# Therapeutic Categories

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

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

…c.f. the Merck Index

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


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:

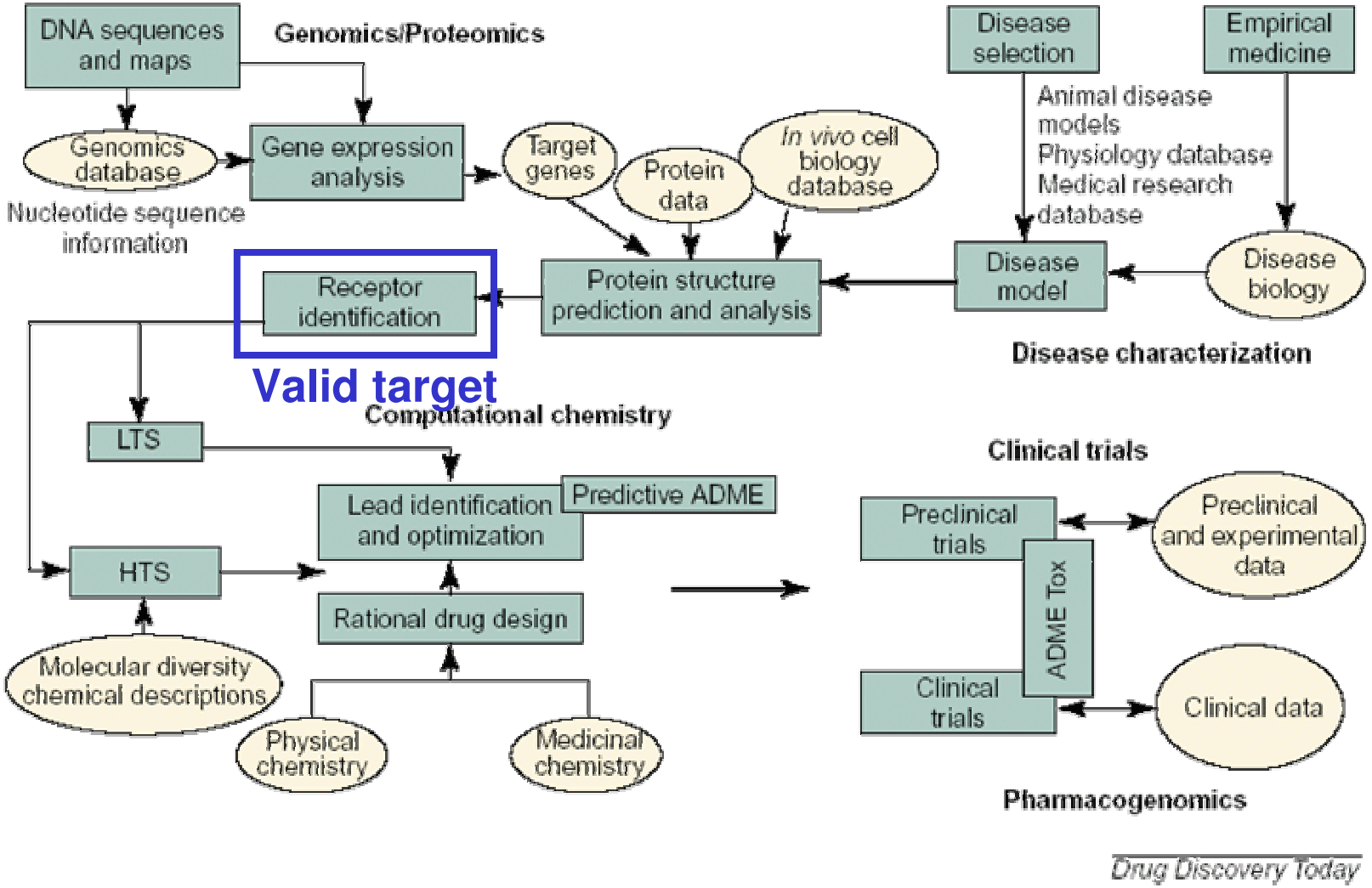
A wealth of information about the disease, its causes, and the clinical symptoms were readily available. Thus the starting point for the pharmacological therapy was known.

Example: inhibition of an enzyme

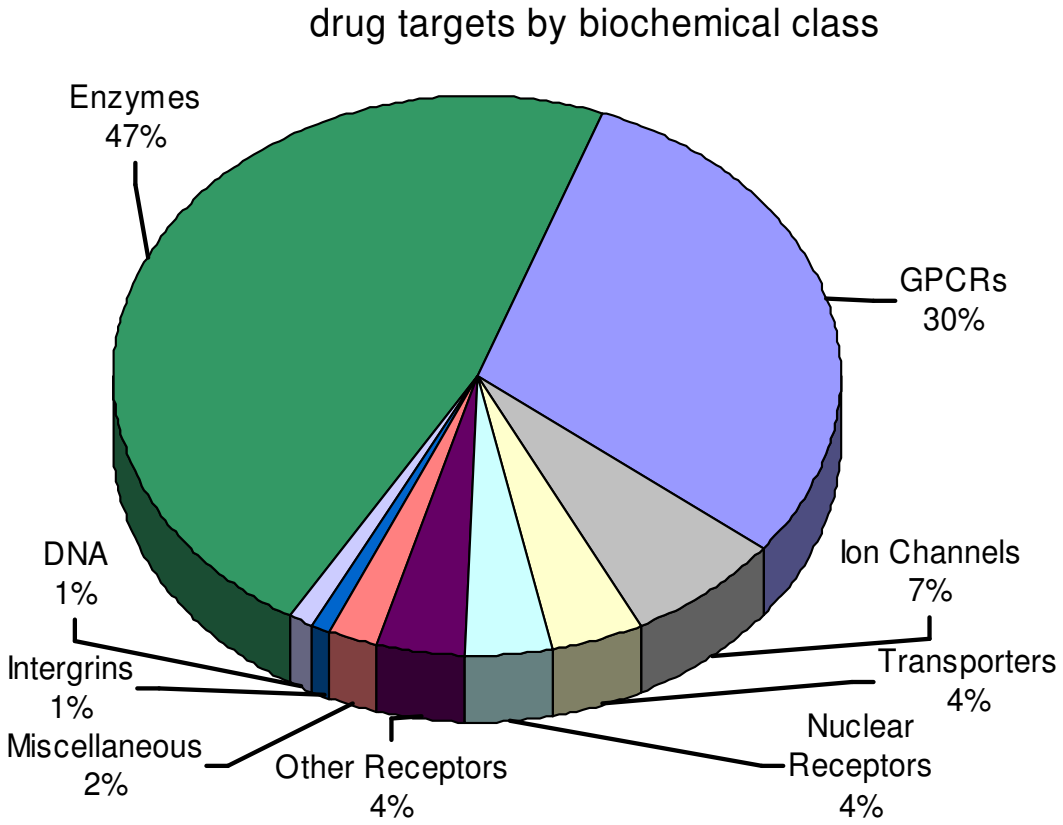
Thus the target was fixed. Frequently, experience with existing medications was available. Therefore a *valid target* or at least a *drugable target* was present.

