**Drug Design**  
**Past, Present, Future**

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**Drug**

- Drug is an exogenous molecule that affects biological processes and used to prevent, diagnose or/treat a disease.
- Requirements for the ideal drug:
  - Specific action
  - Safe to use, no side effects
  - Chemically and metabolically stable
  - Synthetically feasible
  - Soluble in water and lipids
  - Unique

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**Drug - Body Interactions**

- Pharmacodynamics - the science of drug effects on living systems = Pharmacology
- Pharmacokinetics - the science of living systems effects on drug = Absorption, Distribution, Metabolism, Excretion (ADME)

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**Drug Discovery and Development**

1. Drug discovery  
2. Preclinical development  
3. Clinical development

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**Big Pharma Industry 2011-2020**

Cost of goods sold  
Selling, general and administrative expenses  
Research and development  
Net income

Source: FactSet Fundamentals 2021 September

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**Cost of Developing a Drug**

Source: Statista 2021 September
**Long Process with Low Efficiency**

- 30,000 compounds synthesized
- 100 compounds tested clinically
- 1 compound approved

Years taken from synthesis to approval.

**A High-Risk Business**

| Year | Project 1 | Project 2 | Project 3 | Project 4 | Project 5 | Project 6 | Project 7 | Project 8 | Project 9 | Project 10 |
|------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|      |           |           |           |           |           |           |           |           |           |           |
|      | check     | check     | canceled  | canceled  | canceled  | canceled  | canceled  | canceled  | canceled  | canceled  |

**Attrition Rate**

- 1990s: 10% non-commercial
- 2010s: 15% non-commercial

**Drug Discovery**

- Serendipity
- Chemical modifications
- Screening
- Rational drug design

**Serendipity**

- “Luck favors the prepared.”
  
  Louis Pasteur

**Chemical Modifications**

1897 Felix Hoffman, Bayer
Screening

The dye Prontosil (the first sulfonamide drug) showed high antibacterial activity.

Rational Drug Design

Ligand-Based Drug Design
Structure-Based Drug Design

Source: Wasko et al. Front. Neurol., 2015

Understanding Drug-Receptor Recognition

- Model "lock and key" 1895 Emil Fischer static model
- Model "induced fit" 1958 Dorothy Crowfoot Hodgkin dynamic model

Both ligand (drug) and macromolecule do not undergo conformational changes when interact.

Target Macromolecules

Illuminating the Druggable Genome funded by NIH, 2014-2017
Genetic Engineering and Biotechnology News funded by NIH, 2018-2024

https://pharos.nih.gov/

Source: Oprea et al., Nature Rev. Drug Discovery, 2018

Determination of Proteins 3D Structures

Protein Data Bank

http://www.rcsb.org
181 969 structures (2021 September)

Automated Methods in Synthetic Chemistry: Combinatorial Libraries + High-throughput Screening

Source: Allen et al., PNAS, 2020
In Silico Modelling Technologies

Molecular Structure Encoding

Binary string

1D

2D

3D

Molecular Descriptors

1D descriptors
- Element composition
- Molecular weight
- Topological PFA (TPFA)
- Number of H-bond acceptors
- Number of H-bond donors
- LogP or LogD
- Number of rotatable bonds
- Number of molecular fragments
- E-state index
- Topological index

2D descriptors
- Polar surface area (PSA)
- Molecular surface area
- Molecular volumes

3D descriptors
- All-atoms descriptors
- Valence descriptors
- Total surface descriptors

Descriptor sets

Data Analysis

- Statistical Analyses - Corwin Hansch, 1960s
  
  Journal of Medicinal Chemistry

  Corwin Hansch (1918 – 2011)

  Quantitative Structure – Activity Relationship (QSAR)

- Chemometrics - Swante Wold, 1970s
- Chemoinformatics - 1990s
- Bioinformatics - 1990s

- Machine Learning Methods:
  - Random Forest
  - Decision Trees
  - Xgboost
  - Neural Networks
  - k Nearest Neighbours
  - Support Vector Machines
  - Random subspace method
Data Analysis

- Artificial Intelligence

Source: Paul et al., Drug Discovery Today, 2021

Swiss Drug Design, SIB:
- SwissDock
- SwissPerez
- SwissADME
- SwissTargetPrediction
- SwissADME

AlphaFold, DeepMind

Contingent AI™, BioSymetrics

Synthia™, Merck

Ligand Express®, Cyclica

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Data Visualization

- Artificial Intelligence

Visualization of Drug-Receptor Interactions

- Molecular Mechanics - 1980s

Visualization of Drug-Receptor Interactions

- Molecular Dynamics - 1980s

Visualization of Drug-Receptor Interactions

- Molecular Docking - 1990s

Visualization of Drug-Receptor Interactions

- Virtual Screening - 1990s

https://www.biosolveit.de/webinar/ai-drug-discovery-with-reinvent/
I, Robot Scientist

Adam, 2004

Eve, 2015

Source: King et al., Nature, 2004; Williams et al., Interface, 2015

Success stories @ DDB Lab, MUS

Novel hits for acetylcholinesterase inhibition derived by docking-based screening on ZINC database

Success stories @ DDB Lab, MUS

MD simulation

IC<sub>50</sub> = 0.8 μM

IC<sub>50</sub> = 5.5 μM
ddg-pharmfac.net

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