Drug Design

INTRODUCTION

What are drugs?

The vast majority of drugs are small molecules designed to bind, interact, and modulate the activity of specific biological receptors.

Receptors are (most often) proteins that bind and interact with other molecules to perform the numerous functions required for the maintenance of life.

RECEPTOR :
A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell.

They include an immense array of cell-surface receptors (hormone receptors, cell-signaling receptors, neurotransmitter receptors, etc.), enzymes, and other functional proteins.

INTRODUCTION

Due to genetic abnormalities, physiologic stressors … the function of specific receptors and enzymes may become altered to the point that our well-being is diminished.

These alterations may manifest as minor physical symptoms : runny nose due to allergies or as life threatening and debilitating events, such as cancer, sepsis or depression.

The role of drugs is to correct the functioning of these receptors to remedy the resulting medical condition.

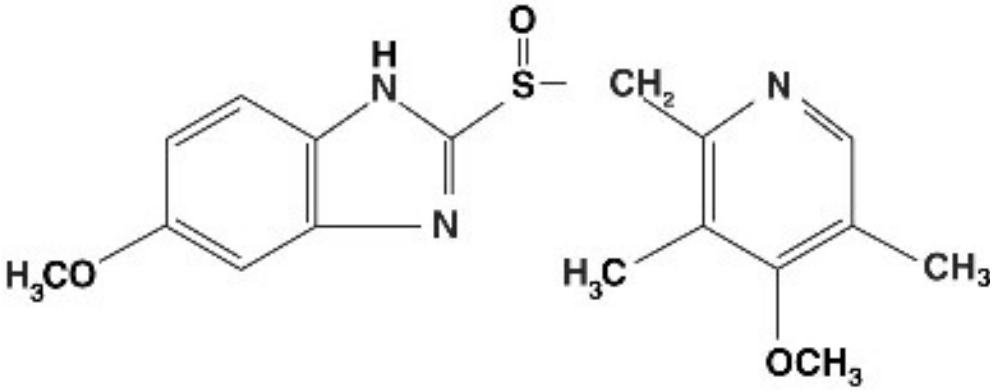
Sepsis is the clinical condition in which infective agents (bacteria, pathogenic fungi) or products of infection (bacterial toxins) enter the blood circulation and profoundly affects the patient's blood pressure, heart rate, and body temperature.

INTRODUCTION

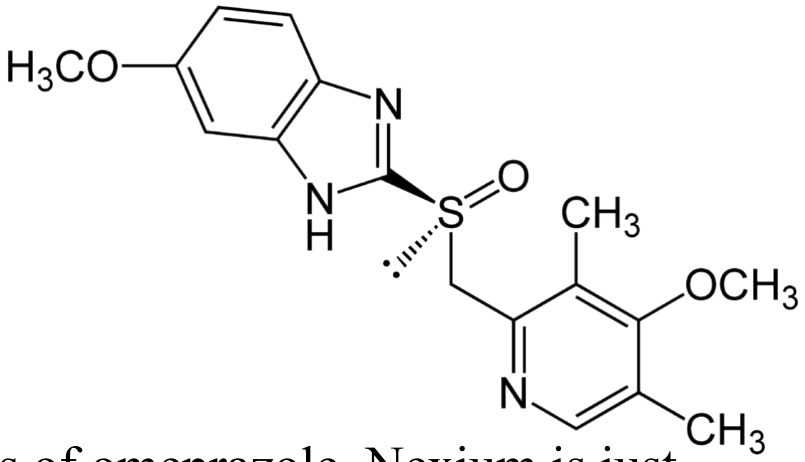
As an example, the highest grossing drug in 2000 was Prilosec, which earned $4.102 billion in sales (AstraZeneca pharmaceutical company).

Prilosec is used to treat stomach ulcers and acid reflux disease.

Prilosec (omeprazole)



Nexium (esomeprazole)
In 2013, 4.4 billions dollars



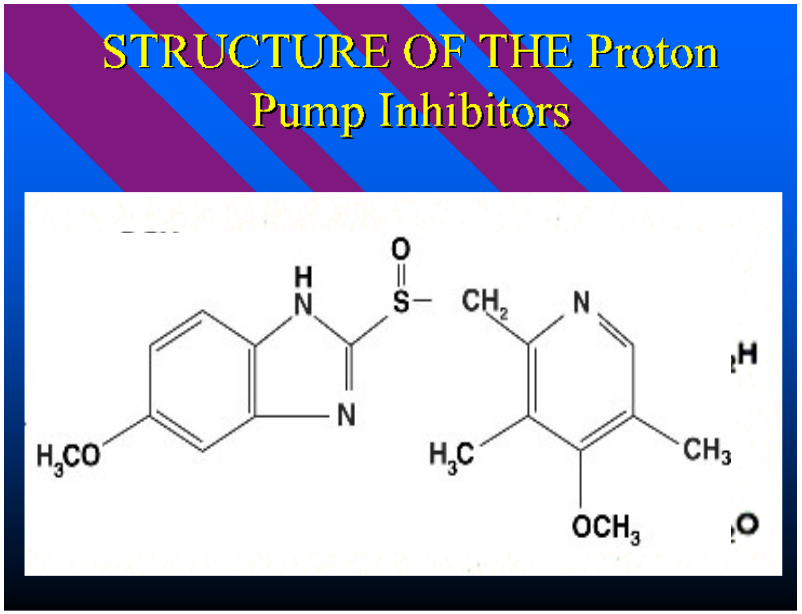
Prilosec is a mixture of R and S enantiomers of omeprazole. Nexium is just the S enantiomer of omeprazole.