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

# Flow of information in a drug discovery pipeline



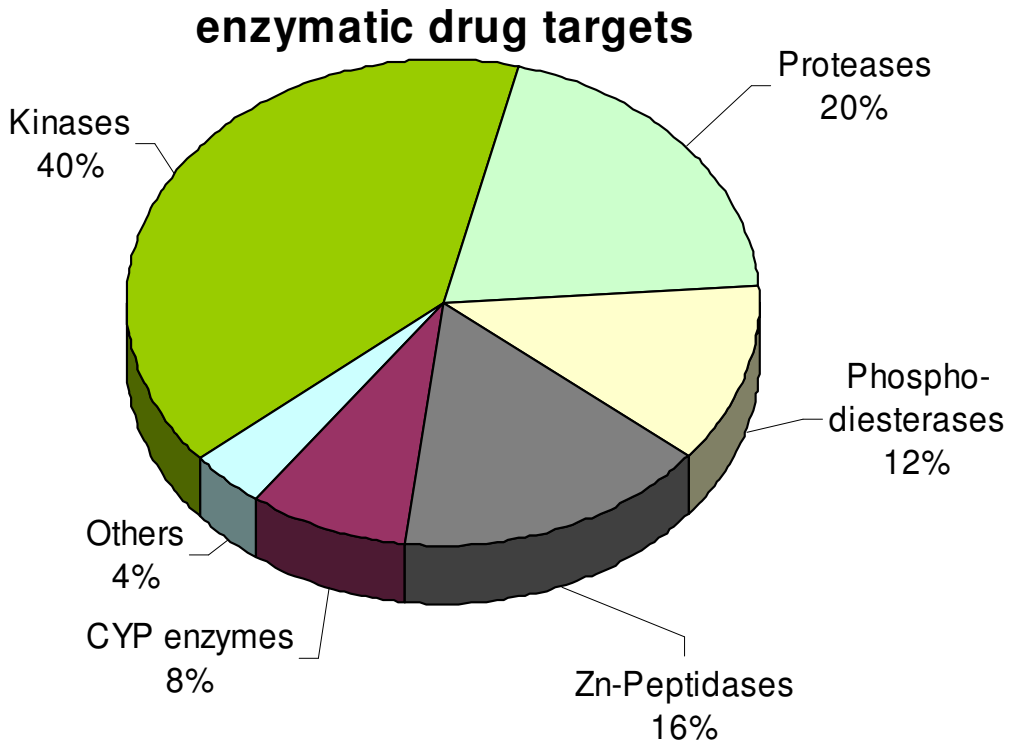
# typical targets




Fractional content of marketed drugs according to their biochemical targets

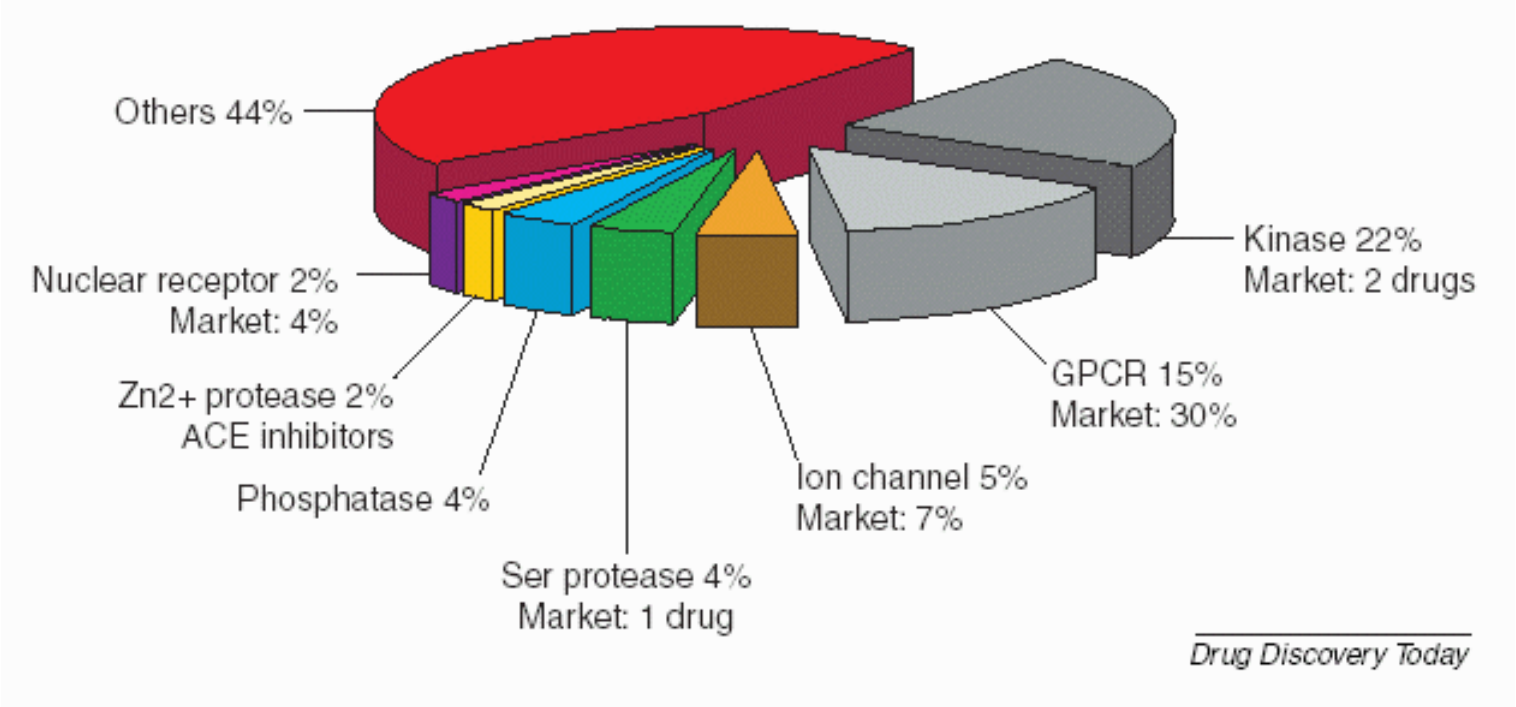
data: Hopkins & Groom, *Nat.Rev.Drug.Disc.* **1** (2002) 727

# Enzymatic targets



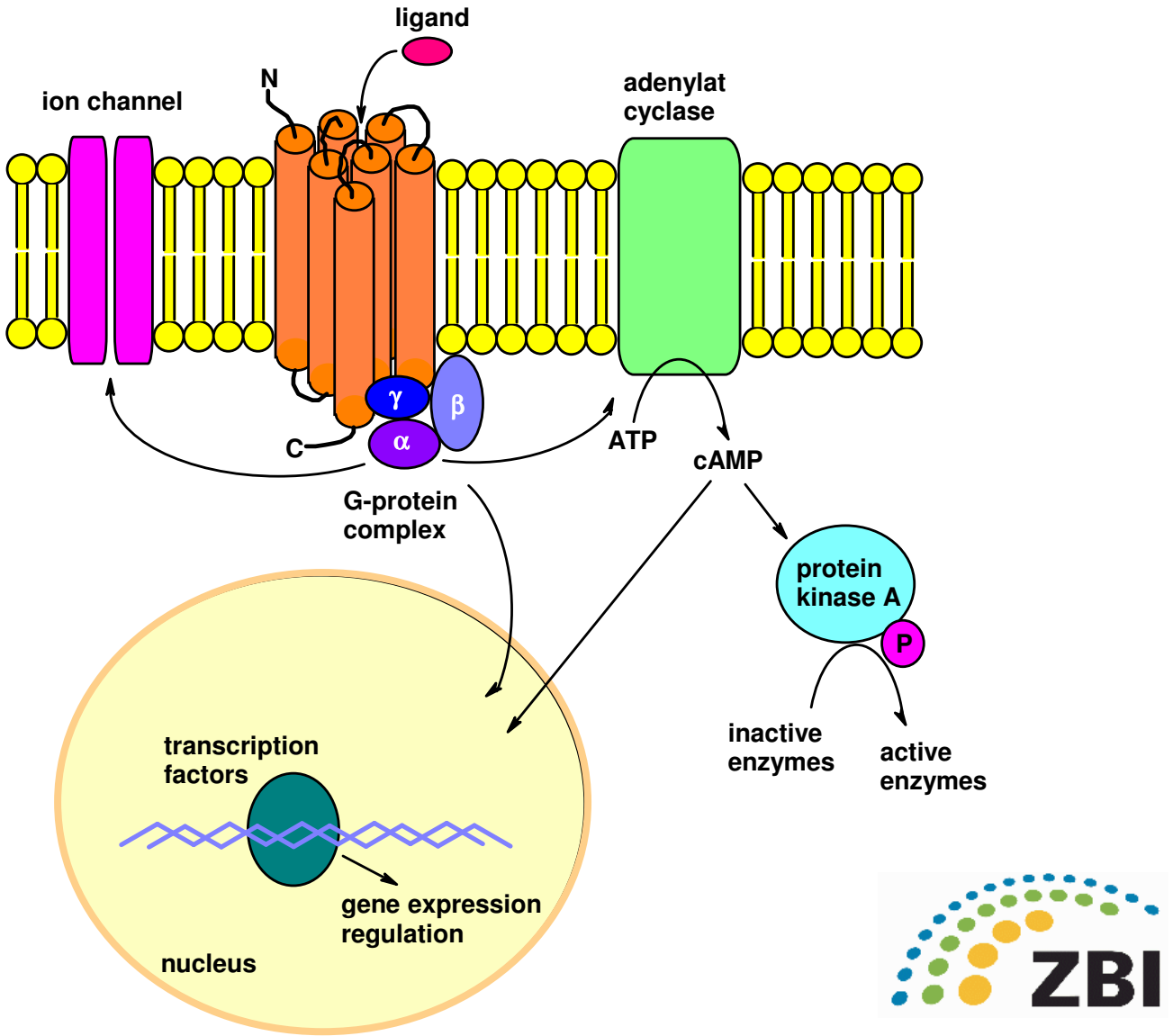

Distribution within the class of enzymes

# typical targets



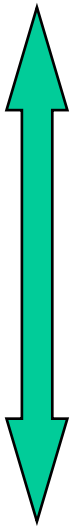

contribution to the human genome and marketed drugs
about 500 enzymes have been used as targets
100,000 estimated potential targets in the genome

# 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, groves, etc.

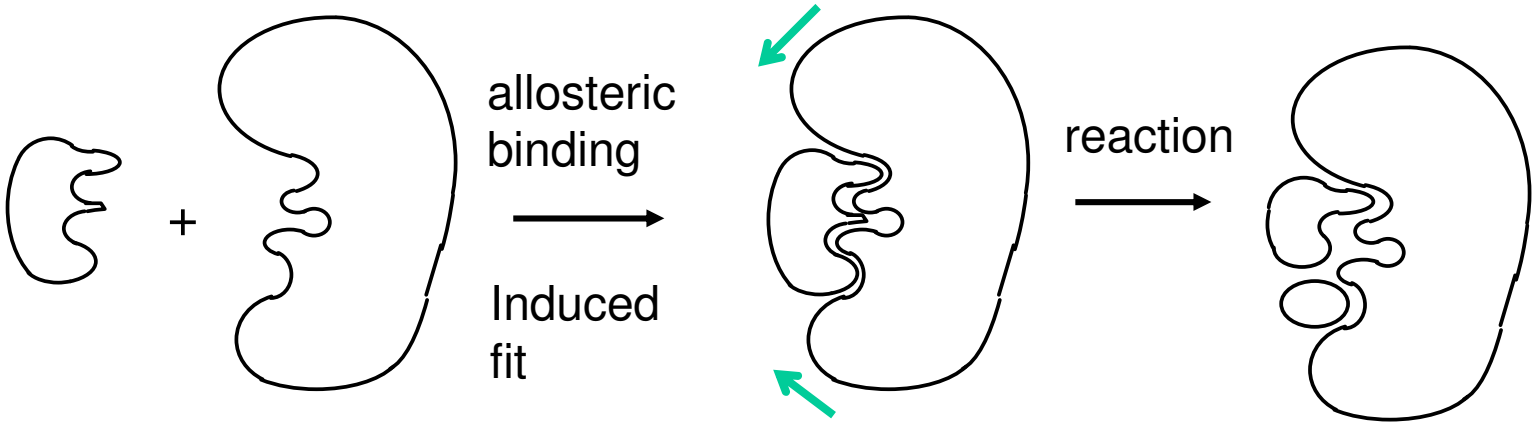
genome

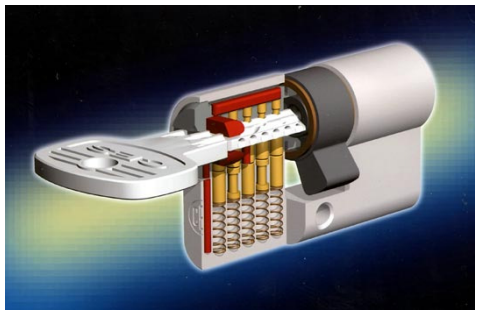
→ Possible targets can be found in a multitude of cell compartments and at different loci.

