Empirical Foundations of Design.

The history of drug research can be divided into several sequential phases:

- the beginning, when empirical methods were the only source of new medicines,
- targeted isolation of active compounds from plants
- the use of molecular and other in vitro test systems as precise models and as a replacement for animal experiments,
- the introduction of experimental and theoretical methods such as protein crystallography, molecular modeling, and quantitative structure–activity relationships
- the discoveries of new targets and the validation of their therapeutic value through genomic, transcriptomic, and proteomic analysis, knock-in and knockout animal models, and gene silencing with siRNA.

The history of drug research

The beginnings of drug therapy can be found in traditional medicines. The dried herbs and extracts from these and other plants have served as the most important source of medicines for more than 5,000 years.

Animal Experiments as a Starting Point for Drug Research

The wealth of experience gained by traditional medicine is based on many thousands of years of sometimes accidental, sometimes intentional observations of their therapeutic effects on humans.

Animal Experiments as a Starting Point for Drug Research

Planned investigations on animals were relatively seldom. The biophysical experiment of Luigi Galvani, an anatomy professor in Bologna, which was first described in his book De viribus electricitatis in motu musculari in 1791, has become famous.

Animal Experiments as a Starting Point for Drug Research

The systematic investigation of the biological effects in animals of plant extracts, animal venoms, and synthetic substances began in the next-to-last century.

Animal Experiments as a Starting Point for Drug Research

The famous pharmacologist, Sir James W. Black, who developed the first b-blocker at ICI, and later took part in the development of the first H_2 antagonists at Smith, Kline & French, compared pharmacological testing to a prism: what pharmacologists see in their substances' properties directly depends on the model that was used to test the substances.

Animal Experiments as a Starting Point for Drug Research

Typical mistakes in the selection of models and interpretation and comparison of experimental results arise from different modes of application and the correlation of results obtained in different species of animals. It does not make sense to optimize the therapeutic range of a substance in one species, and the toxicology in another.

Animal Experiments as a Starting Point for Drug Research

Further, comparing effects after a fixed dose, without determining an effective dose also distorts the results because very strong and weak substances fall outside the measurement range.

Animal Experiments as a Starting Point for Drug Research

Measuring the effect strictly according to a schedule is also questionable because neither the latency period, that is the time before an effect is seen, nor the time of maximum biological effect are recorded.

Animal Experiments as a Starting Point for Drug Research

In whole-animal models, auxiliary medications are usually applied, which can also influence the experimental results. Anesthetized animals often give entirely different results than conscious animals.

In Vitro Models and Molecular Test Systems

Around 40 years ago, we began to think about testing substances in simple in vitro models. With these models biological testing takes place in test tubes rather than animals. There are many compelling reasons to avoid animal experiments. They increasingly provoke public criticism and are time and cost intensive.

In Vitro Models and Molecular Test Systems

In the beginning cell culture models were preferentially employed, for example tumor cell cultures for testing cytostatic therapies, or embryonic chicken heart cells for cardio-active compounds. Later these were joined by receptor-binding studies.

In Vitro Models and Molecular Test Systems

The first molecular test models were enzyme-inhibitor assays in which the inhibitory activity of a molecule could be evaluated on one particular target protein in the absence of interfering side effects.

In Vitro Models and Molecular Test Systems

With the progress of gene technology methods, not only is the preparation of the enzyme simplified, but also receptor-binding studies can be carried out on standardized materials.

In Vitro Models and Molecular Test Systems

Today it is possible to achieve an exact evaluation of the entire activity spectrum of any substance on any enzyme, receptors of all types and subtypes, ion channels, and transporters.

In Vitro Models and Molecular Test Systems

In the meantime, in industrial drug discovery this procedure has become routine. Before biological screening begins, the following questions have to be answered: what therapeutic goal should be achieved and is this goal achievable?

In Vitro Models and Molecular Test Systems

Therapeutic concepts are established based on the pathophysiology and the causes of its alteration. Regulatory interventions with drugs should re-establish the normal physiological conditions as closely as possible. In doing so, a distinct problem occurs.

In Vitro Models and Molecular Test Systems

Nature works on two orthogonal principles: the specificity of the mode of action and an accentuated spa separation of effects; the compartmentalization.

In Vitro Models and Molecular Test Systems

Through the progress made in gene technology we can investigate active substances much more exactly than before; but by using isolated enzymes and binding studies we are a long way away from the reality of animal models, and even further away from humans.

Modeling and Computer-Aided Design

An extremely capable tool is available for modeling the properties and reactions of molecules, and particularly their intermolecular interactions: the computer. In addition to processing complex numerical problems, it is the translation of the results into color graphics that exceedingly accommodates the human ability to grasp pictures faster and more easily than text or columns of numbers.

Modeling and Computer-Aided Design

Our brains process text sequentially, but pictures are comprehended in parallel. X-ray crystallography and multidimensional NMR spectroscopic techniques contribute to our understanding of molecules as much as quantum mechanical and force field calculations.