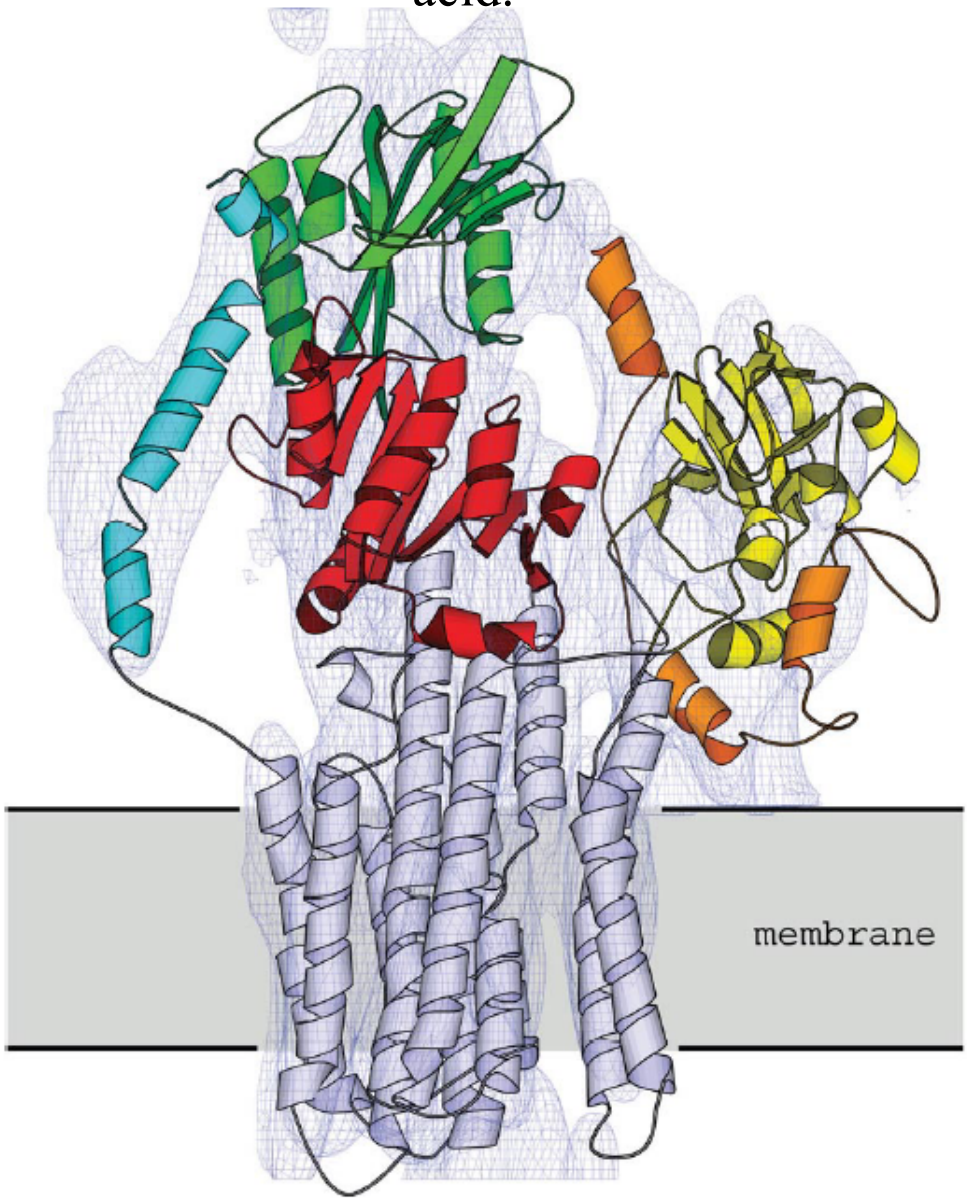
Enantiomers are forms of molecules that are almost exactly the same, but are "opposites.

INTRODUCTION

This enzyme (H+/K+ ATPase)is responsible for the production of stomach acid.

Prilosec targets a specific enzyme, the proton pump, which is located in the acid producing cells lining the stomach wall.





INTRODUCTION

Due to genetic reasons, such as deficient enzymes that regulate acid secretion, or physiologic causes, such as stress, too much acid may be produced.

This leads to ulceration of the stomach lining or acid reflux disease and heartburn.

Prilosec binds to the proton pump and shuts it down, thereby diminishing the production of stomach acid and its associated symptoms.

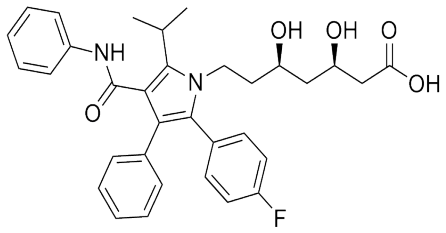
INTRODUCTION

The prescription drug league table will look very different, reflecting the growing commercial dominance of injectable biotech drugs, especially for cancer and rheumatoid arthritis.

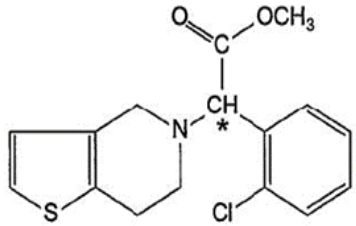
Consensus forecasts for 2010:

1. Lipitor (cholesterol) Pfizer $11.7 bln
2. Plavix (anticlotting) Sanofi/Bristol (BMY.N) $9.6 bln
3. Advair (asthma/COPD) GlaxoSmithKline $9.0 bln
4. Remicade (arthritis) Merck/J&J $7.4 bln
5. Enbrel (arthritis) Pfizer/Amgen $7.1 bln
6. Humira (arthritis) Abbott $6.8 bln
7. Avastin (cancer) Roche $6.7 bln
8. Rituxan (cancer) Roche $6.1 bln
9. Diovan (hypertension) Novartis $6.0 bln
10. Crestor (cholesterol) AstraZeneca $5.8 bln

LIPITOR



PLAVIX



PLAVIX

INTRODUCTION

Top 10 Drug Products by Sales in 2013

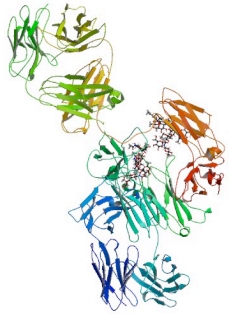
1 Abilify depressive disorder
2 Nexium
3 Humira anti inflammatory (antibody)
4 Crestor
5 Cymbalta
6 Advair Diskus
7 Enbrel
8 Remicade
9 Copaxone
10 Neulasta

Approval of avastin by FDA was revoked on 18 November 2011 !!

Avastin, blocks blood vessels development needed to tumor growth

Not in the top 10 in 2011

More Biotech drugs and less small molecules



Top 10 Drug Products by Sales in 2008

Rank	Product	Company	Technology	WW Sales ($m)
1	Lipitor	Pfizer, Astellas & Almirall	Chiral chemistry	13,507
2	Plavix	BMS & Sanofi-Aventis	Small molecule chemistry	9,447
3	Advair	GlaxoSmithKline	Small molecule chemistry	7,828
4	Enbrel	Wyeth, Amgen & Takeda	Recombinant product	6,455
5	Diovan	Novartis & Ipsen	Small molecule chemistry	5,825
6	Rituxan	Roche	Monoclonal antibody	5,481
7	Remicade	SGP, J&J & Mitsubishi Tanabe	Monoclonal antibody	5,293
8	Nexium	AstraZeneca	Chiral chemistry	5,200
9	Epogen/Procrit	J&J, Amgen & Kirin	Recombinant product	5,162
10	Avastin	Roche	Monoclonal antibody	4,818

INTRODUCTION

Designing a drug with a therapeutic activity is a long and multi-disciplinary process.

Currently the advent of a drug results from the work of synthesis chemists, biologists, spectroscopists, pharmacists, physicians, modelling scientists...

This inter-disciplinary work took place two centuries ago and represents the outcome of several thousand years of human activity to protect from suffering and diseases.

In this course we will discuss only a part of the process of devising a drug : the design of molecules forming a complex with a biological receptor.

INTRODUCTION

Several steps are indeed required before an active molecule can be found**: ONE IS THE IDENTIFICATION OF THE TARGET MOLECULE.**

- A ‘target’ molecule is a biological receptor identified beforehand to be part of a physiological mechanism which one tries to activate, inhibit or modulate.

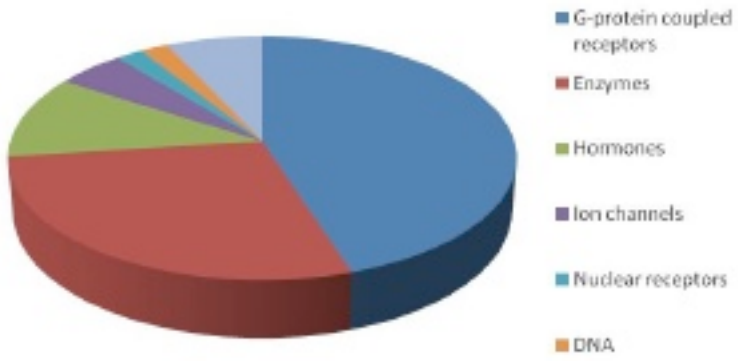
- A target is a broad term which can be applied to a range of biological entities which may include for example proteins, genes and RNA.