Problems: Drug delivery and drug transport / distribution

# Drugs: mode of action (I)

Normal enzymatic turn-over

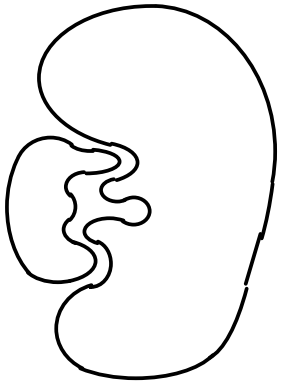


# Drugs: mode of action (II)

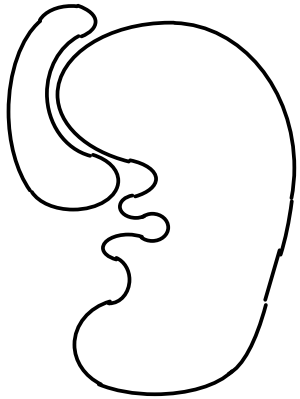
competitive inhibitor:

higher affinity than natural substrate, directly acting



allosteric inhibitor/effector:

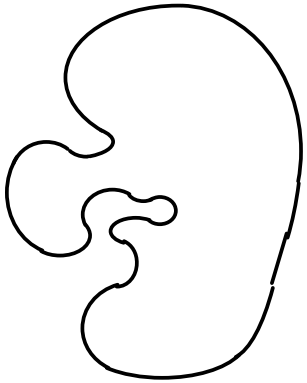
prevents binding by modifying the conformation



Irreversible binding:

chemical reaction leads to inactivation of the enzyme

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



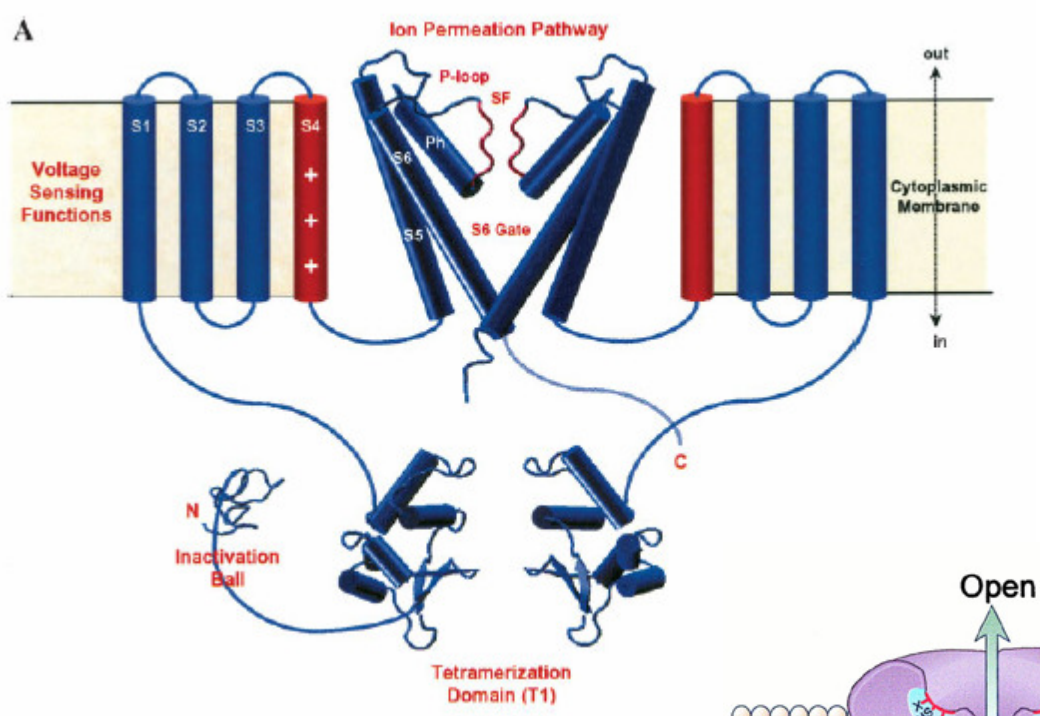
Anti-metabolite:

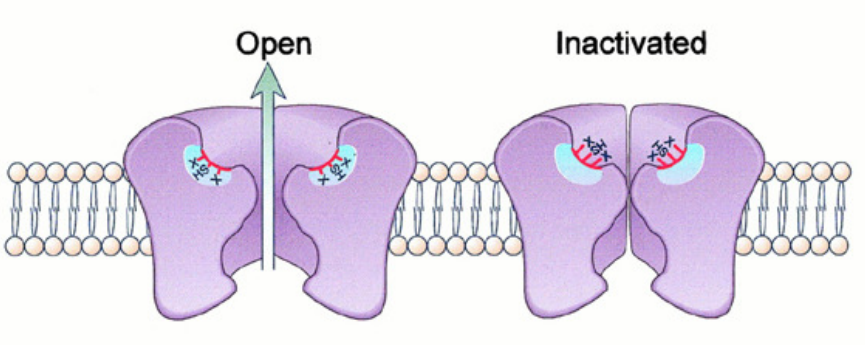
Competitive alternate („wrong“) substrate

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

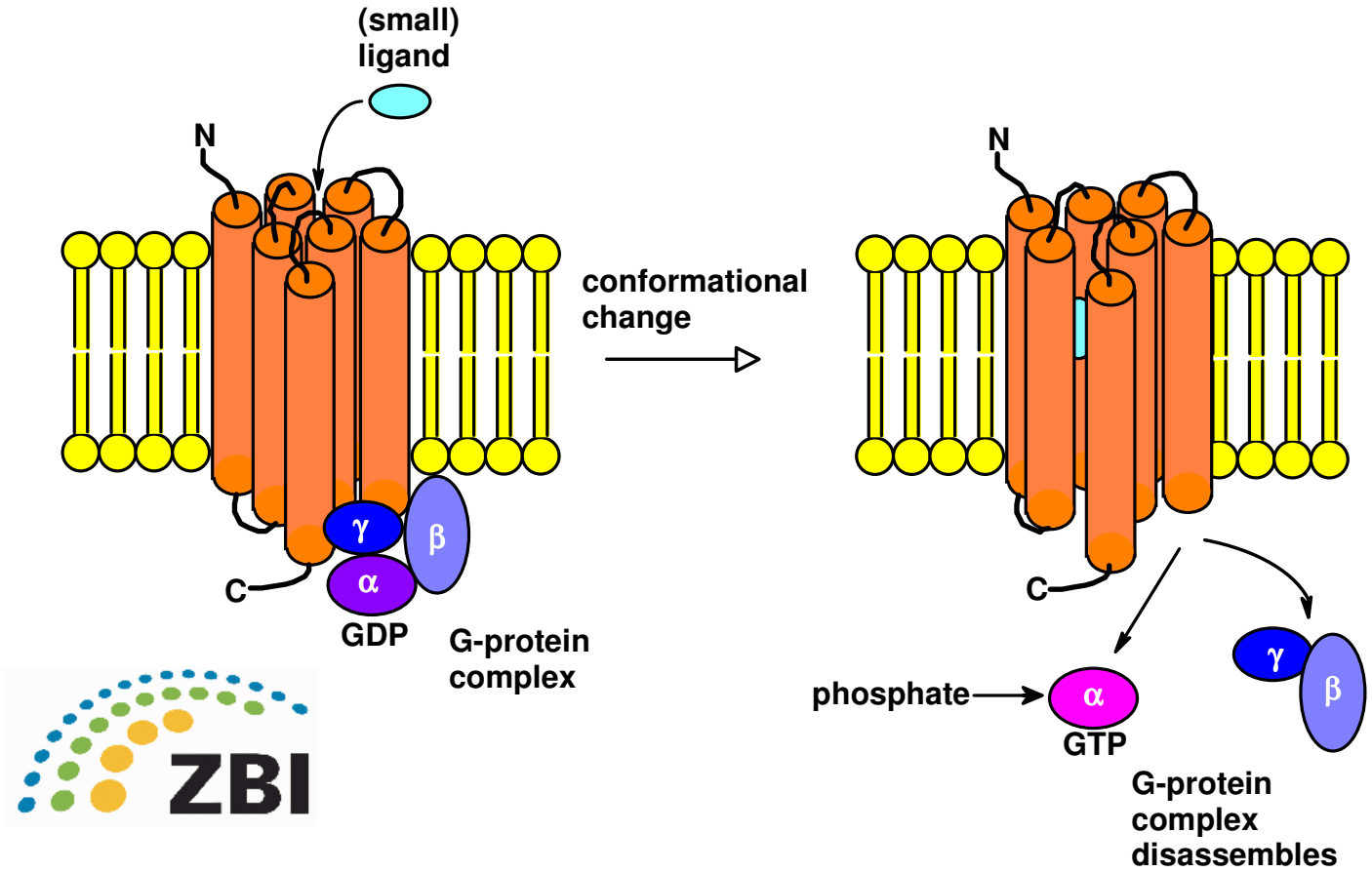
# Drugs: mode of action (III)