Modeling and Computer-Aided Design

More and more today we place the three-dimensional structure, the steric dimensions, and the electronic qualities of molecules in the foreground. Advances in theoretical organic chemistry and X-ray crystallography have made this possible.

Modeling and Computer-Aided Design

The first structure-based design was carried out on hemoglobin, the red blood pigment, in the research group of Peter Goodford. Hemoglobin's affinity for oxygen is modulated by so-called allosteric effector molecules that bind in the core of the tetrameric protein.

Modeling and Computer-Aided Design

From the threedimensional structure he deduced simple dialdehydes and their bisulfite addition products. These substances bind to hemoglobin in the predicted way and shift the oxygen-binding curve in the expected direction.

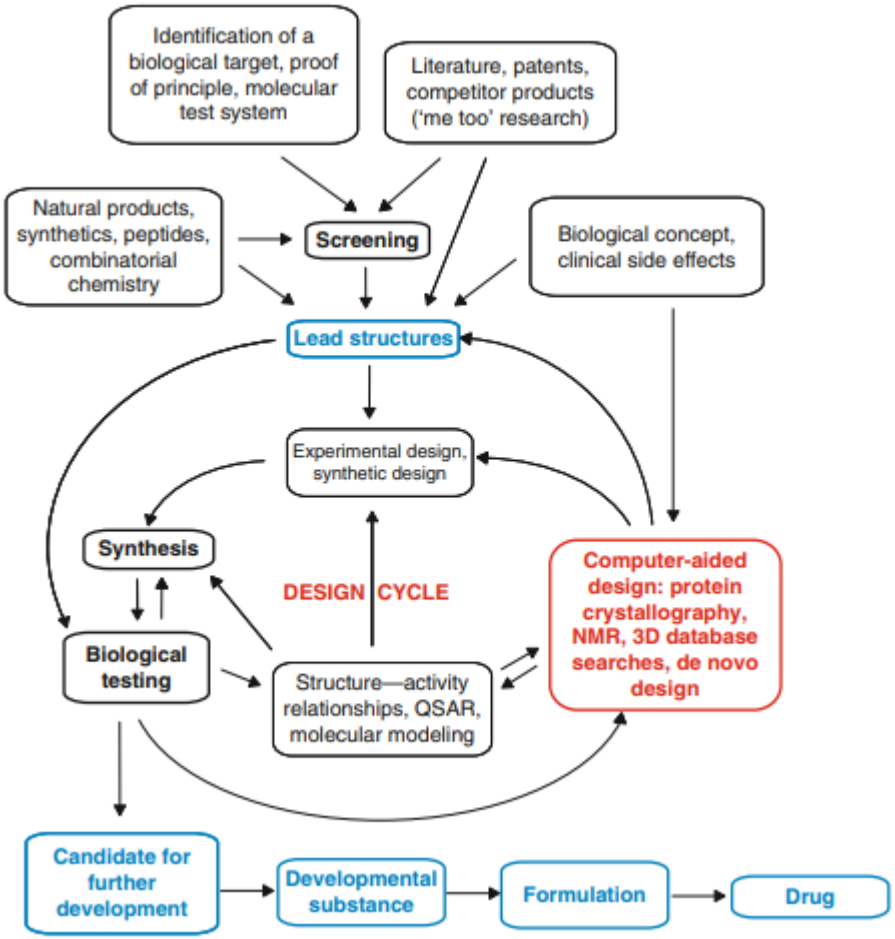
Modeling and Computer-Aided Design

The first drug developed by using a structure-based approach is the antihypertensive agent captopril, an angiotensin-converting enzyme (ACE) inhibitor. Although the lead structure was a snake venom, the decisive breakthrough was made after modeling the binding site. For this, the binding site of carboxypeptidase, another zinc protease, was used because its three-dimensional structure was known at the time.

Modeling and Computer-Aided Design

The road to a new drug is difficult and tedious. A nested overview of the interplay between the different methods and disciplines from a modern point of view is illustrated in the scheme:

Modeling and Computer-Aided Design



Modeling and Computer–Aided Design

In the last few years molecular modeling and particularly the modeling of ligand– receptor interactions have gained importance. Although modeling is employed predominantly for the targeted structure modification of lead compounds, it is also suitable for the structure-based and computer-aided design of drugs and lead structure discovery.

Modeling and Computer-Aided Design

In addition to modeling and computer-aided design, structure–activity relationship analysis has contributed to the understanding of the correlation between the chemical structure of compounds and their biological effects. By using these methods, the influence of lipophilic, electronic, and steric factors on the variation of the biological activity, transport, and distribution of drugs in biological systems could be systematized for the first time on statistically significant foundations.