INTRODUCTION

- A good target needs to be efficacious, safe, meet clinical and commercial needs and, above all, be ‘druggable’.

- A ‘druggable’ target is accessible to the putative drug molecule, be that a small molecule or larger biologicals and upon binding, elicit a biological response which may be measured both in vitro and in vivo.

It is now known that certain target classes are more amenable to small molecule drug discovery, for example, G-protein-coupled receptors (GPCRs), whereas antibodies are good at blocking protein/protein interactions.



INTRODUCTION

- Identification of a pathophysiologically relevant molecular target, e.g. an enzyme, receptor, ion channel, or transporter
- Determination of its sequence
- Elucidation of the function and mechanism of the protein
- Proof of the therapeutic concept in organisms

INTRODUCTION

- **ANOTHER STEP IN THE PROCESS OF GETTING A DRUG IS THE OBTAINING OF AN ACTIVE MOLECULE**: this is the pharmacochemistry domain.

- Several other stages are needed to make the active molecule a used drug.

INTRODUCTION

Drug Targets and Mechanisms of Drug Action

Enzymes - reversible and irreversible inhibitors

Receptors - agonists and antagonists

Ion Channels - blocker and opener

Transporters - uptake inhibitors

DNA - alkylating agents, „minor groove binders“, intercalating agents,

INTRODUCTION

Mechanisms of Drug Action, Definitions

Ligand: Any molecule that binds to a biological macromolecule.

Enzyme: Endogeneous biocatalyst; converts one or several substrate/s into one or several product/s.

Substrate: Any educt of an enzymatic reaction.

Inhibitor: Ligand that prevents the binding of a substrate to its enzyme, either in a direct (competitive) or indirect (allosteric) manner, reversibly or irreversibly.

Receptor: A membrane-bound or soluble protein or protein complex, which exerts a physiological effect (intrinsic effect), after binding of an agonist, via several steps.

Agonist: A receptor ligand that mediates a receptor response (intrinsic effect).

Antagonist: A receptor ligand, which prevents the action of an agonist, in a direct (competitive) or indirect (allosteric) manner.

Partial Agonist: A (high affinity) antagonist, which itself has more or less pronounced intrinsic activity.

INTRODUCTION

As early as the third millennium BC a Sumerian tablet from Nippur contains the first known compilation of plant compositions to alleviate pain or cure illnesses.

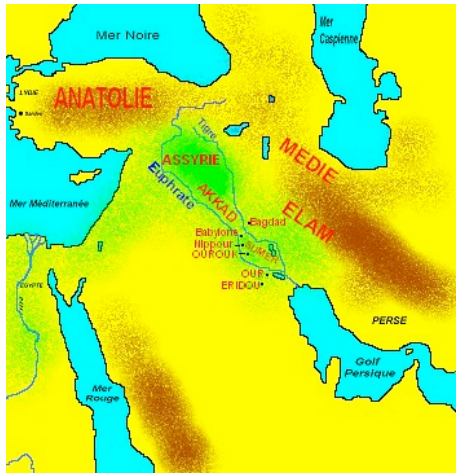


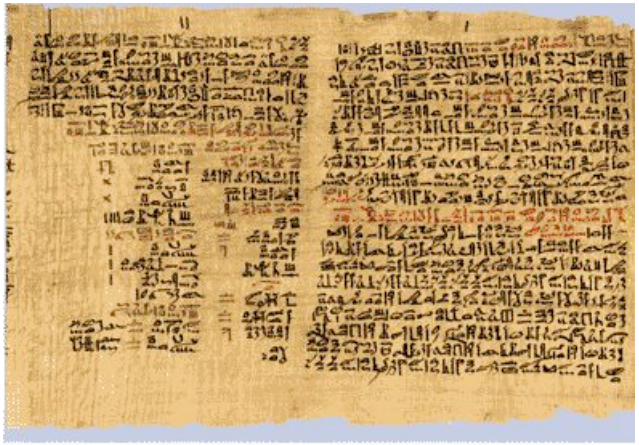
Figure 1: (Gauche) Tablette sumérienne de Nipur répertoriant 15 prescriptions médicales (Source : *Almanac*, University of Pennsilvanya, **42**, issue 14). (Droite) Extrait du papyrus Ebers. Ce papyrus de 108 pages est un ouvrage pratique et non théorique qui indique le traitement contre de nombreux maux. Cette page traite des affections des dents et des malades pestilentielles « Remède pour maintenir en état une dent : farine d'épeautre-mimi. Ce sera préparé en une masse homogène. Bourrer la dent avec cela. Autre remède: poudre de pierre à meule. En bourrer la dent ... »
(Source : http://www.silland.com/index.htm Site *L'Egypte en majesté*).

INTRODUCTION

Some medications used at the same time by the Chinese reached us through the *Ben cao jing (Chinese emperor Shennong, 2800 BC)*.

At the next millennium (1600-1500 BC) a papyrus found by Ebers in Louqsor, in 1872 described the preparation of remedies for different diseases.

In these documents one finds plants still employed today or at least their active principle in the domain of sedatives, diuretics and purgatives.



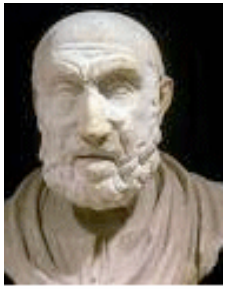
INTRODUCTION

The earliest medical school that we have knowledge of was that of Cnidus (700 BC), North of the Rhodes island (Greece).

Democede of Cnidus is the author of the first treatise of medicine of Greek origin.

The school of Cnidus together with that on the Cos island changed the traditional medicinal practice into a scientific procedure.

These changes are essentially attributed to Hippocrates of Cos.



Hippocrate

The Hippocrates'method is an inductive one that is based on a series of observations subsequently generalised in a theory which is then confronted to the reality test.

INTRODUCTION

Among the Romans Galen (131-201) described about four hundred medicinal plants.

From the fall of the Roman Empire to the end of the Middle Age period the art of healing becomes the privilege of the religious community.

It developed only in monasteries of the Christiandom and in the Arab Empire.

From the end of the Middle Age period the authority of the Ancient was rejected.

INTRODUCTION

There was a rebirth of the pharmacotherapy essentially at Padoua and Bologna in Italy and at Oxford in England.

At that time lived one of the pioneers of chemotherapy : Theophratus Bombatus von Hohenheim also named Paracelsus (1493-1541).

He introduced mineral compounds in therapeutics thereby rejecting the teachings of the Greeks.

The first experimental work in pharmacology was performed by Menghini in 1755 on the camphor.

In the 19th century the extraction of the active principles from plants developed.

When the progress of the chemistry industry permitted to produce new chemical compounds for pharmacology the era of the modern drug began.