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



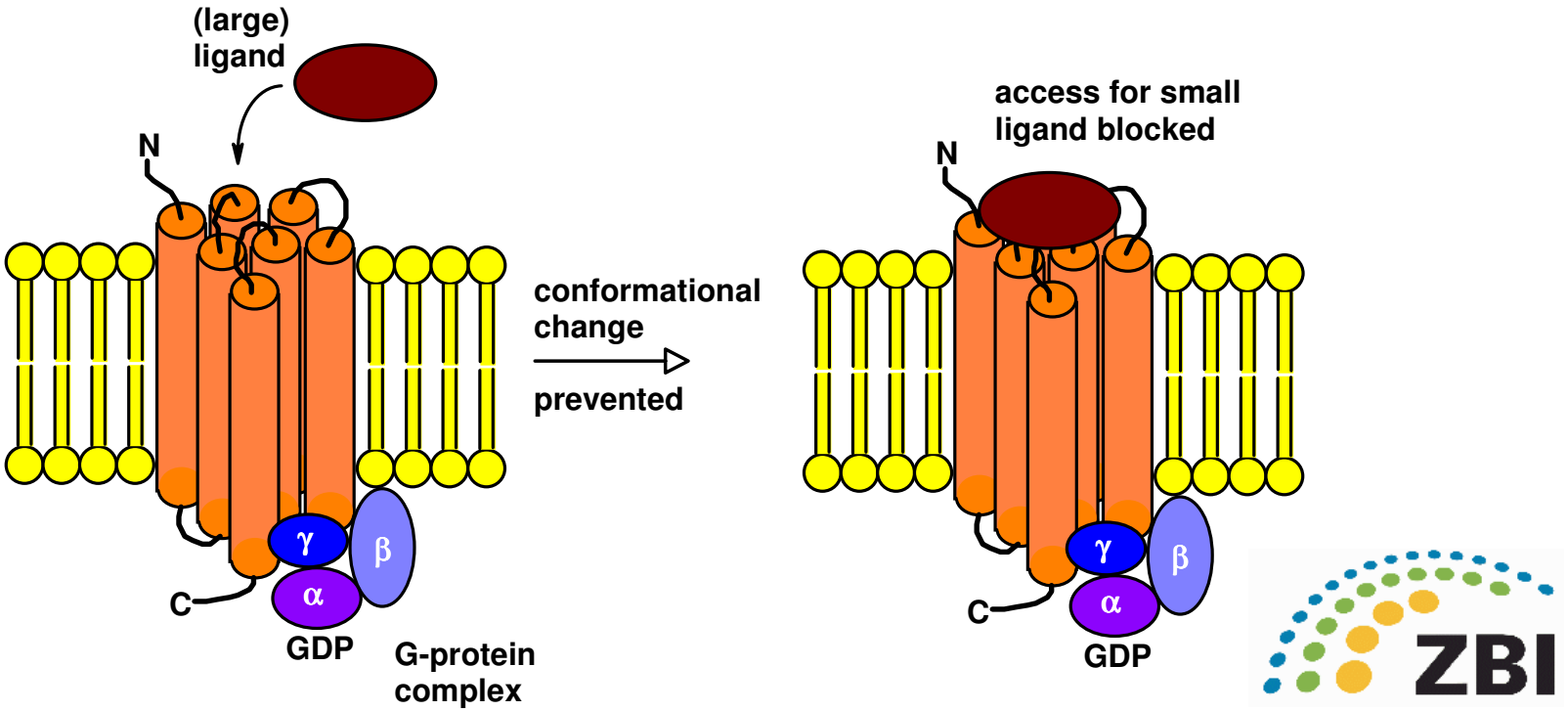
# Drugs: mode of action (IV)




**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)

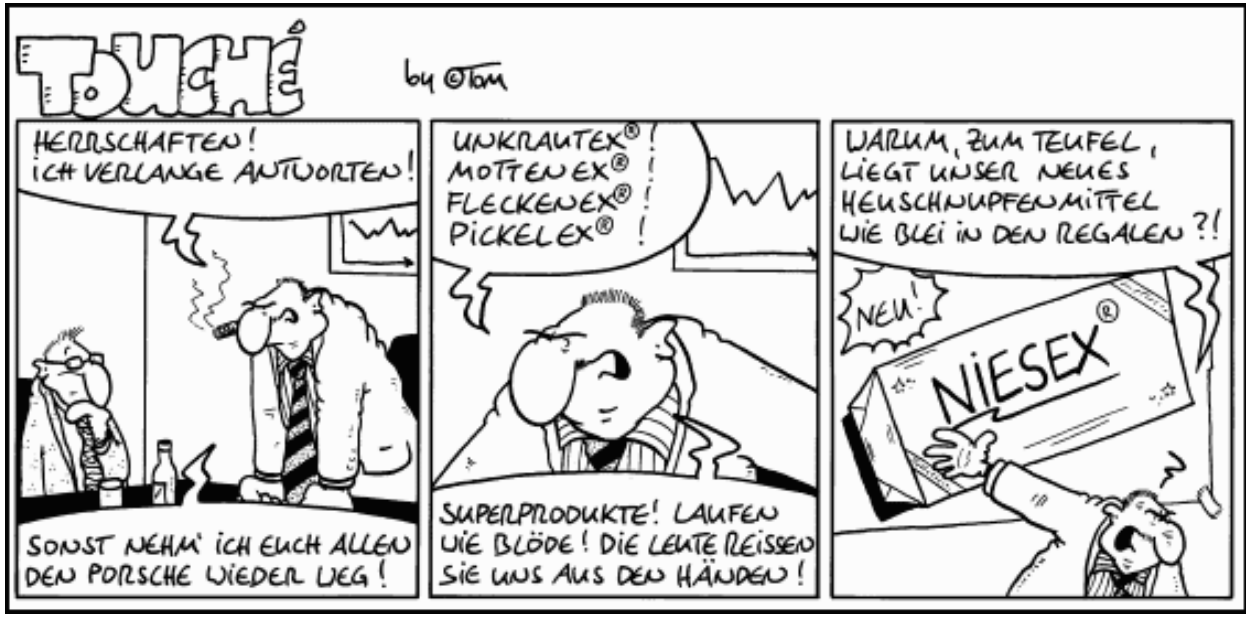



**antagonist**: ligand that prevents binding of the agonist, either directly (competitive binding) or indirectly (allosteric, prevents adoption of the reactive conformation)

**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 !

2nd Lecture

# Naming of drugs (I)

The trade name of a drug is usually chosen very carefully. Associative and speach-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 Nonproprierary Name“ (INN) or „United States Adopted Name“ (USAN) at the lastest 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 cycloxygenase inhibitors:

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

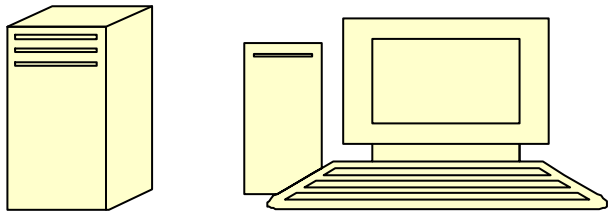
In such cases the drug target is obvious.


http://www.2l.no/2L23details.htm

# Compound Databases

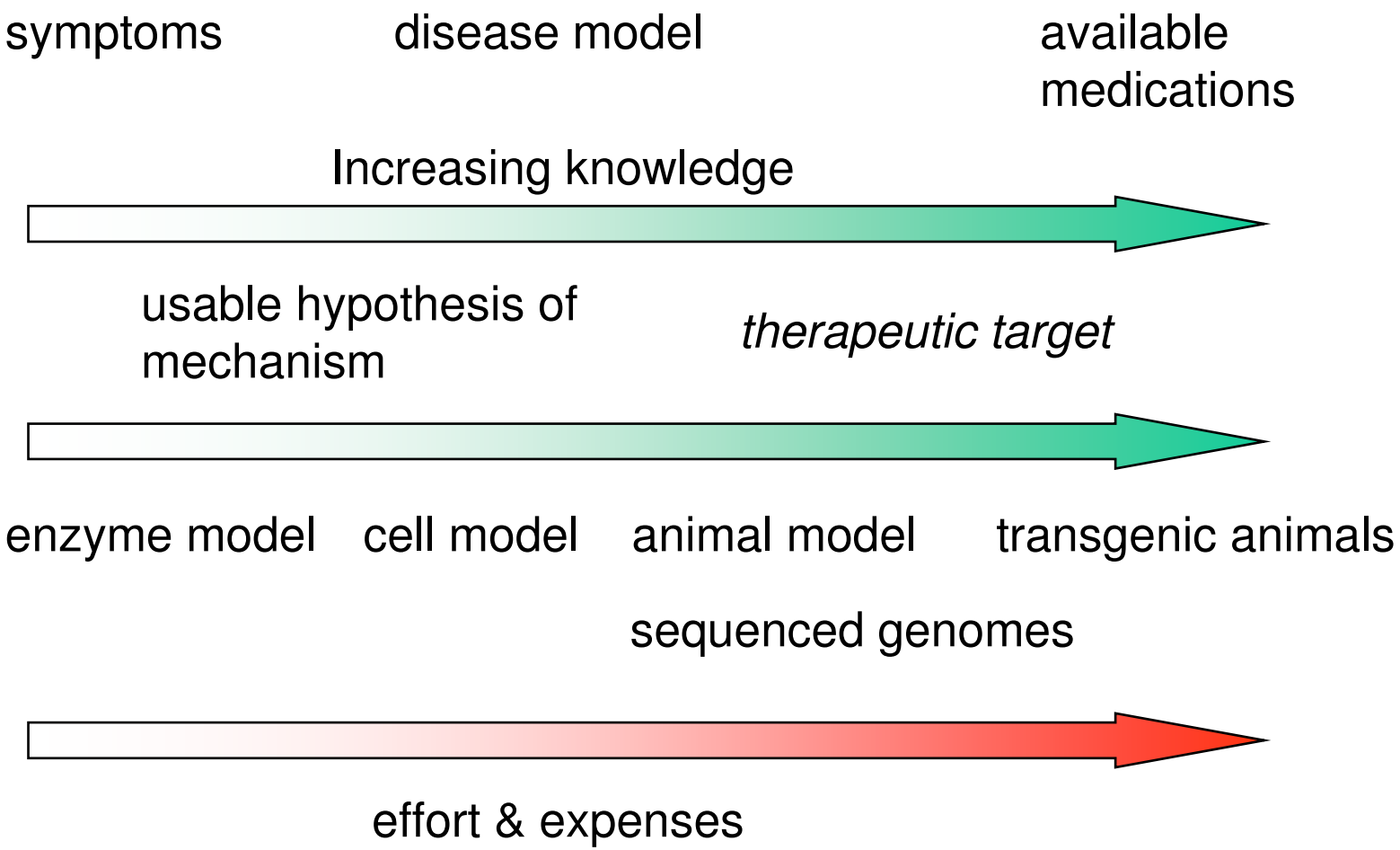
## existing substance libraries

| | | | |
|---|---|---|---|
| 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