Drugs Are High Value-Added Products

Drug discovery and development is a high-risk business. In average, 7 out of 10 projects are cancelled preliminary because of different reasons. The main reason is the lack of efficacy, i.e., the drug is effective on animals but when administered to humans the therapeutic effect is absent or is negligibly smal.

Drugs Are High Value-Added Products

The second main reason in the past was the pharmacokinetics of the new drug—low bioavailability, toxic metabolites, short or extremely long half-lives. However, during the last 20 years many in silico tools and models have been developed to assess the physicochemical and ADME properties of drug candidates during the experimental stage and the attrition rate due to decreases in pharmacokinetics from 39% in the past [13] to the current negligible 1%.

Drugs Are High Value-Added Products

There are different approaches for drug discovery. The oldest one is by serendipity. Serendipity means discovery by chance—trial and error. There are many examples in the history of pharmacy for drugs discovered by serendipity, starting with the most popular—the story about penicillin.

Chemical modifications

Another approach for drug discovery is by chemical modifications of known drugs or natural products. Aspirin was discovered by chemical modification. The natural product salicylic acid was acetylated in order to increase the stability and reduce the irritating effect on stomach mucosa.

Chemical modifications

Small chemical modifications lead to improved therapeutic profiles in drugs of different generations. For example, ranitidine is a chemical modification of cimetidine with higher potency and prolonged half-life, pindolol originates from propranolol but avoids the first-pass effect in the liver and shows a higher degree of bioavailability.

Screening

Screening of databases, virtually or by high throughput (HTS) assays, is another way to discover new drugs. The first sulphonamide drug Prontosil was discovered by random in vitro screening, when a great number of colorants were screened for antibacterial.

Rational drug design

Nowadays, the most advanced method for drug discovery is the rational drug design. This is the smartest and the cheapest approach of drug discovery.

Rational drug design

Drug design begins with an identification of a biological target (a biomacromolecule involved in the disease). Then, a ligand interacting with this macromolecule, known as a hit molecule, has to be discovered. It follows an iterative process of structure optimization until a compound is derived with optimal affinity, selectivity, non-toxicity, solubility, permeability, bioavailability, etc., properties which are needed for a molecule to become a drug.

Rational drug design

There are two main approaches in drug design: ligand-based and structure-based. When the structure of the target macromolecule is unknown, the structure of the ligand is designed and optimised based on the relationship between structure and activity. In the structurebased drug design, the 3D structure of the target macromolecule is known and the ligand is designed to be complementary to the binding site on the macromolecule. Complementarity means a steric, electrostatic and hydrophobic fit between the ligand and the target.

Ligand based drug design (Indirect drug design)

Ligand based drug design (Indirect drug design): Ligand based drug design is based on the knowledge of other molecules that bind to the biological target of interest so as to derive a pharmacophore which will bind to the target.

- (A) Q SAR
- (B) Analog drug design
- (C) Combinatorial chemistry
- (D) Natural Products as a lead, etc

Structure based drug design (Direct drug design)

Structure based drug design (Direct drug design): Structure based drug design is based on the knowledge of the three dimensional structure of the biological target. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed.

QSAR(Quantitative Structure Activity Relationships)

- QSAR is a computational modeling method for revealing relationships between structural properties of chemical compounds and biological activities
- Hansch, (1964)- Structural properties of a chemical influence its biological activity and similar compounds behave similarly.
- QSAR is mathematical or statistical approaches to define the relationship between biological activity (experimental data) of a molecular system and its geometrical, physical, electronic, and chemical properties

Activity = function (property 1 , property 2…….)

Activity = function (xi)

xi- descriptor

Property- geometry, steric, or steric etc

QSAR(Quantitative Structure Activity Relationships)

- In molecular docking the geometrical structure of both the ligand and the target protein must be known. But the Quantitative Structure-Activity Relationships (QSAR) is a method which can be applied regardless of whether the structure is known or not.
- QSAR explore how a given protein interacts with some tested compounds. As an example, it may be known from previous experiments that the protein under investigation shows signs of activity against one group of compounds, but not against another group. In terms of the lock and key metaphor, we do not know what the lock looks like, but we do know which keys work, and which do not.

QSAR(Quantitative Structure Activity Relationships)

In order to build a QSAR model for deciding why some compounds show sign of activity and others do not, a set of descriptors are chosen. These are assumed to influence whether a given compound will succeed or fail in binding to a given target. The parameters such as molecular weight, molecular volume, electrical and thermodynamical properties are used as descriptors.

Future Trends in Drug Design

Any advance in science and technology finds immediately its application in medicine, in pharmacy, in drug discovery and development. Investments in drug design are worthwhile because as better is designed a given drug candidate during the experimental stage, as less likely is for the drug to fail in the late stages where the tests are more expensive, especially in the clinical trials. The ultimate goal of the future drug design is to be able to design and develop a specific, non-toxic, effective and patient-tailored drug over a period of several hours. Although this goal seems fantastic at the moment, it is completely achievable in the near future.