INTRODUCTION`

Successive contributions from chemistry, microbiology, biochemistry, molecular biology, spectroscopy, computer sciences to drug design

Chemistry and pharmaceutical research : chemotherapy, concept of receptor

The end of the 19th century corresponds to the beginning of the modern pharmaceutical research.

Paul Ehrlich (Nobel prize in medicine, 1908) observed the affinity of dyes for living tissues in animals and postulated the existence of chemoreceptors.

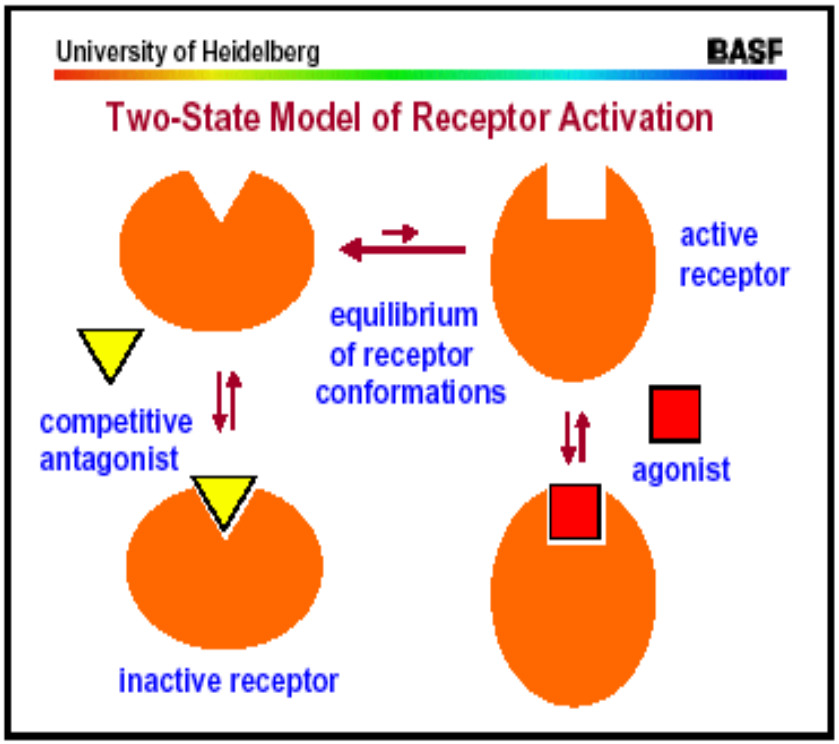
The concept of receptors was then extended by Langley (1852-1925) who introduced the notion of agonists and antagonists.

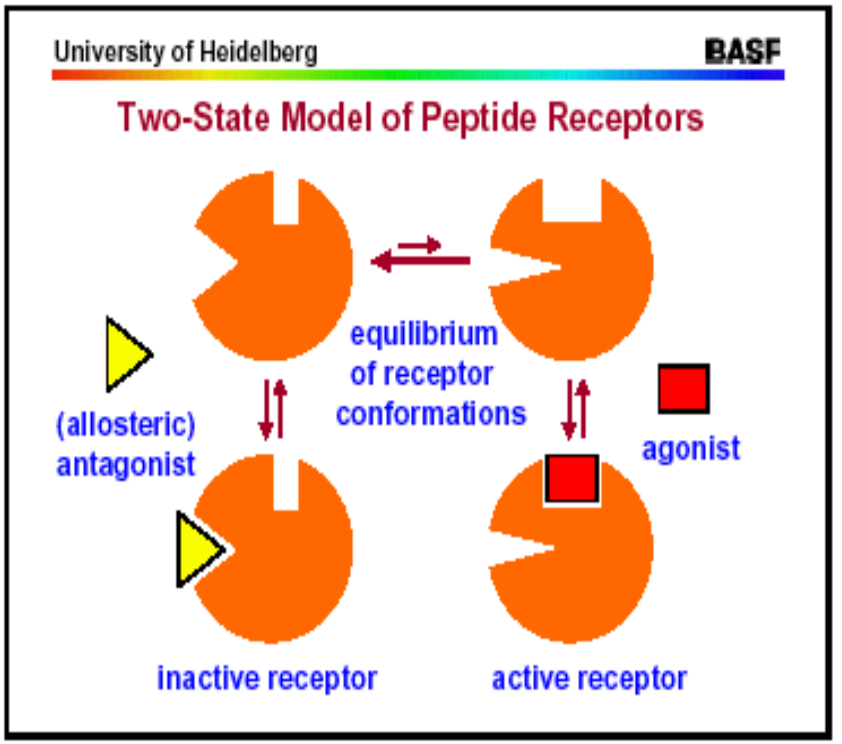
INTRODUCTION

During the next century receptors were characterised in all organs including the brain.

It was only in the 1970s that receptors began to be isolated as specific proteins of the cell membrane.

INTRODUCTION





INTRODUCTION

AGONISTS

Dopamine is a neurotransmettor that acts on D-receptors (involved in Parkinson's disease)

Epinephrine, also known as **adrenaline**, is a hormone which triggers a variety of physiological events, such as increasing depth and frequency of heartbeats, acts on β2-receptor.

Morphine, an opium-derived substance, and other molecules of the opiate family, has strong pain-killing virtues (opioid receptors).

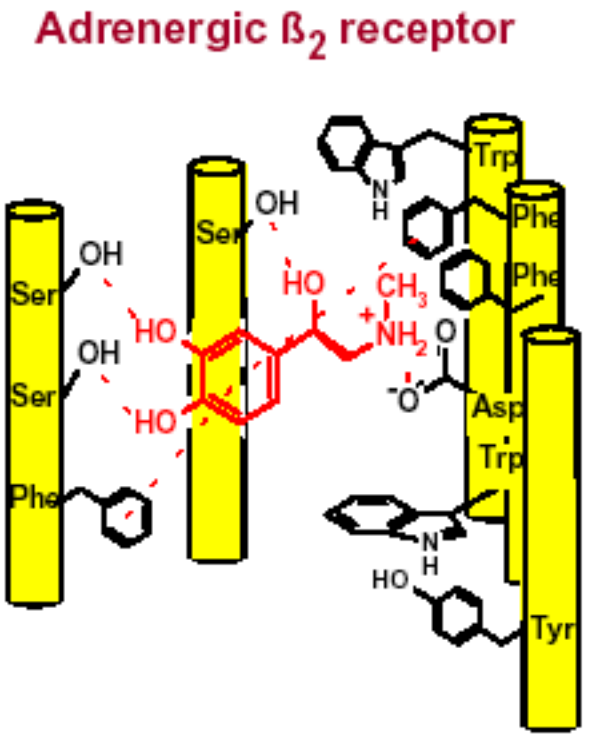
ANTAGONISTS

Curare. (binds to nicotinic acetylcholine receptors) This is a powerful acetylcholine antagonist, It functions by competitively and reversibly inhibiting the sub-type of nicotinic acetylcholine receptors found at the neuromuscular junction. This causes eventual death by asphixiation due to paralysis of the diaphragm.

Dibenzycholorethamine is used as an antagonist against epinephrine (agonist).

INTRODUCTION

Epinephrine, also known as **adrenaline**, is a hormone which triggers a variety of physiological events, such as increasing depth and frequency of heartbeats, acts on β2-receptor.