1800 1900 2000

Disease causing agents
lack of hygiene
germs, bacteria
viruses

enviromental
influence
carcinogens

*life style*

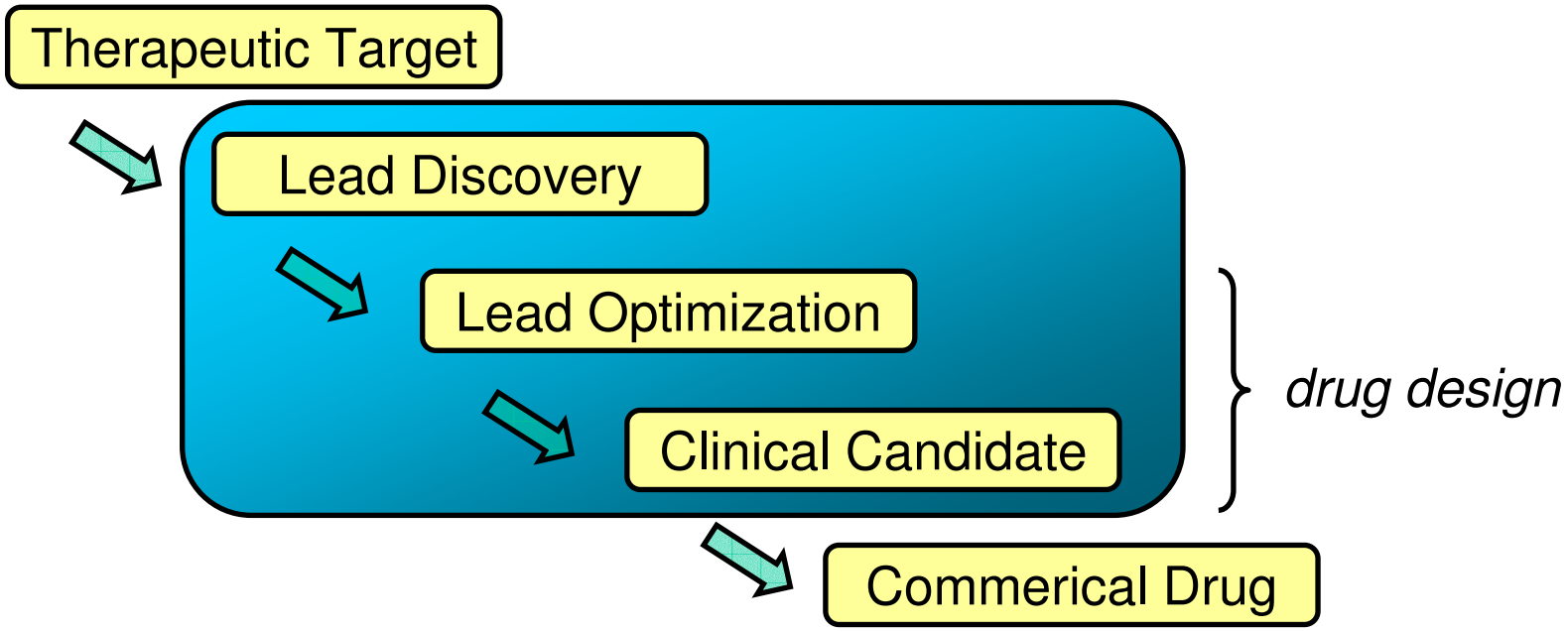
genetic
disposition
susceptibility

bioethic component

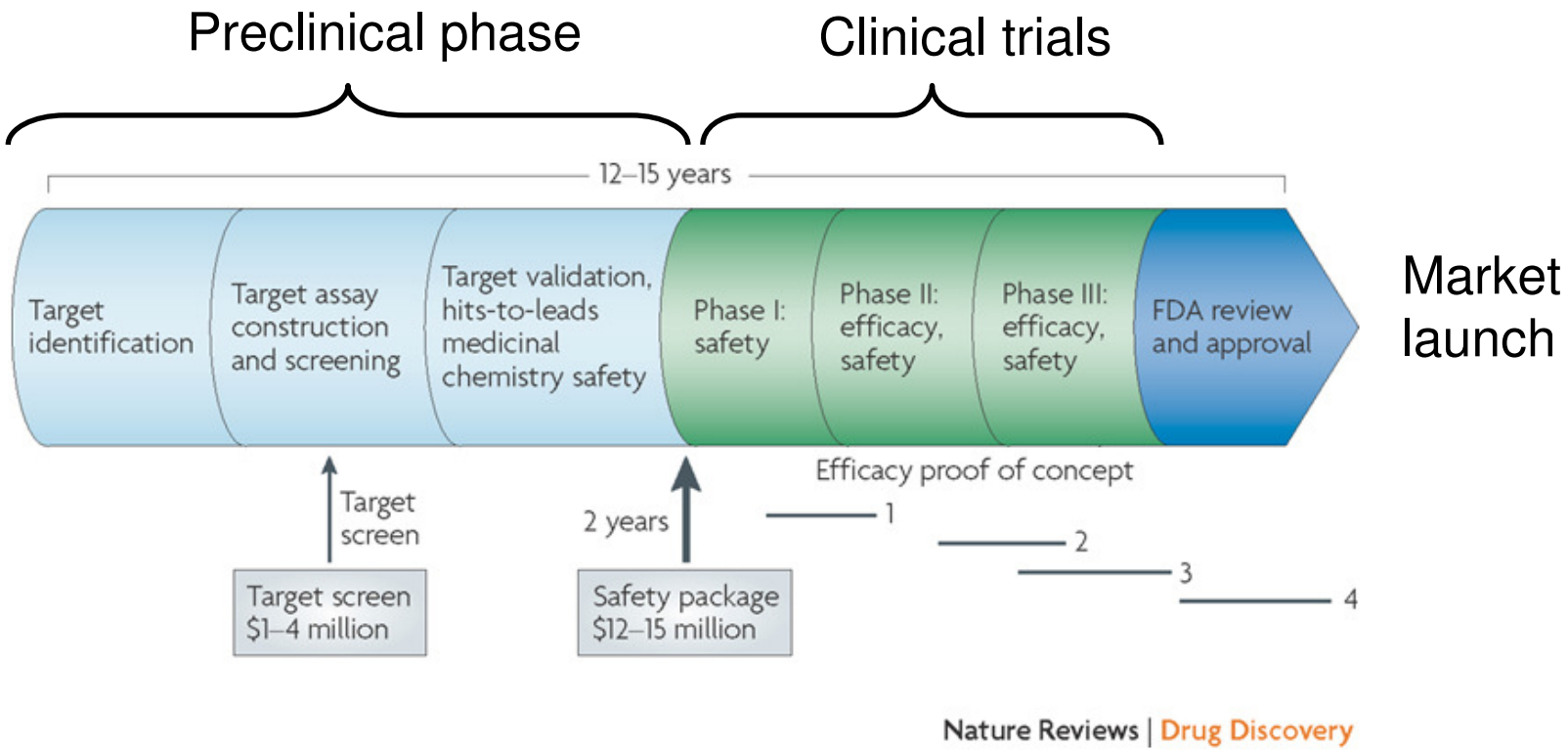
accepted legal definition of diseases

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

# The preclinical phase



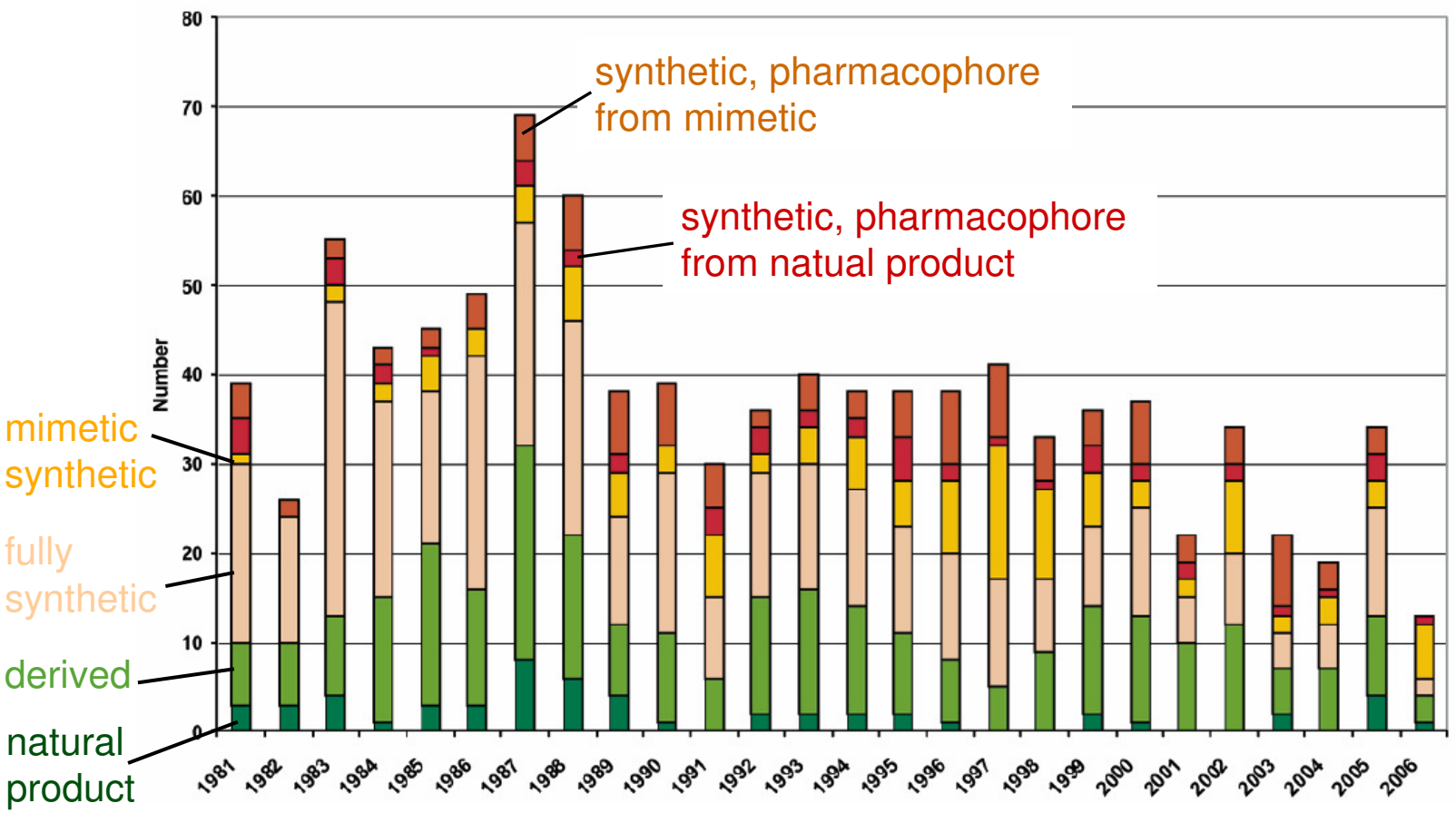
# The drug discovery pipeline




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



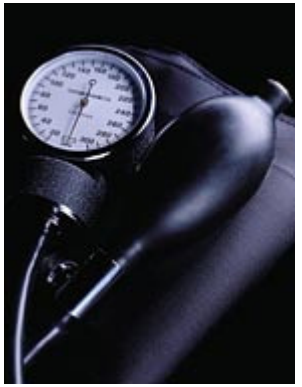

Lit: D.J. Newman, G.M. Cragg *J.Nat.Prod.* **70** (2007) 461-477.

# towards the drug (II)

## Example: arterial hypertension

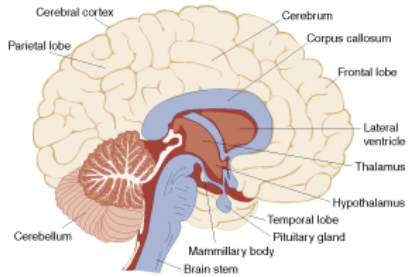
Arterial hypertension [Arterielle Hypertonie] is a frequently observed condition (about 10 - 25% of all adults are affected). Persisent hypertension can lead to damage of blood vessels, the eyes, and the kidneys. → symptoms

| 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.

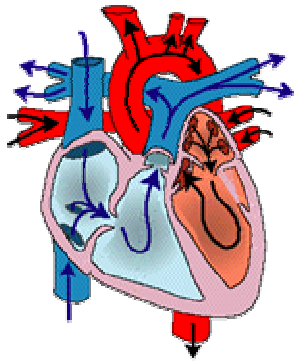
# Regulation of the blood pressure (simplyfied)



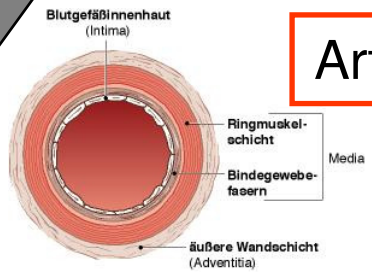

blood volume

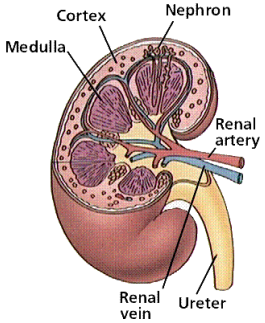
hormones

