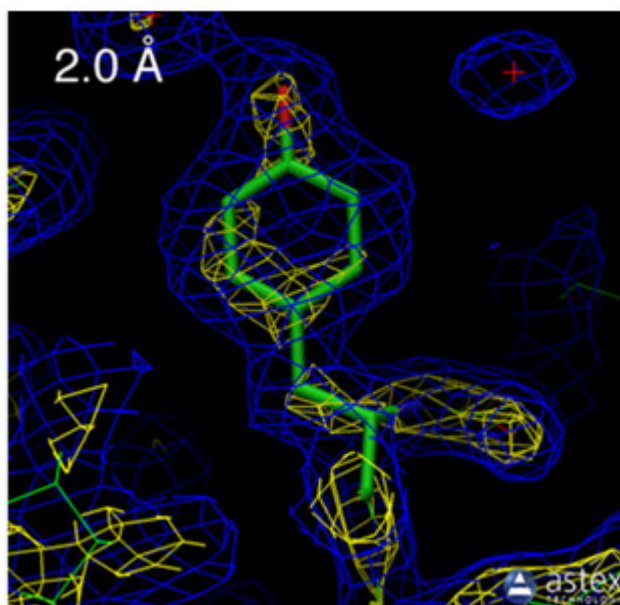
Backbone and putative positions of side chains



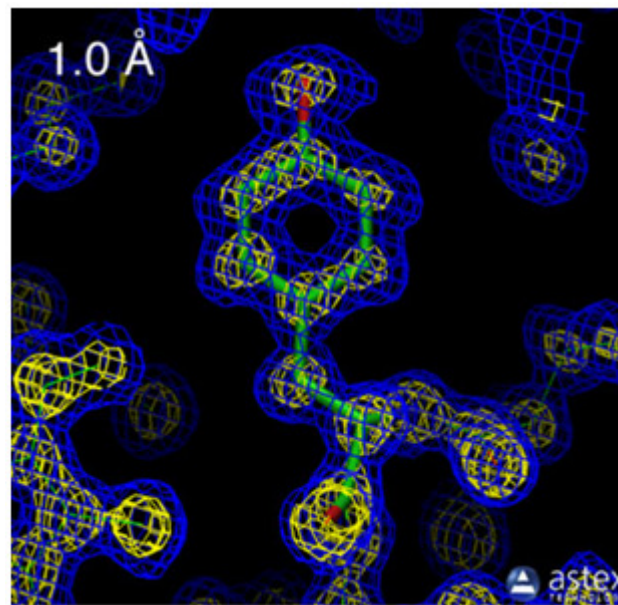
Distinguishing large and small side chains

Accuracy of X-Ray structures (II)

The atomic coordinates are fitted into the electron density grid using a force field



Different rotamers of the side chains can be assigned

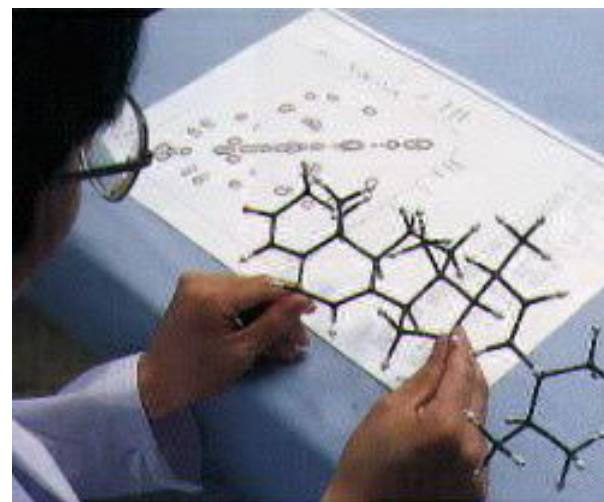
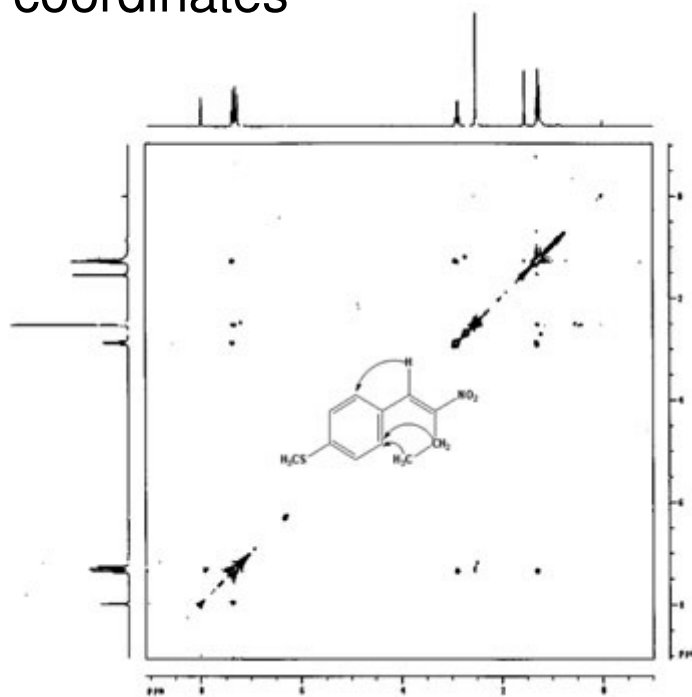


Atomic coordinates can be assigned unambiguously

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 and the resulting averaged structure.