INTRODUCTION

Successive contributions from chemistry, microbiology, biochemistry, molecular biology, spectroscopy, computer sciences to drug design

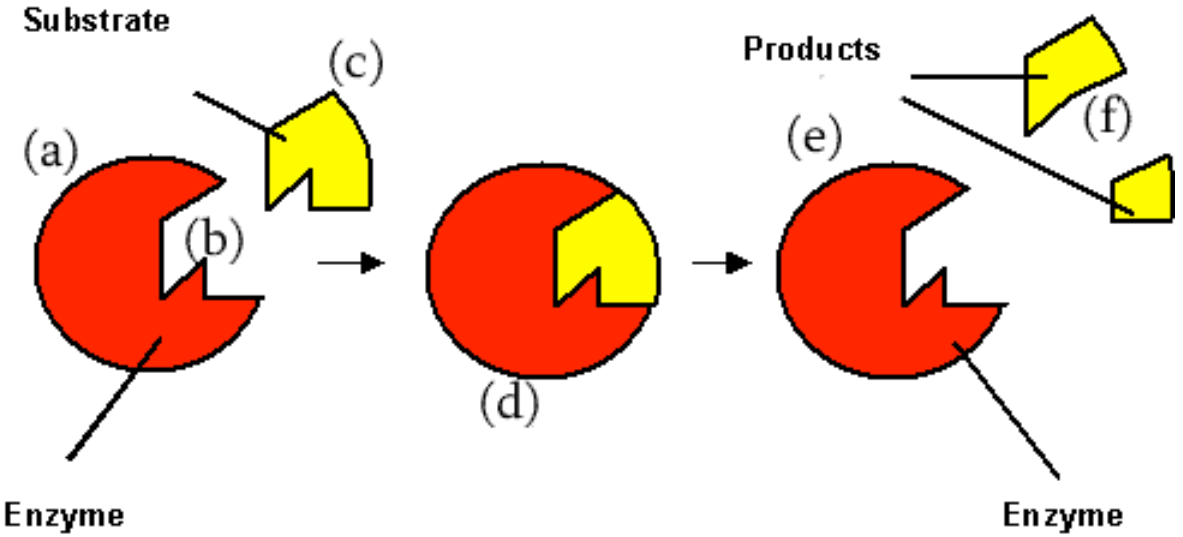
Analytical chemistry also enabled important advances,
in particular isolation and purification of active substances from medicinal plants (extraction of morphine from opium in 1815, isolation of papaverine from opium in 1848 (vasodilator, spasmolytic).

INTRODUCTION

Emil Fischer (Nobel prize in Chemistry, 1902) proposed a founding concept of supramolecular chemistry: the key-lock complementarity of the enzyme-substrate complex (1894).

(while studying the α or β configuration of glycosides in the enzymatic cleavage).

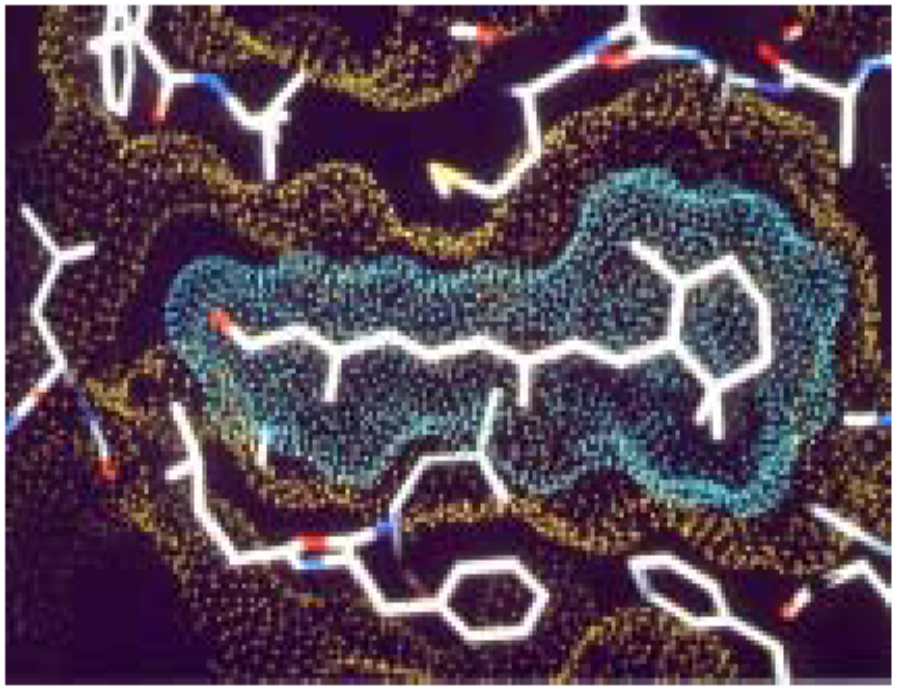
"The specificity of an enzyme (the lock) for its substrate (the key) arises from their geometrically complementary shapes".

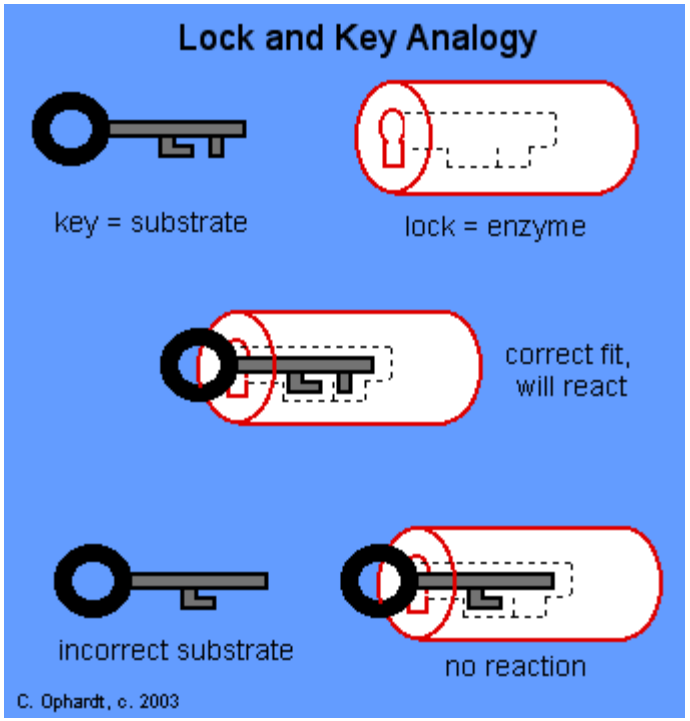


Lock & Key Hypothesis

INTRODUCTION

The lock and key theory is simply a way of describing how specific an enzyme is for its substrate. Just like a lock requires a specifically shaped key for it to work so does an enzyme.