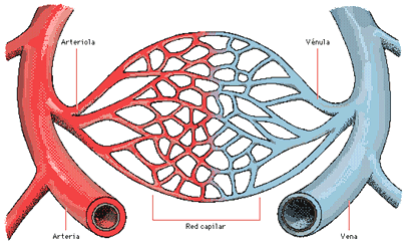
sympathicus ↑ parasympathicus ↓



Arterial blood pressure



heart (pumping) capacity

peripheral resistance

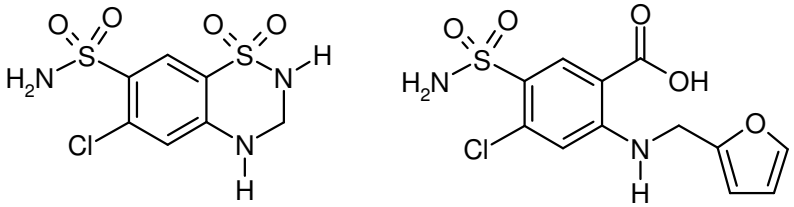
salt deposits $Na^+$, $K^+$, $Ca^{2+}$

# 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

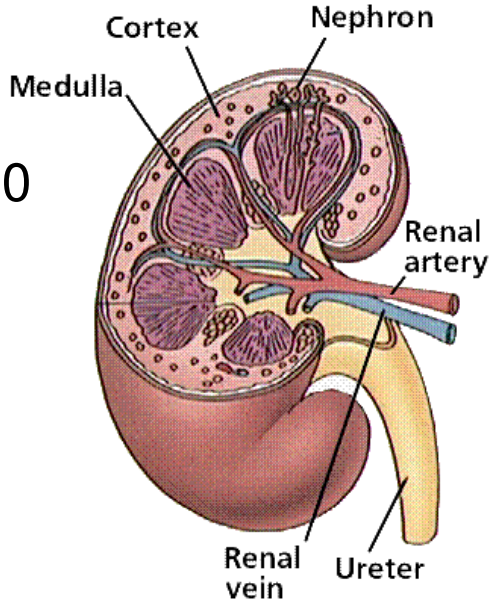




Therapeutic administration of thiazides since 1960

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.

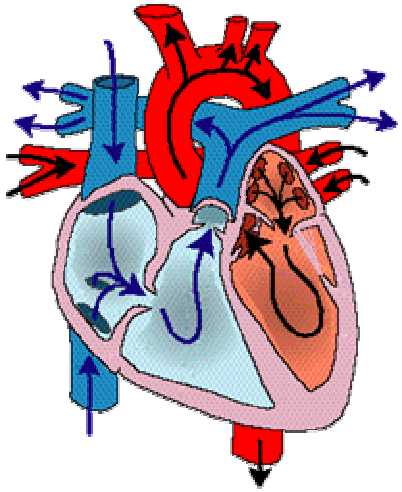
Examples: prasozin, tetrazosin, doxazosin,
propanolol, atenolol, labetalol, pindolol

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

Therapeutic administration since 1970

Disadvantages and side effects:

withdrawl symptomes
reduced capacity of the heart [Herzinsuffizienz]
increased levels of fatty acids in the serum
effects on the central nervous system

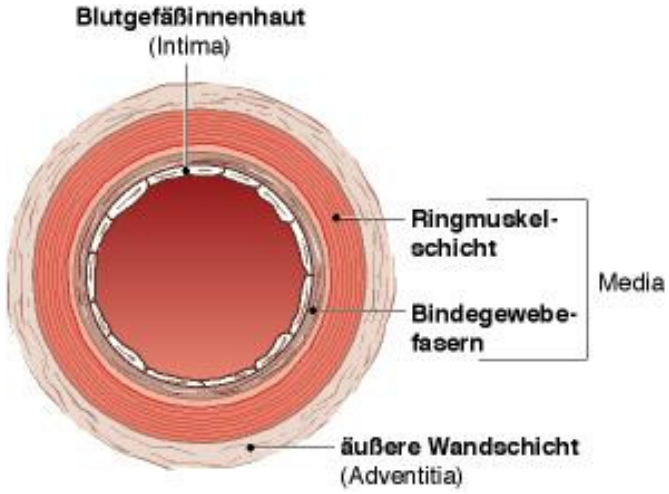


# vasodilators and calcium antagonists

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

Bind to the *h*$AT_2$-receptor or inhibit the calcium pump

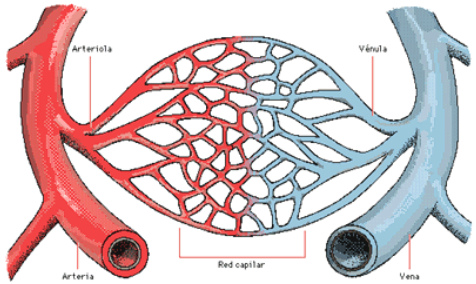
Examples: hydralazine, minoxidil, diazoxide, verapamil, diltiazem, nifedipine




Therapeutic administration since 1980

Disadvantages and side effects:

Predominately on the function of the heart



# Angiotensin Coverting Enzyme Inhibitors

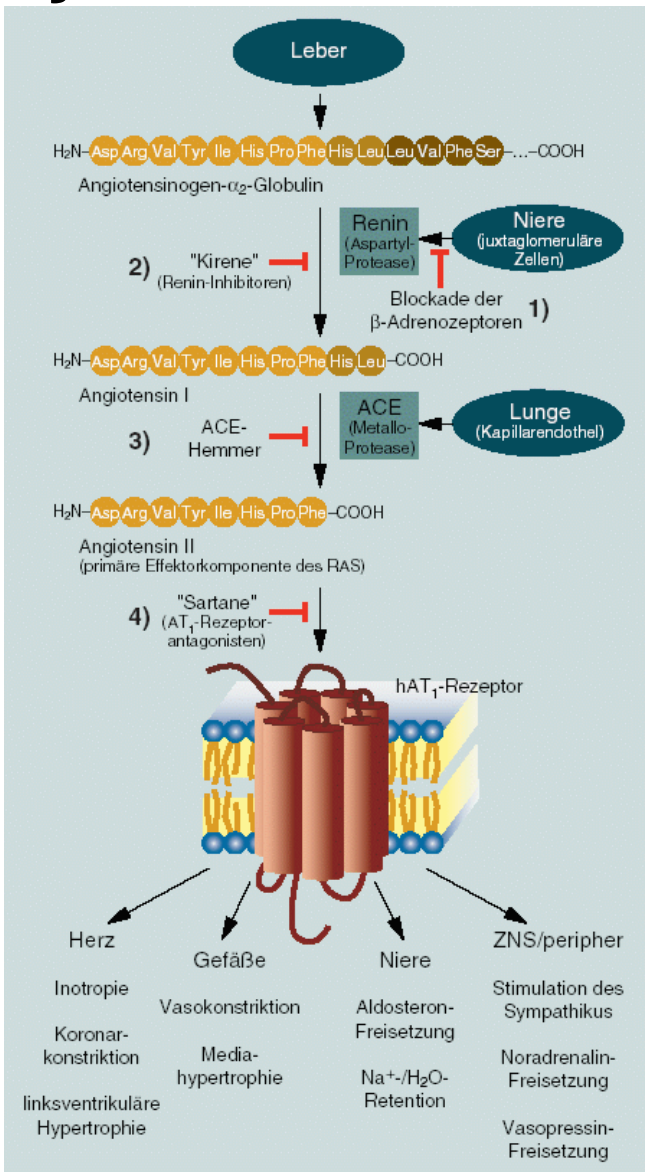
The endogenic oligopeptide Angiotensin II is one of the strongest vasoconstrictors. By inhibiting the angiotenisn converting enzyme (ACE) the synthesis of Angiotensin II is disabled.

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

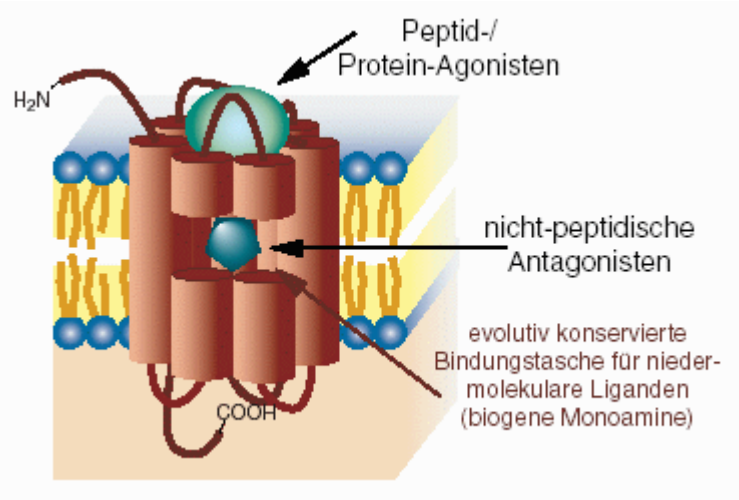
competitive binding of non-peptidic compounds to the *h*$AT_1$-receptor (GPCR), which is the binding site of Angiotensin II.

Examples: losartan, valsartan, irbesartan, candesartan, telmisartan
Furthermore in clinical testing: olmesartan, forsartan

therapeutic administration since 1995

disadvantages:

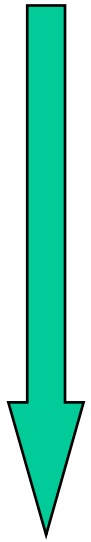
same as for ACE-inhibitors




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

# Evolution of targets over time

| targets | therapeutic class |
|---|---|
| kidney | diuretica, saluretica |
| nervous system | α and β-blocker |
| *h*$AT_2$-receptor | vasodilators |
| ACE | ACE-inhibitors |
| *h*$AT_1$-receptor | Angiotensin II antagonists |



increasing specificity

# Methods for Determining Atomic Structures

**X-ray and electron microscopy**

Diffraction and Scattering of electromagnetic waves, respectively electrons

Pro: resolution Con: „artificial“ conditions

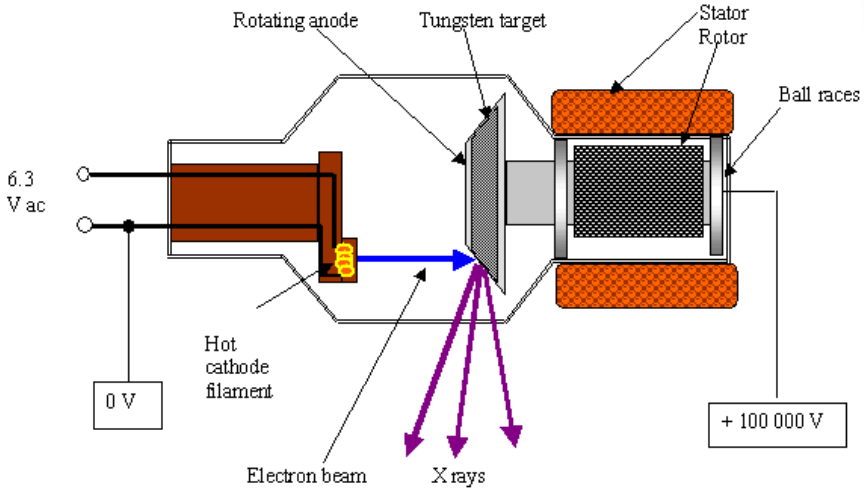
**NMR** (nuclear magnetic resonance)

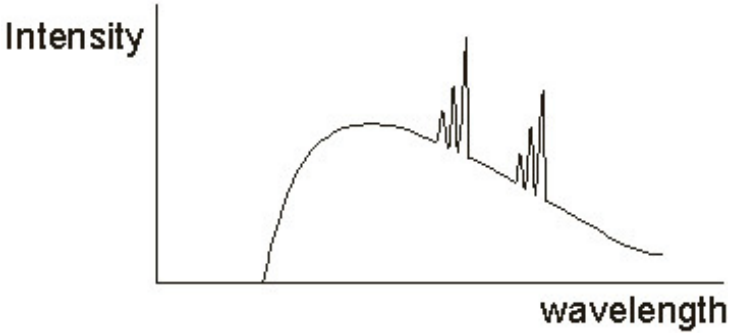
Absorption of electromagnetic waves

Pro: „natural“ conditions Con: only for small proteins

# Obtaining X-Ray structures (I)

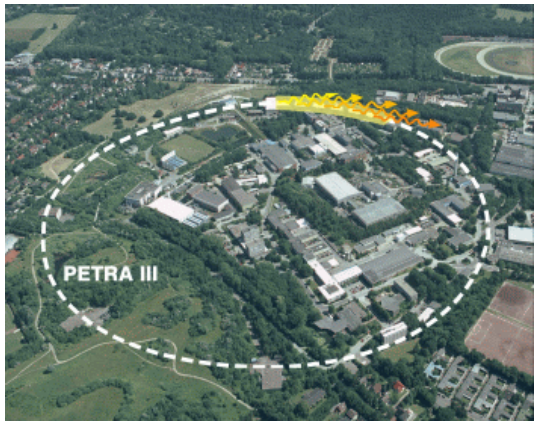
## Conventional X-Ray scattering

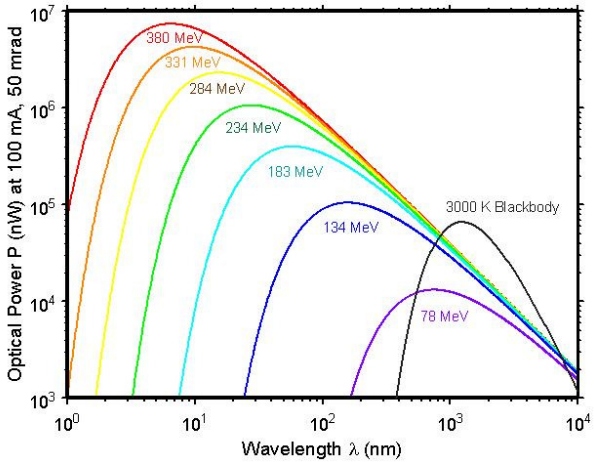



Uneven distribution of wave lengths: characteristic intensity peaks

## Synchrotron scattering

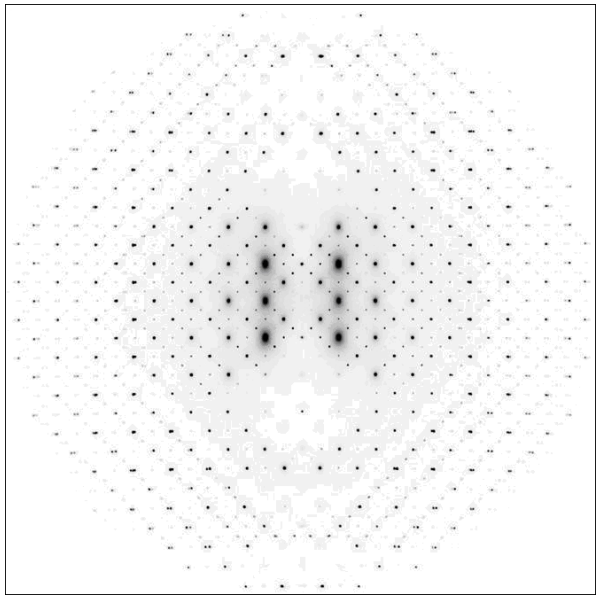



Continuous distribution of wave lengths

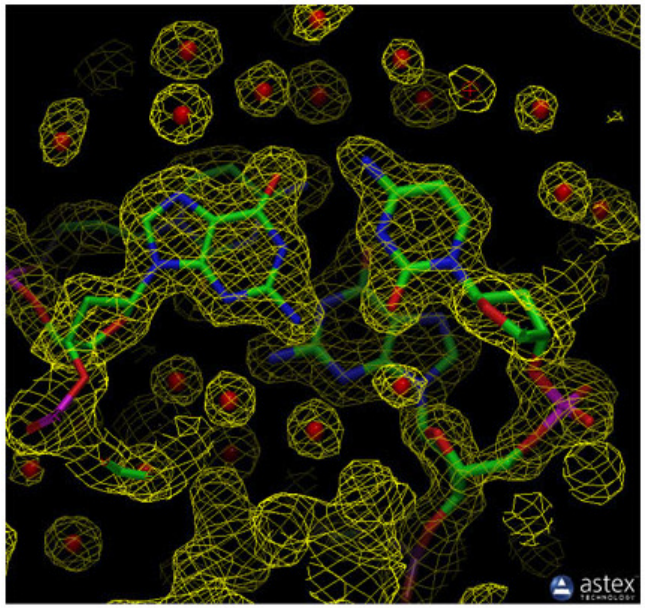
# Obtaining X-Ray structures (II)