! Lock and key theory is a simplification of reality as protein structures are flexible

INTRODUCTION

1) Enzymes

Reversible noncovalent inhibitors

Transition state inhibitors (e.g. cytidine deaminase)

biproduct inhibitors

$HOOC\text{-}CH_2CH_2\text{-}CH(CH_2Phe)COOH$, enalaprilate

Reversible covalent inhibitors (e.g. serine proteases)

-CHO + HO-Ser → -CH(OH)-O-Ser

Irreversible covalent inhibitors

$-CH_2Cl$ + HO-Ser → $-CH_2$-O-Ser

ASS + HO-Ser → CH_3CO-O-Ser + salicylic acid

Penicillines (acylation of transpeptidase)

Omeprazole (disulfide formation with H^+/K^+-ATPase)

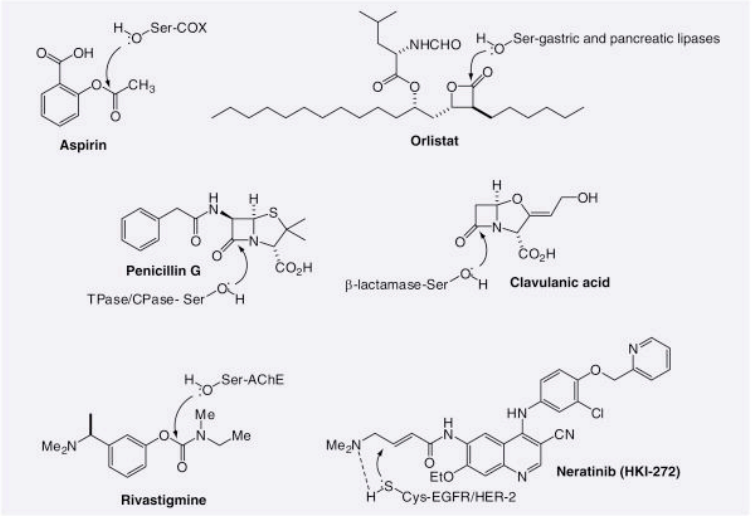
"Suicide" inhibitors

Eflornithine, α-(CHF_2)-ornithine, as ornithine decarboxylase inhibitor

"Non-substrate binding pocket" inhibitors

e.g. hirudin[56-65]

Irreversible inhibitors



INTRODUCTION

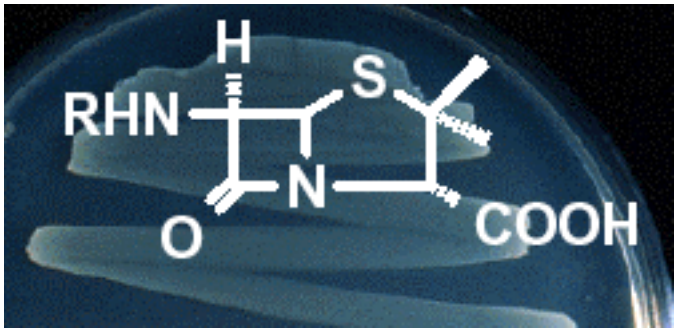
Coal tar, an abundant byproduct of industrialisation (mixtures of **phenols**, **polycyclic aromatic hydrocarbons**), contained most of the aliphatic and aromatic synthons essential to the medicinal chemistry.

INTRODUCTION

Contribution from microbiology

During the first half of the 20th century microbiology appeared in the pharmaceutical research with the use of the penicillin in 1938 following its discovery by Fleming in 1928.
From then on several antibiotics were considered and a large number of pharmaceutical companies then set up microbiology and fermentation laboratories.

Penicillin



INTRODUCTION

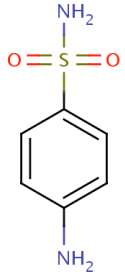
Advances of biochemistry

Concepts of enzymes and receptors introduced by biochemistry were integrated to the pharmaceutical research in the middle of the 20th century.

Biochemistry deals with the structures, functions and interactions of these receptors which were considered empirically as good therapeutic targets.

The fortuitous discovery of the inhibition of carbonic anhydrase by sulfanilamide permitted to save many lives from bacterial infections.

This substance was the first “lead” molecule opening the way to numerous derivatives.



INTRODUCTION

Molecular biology

Molecular biology has exerted a profound influence on drug discovery and has integrated the genetic information to the process of drug design.

It permits to understand the processes leading to the disease at the molecular level and thus to determine ideal therapeutic targets.

First the influence of molecular biology = restricted to cloning and expressing genes encoding target proteins

Now the “biotech” drugs = recombinant proteins and monoclonal antibodies

Total Number of Small Molecule Drugs = 6675
Total Number of Biotech Drugs = 150
Total Number of Approved Drugs = 1691

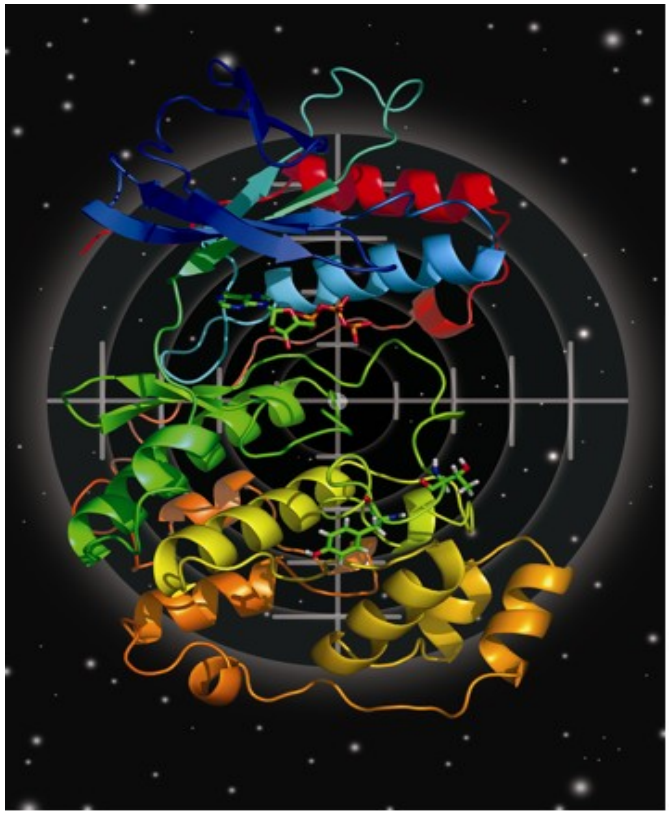
INTRODUCTION

Technology : Molecular imaging and computer sciences

Technology contributions of imaging molecules and their interactions on the one hand and of computer sciences on the other hand were conclusive in the biological research of active molecules.

Xray diffraction and NMR enable "visualization" of atoms within the molecules (3D structures of the targets and the target-ligand complexes)

This information is crucial as the three-dimensional arrangement of the atoms in a molecule of life induces most of its chemical and biological properties.



INTRODUCTION

The contribution of computer sciences is manifold and started from the 80s.

Computer tools permit to use mathematical models of molecular systems that were developed to model the physical phenomena governing the molecules and their interactions.

INTRODUCTION

Genomics and Proteomics

Genomics and deciphering of genomes should permit to discover new potential therapeutic targets for the pharmaceutical industries opening new prospects for research.

Genomics needs proteomics to identify the potential targets.

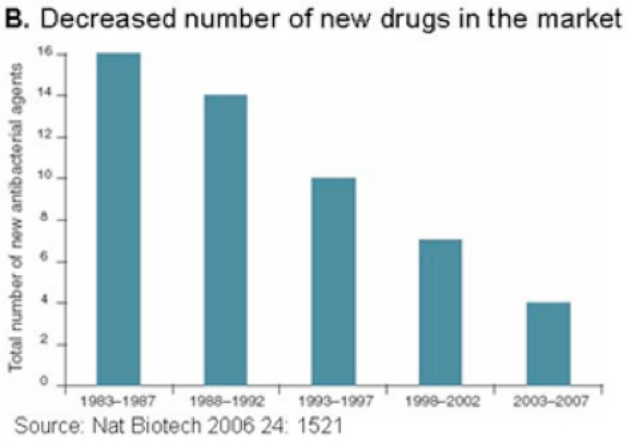
INTRODUCTION

Pharmaceutical industry is short of new drugs.

Whereas in past decades about 50-60 new drugs were approved every year and introduced into therapy, this number declined significantly in the last few years, reaching its historical low in the year 2000 with 27 new drugs, 2001 with 24, 18 in 2002, 40 in 2003, 24 in 2004 and 15 in 2005 approved by the FDA.

Research costs for a new drug are estimated to be in the US-$ 500-900 millions (difficult to estimate accurately!).

Considering all failures in drug research, this figure might be even higher.



Source: Nat Biotech 2006 24: 1521

INTRODUCTION

The decline in the number of new drugs has quite different reasons.

One reason seems to be an already achieved high therapeutic standard.

Research focuses now on chronic degenerative and other fatal diseases, like coronary heart disease, Alzheimer's disease, arthritis, cancer, and AIDS.

Another reason is that there are enhanced regulatory requirements for efficacy and safety of new drugs (which of course protect the patient).

However, the current situation reflects also a shortage of new lead structures that can be optimised into therapeutically useful drugs.

INTRODUCTION

Very segmented market – The largest companies only have a few % of the market share.

High risk, long term – takes 10-20 years to develop a **drug**, and most drugs fail to get to market.

Highly regulated (by FDA, Agence européenne pour le médicament).

High profit margins for drugs which do make it.

Investors traditionally expect high return on investment.

INTRODUCTION

Four main **phases**: discovery, development, clinical trials and marketing.

Identify disease

Identify and Isolate protein(target) involved in disease (2-5 years)

Find a **drug** effective against disease protein (2-5 years)

Preclinical testing (1-3 years)

Formulation & Scale-up

Human clinical trials (2-10 years)

FDA or other agencies approval (2-3 years)

INTRODUCTION

The general trend in the pharmaceutical research has been to rationalise the process of drug design.

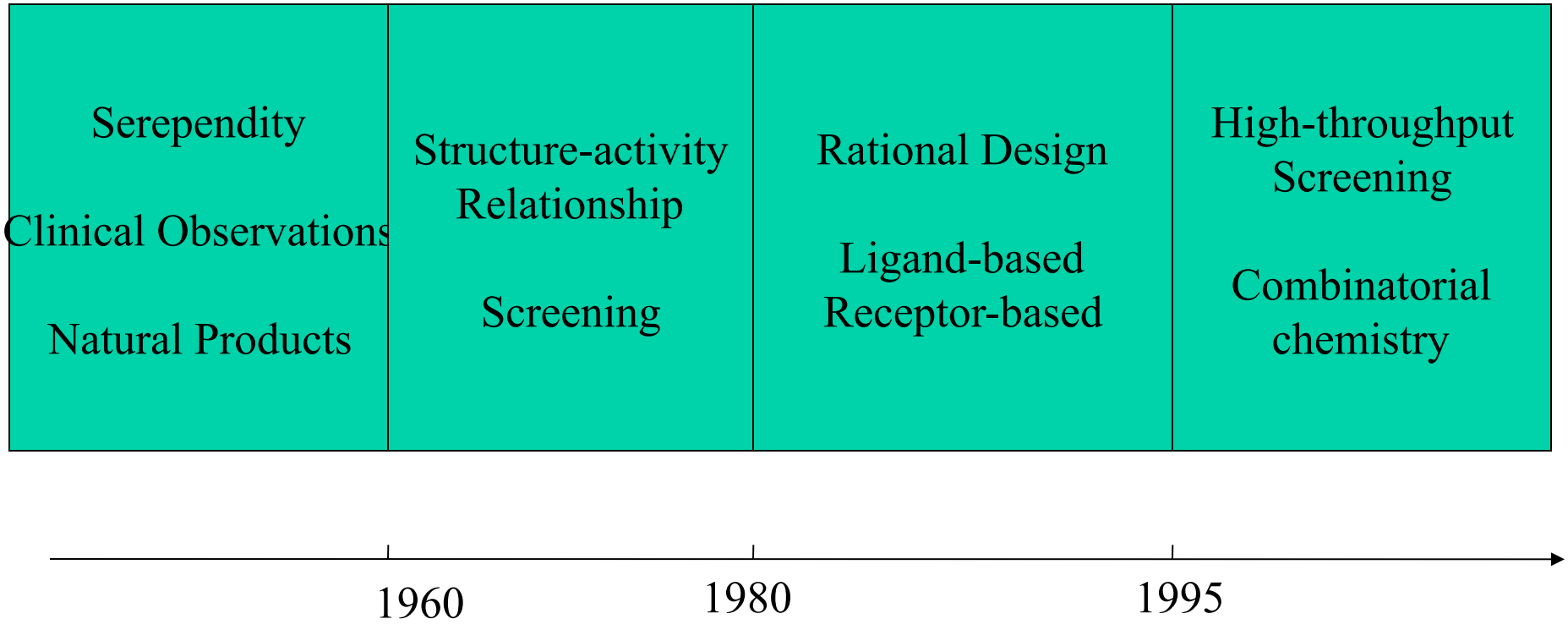
1. Going from the empirical knowledge of medicines to the notion of drug with the substances chemically extracted from natural substances.

2. Concept of the chemical receptor has participated in the rationalisation.

3. Access to the 3D structures of the molecules involved.

4. Then the deciphering of the genomes opening new perspectives.

Drug discovery history



Drug discovery history

Development of Drug Research

Time	Materials	Test systems
- ancient time	plants, venoms minerals ...	humans
- 1806	morphine	
- 1850	chemicals	
- 1890	synthetics, dyes	animals
- 1920		animals, isolated organs
- 1970		enzymes, membranes
- 1990	combinatorial libraries	human proteins, HTS
- 2000	focused libraries	uHTS, virtual screening

Drug discovery history

Important Results in Drug Research, 1806-1981

→	1806	Morphine	Hypnotic agent
	1875	Salicylic acid	Antiinflammatory agent
	1884	Cocaine	Stimulant, local anesthetic agent
	1888	Phenacetin	Analgesic and antipyretic agent
→	1899	Acetylsalicylic acid	Analgesic and antipyretic agent
	1903	Barbiturates	Sedatives
	1909	Arsphenamine	Antisyphilitic agent
	1921	Procaine	Local anesthetic agent
	1922	Insulin	Antidiabetic agent
	1928	Estrone	Female sex hormone
→	1928	Penicillin	Antibiotic agent
	1935	Sulphachrysoidine	Bacteriostatic agent
	1944	Streptomycin	Antibiotic agent
→	1945	Chloroquine	Antimalarial agent
	1952	Chlorpromazine	Neuroleptic agent
	1956	Tolbutamide	Oral antidiabetic agent
	1960	Chlordiazepoxide	Tranquillizer
	1962	Verapamil	Calcium channel blocker
	1963	Propranolol	Antihypertensive agent (beta-blocker)
	1964	Furosemide	Diuretic agent
→	1971	L-Dopa	Anti-Parkinson agent
	1975	Nifedipine	Calcium channel blocker
	1976	Cimetidine	Anti-ulcus agent (H_2 blocker)
	1981	Captopril	Antihypertensive agent (ACE inhibitor)
	1981	Ranitidine	Anti-ulcus agent (H_2 blocker)