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



Mathematical transformation &

Idea how the actual structure looks like

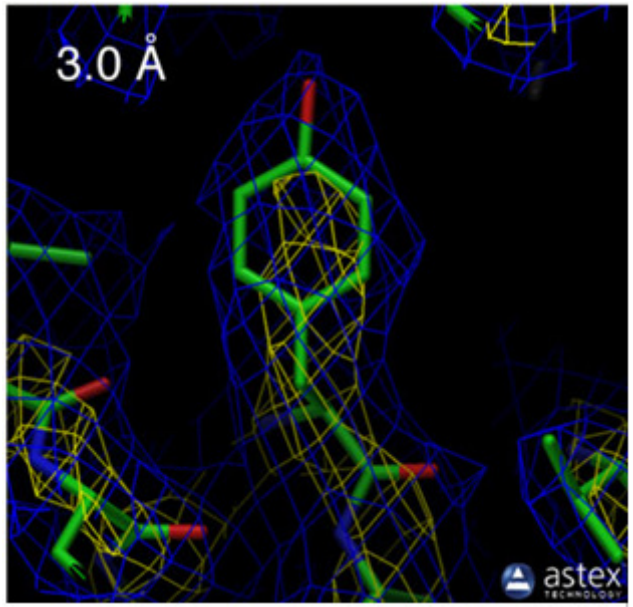



Electron density map

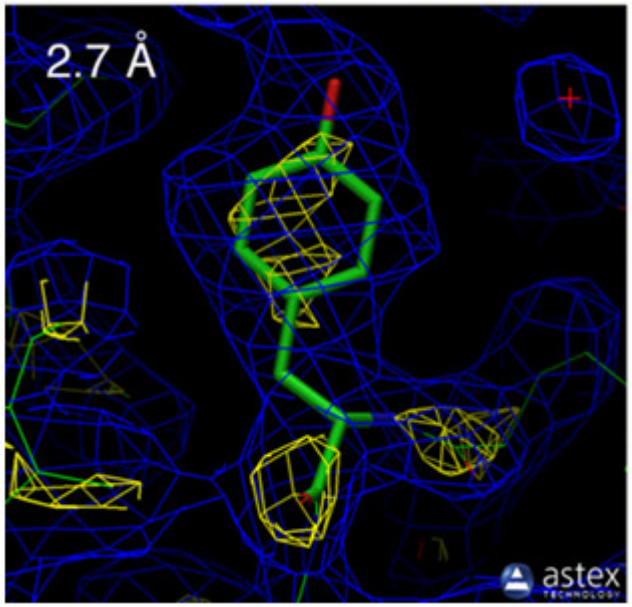
# Accurracy of X-Ray structures (I)

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



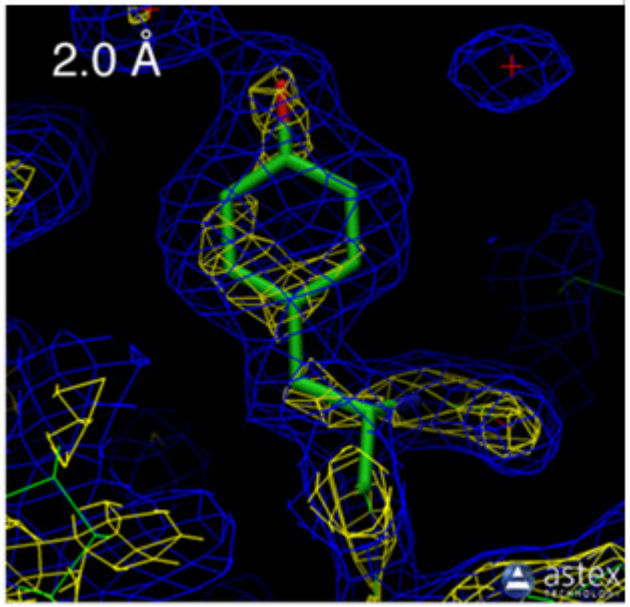

Backbone and putative positions of side chains

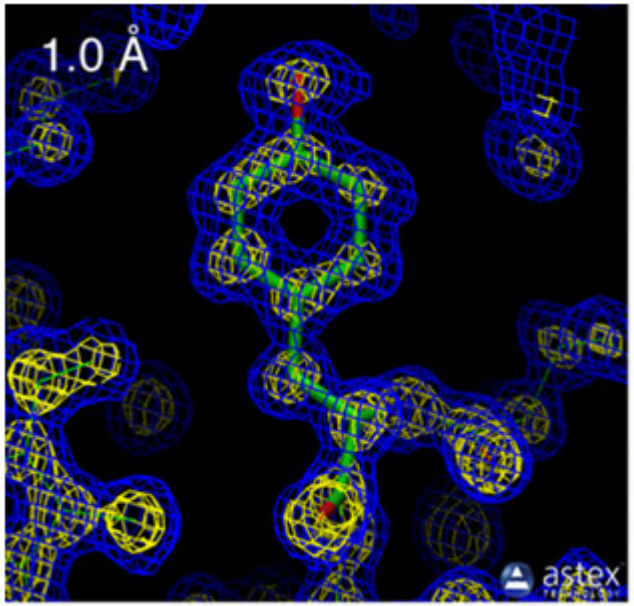



Distinguishing large and small side chains

# Accurracy of X-Ray structures (II)

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



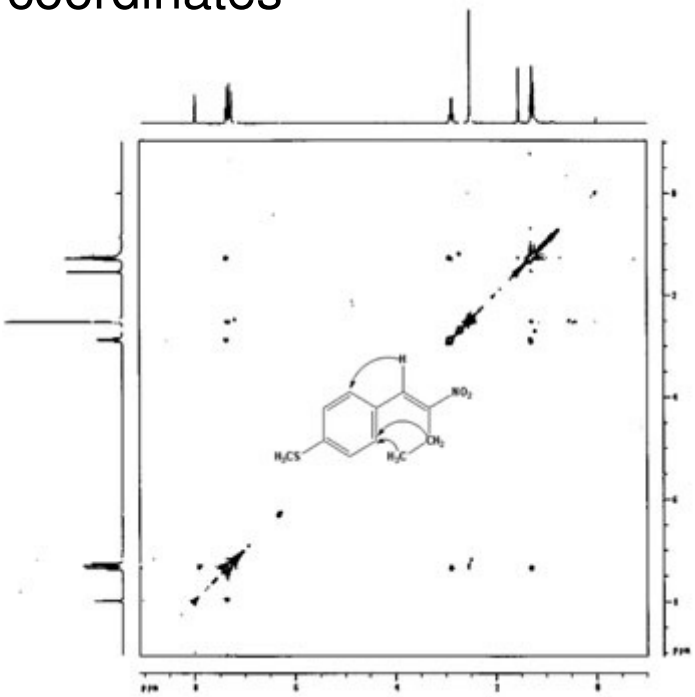

Different rotamers of the side chains can be assigned

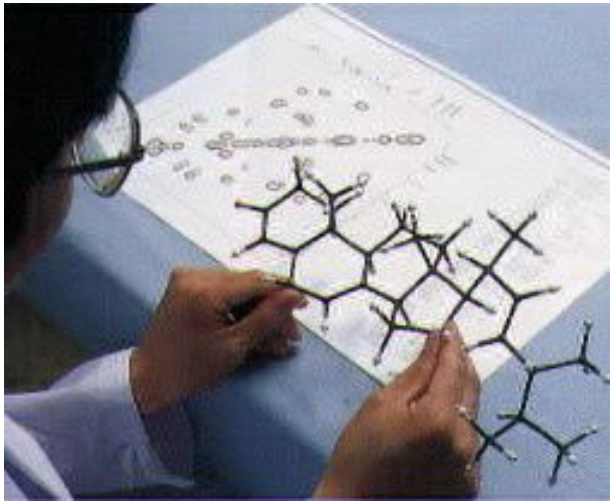
Atomic coordinates can be assigned unambigously

# 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.

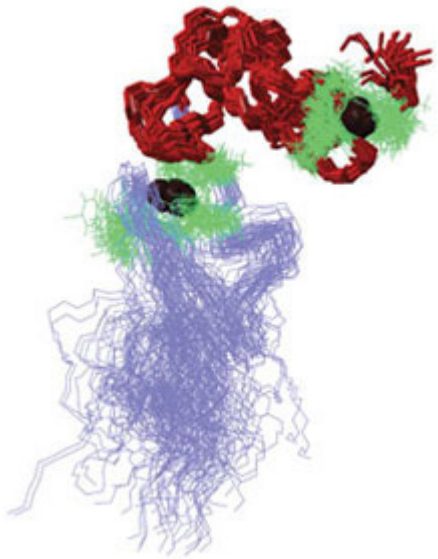
→ constraint force field optimization of the atomic coordinates





# 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.