Drug discovery history

Important Results in Drug Research, 1983-1999

1983	Cyclosporin A	Immunosuppressant
1984	Enalapril	Antihypertensive agent (ACE inhibitor)
1985	Mefloquine	Antimalaria agent
1986	Fluoxetine	Antidepressant (5-HT transporter)
1987	Artemisinin	Antimalaria agent
1987	Lovastatin	Cholesterol biosynthesis inhibitor
1988	Omeprazole	Anti-ulcus agent (H/K-ATPase inhibitor)
1990	Ondansetron	Antiemetic agent (5-HT_3 blocker)
1991	Sumatriptan	Anti-migraine agent (5-HT_1 blocker)
1993	Risperidon	Antipsychotic agent ($D_{2/5}$-HT_2 blocker)
1994	Famciclovir	Anti-herpes (DNA polymerase inhibitor)
1995	Losartan	Antihypertensive agent (A II antagonist)
1995	Dorzolamide	Glaucoma (Carboanhydrase inhibitor)
1996	Meloxicam	Anti-arthritis agent (COX 2 inhibitor)
1996	Nevirapin	HIV reverse transcriptase inhibitor
1996	Indinavir, Ritonavir, Saquinavir	HIV protease inhibitors
1997	Nelfinavir	HIV protease inhibitor
1997	Finasteride	Hair loss
1997	Sibutramine	Adipositas (uptake blocker)
1998	Orlistat	Adipositas (lipase inhibitor)
1998	Sildenafil	Erectile dysfunction (PDE inhibition)
1999	Celecoxib, Rofecoxib	Anti-arthritis agents (COX-2 inhibitors)
1999	Amprenavir	HIV protease inhibitor
1999	Zanamivir, Oseltamivir	Influenza (neuraminidase inhibitors)
2001	Fondaparinux	Thrombosis (synthetic LMWH)
2001	Imatinib	Leukemia (specific abl-TK inhibitor)

Drug discovery in this millenium

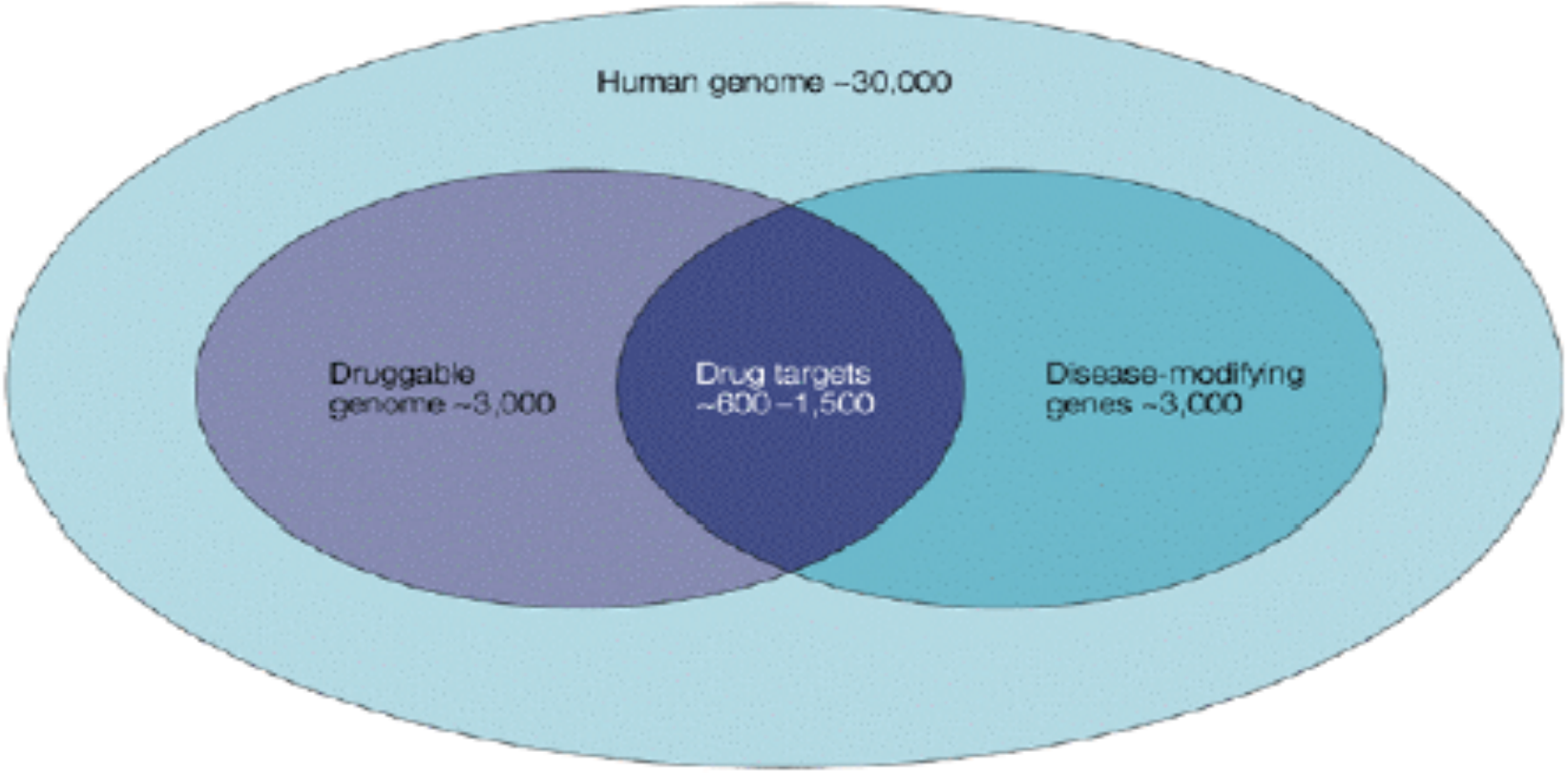
- Human genome sequencing
- Gene identification provides a new paradigm for understanding human diseases at its most fundamental level
- Ability to associate a specific gene with a disease made possible by gene sequencing and information technologies
- Several thousand molecular targets have been cloned (in 2000) and are available as potential novel drug discovery targets
- Target selection and validation

Drug discovery in this millenium

- Bacterial genome sequencing
- New strategies for antibacterial drug hunting
- Identification and evaluation of new drug targets
- Conserved genes in different genomes are attractive targets for new broad-spectrum antibiotics
- Subtractive genome analysis to reveal genes conserved in all or most of the pathogenic bacteria but not in eukaryotes to identify the most obvious drug target candidates

Drug discovery in this millenium

Genome, Druggable Genome and Drug Targets



A. L. Hopkins and C. R. Groom, Nature Rev. Drug Discov. 1, 727-730 (2002); © Nature Reviews Drug Discovery