Early Stages of Drug Discovery in the Pharmaceutical Industry

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Boehringer Ingelheim
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Historical Drug Discovery
From Accidential Discovery to a Drug

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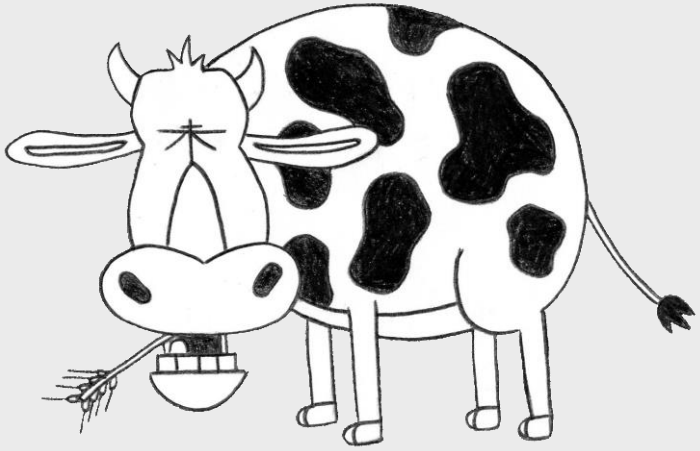
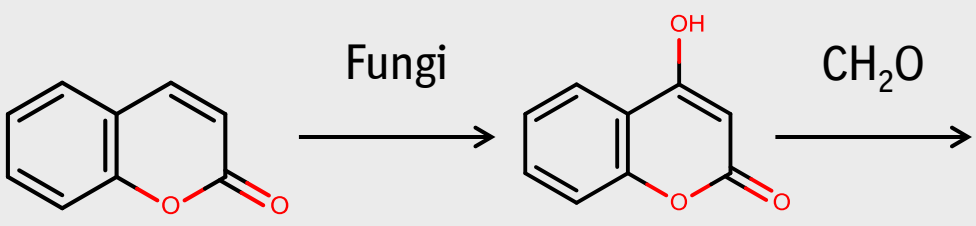


Cattle, 1920s, North Dakota

Dead Cattle, 1920s, North Dakota



Coumarin

4-Hydroxy-Coumarin

Di-Coumarol

Strong anti-coagulant

Historical Drug Discovery
From Accidential Discovery to a Drug

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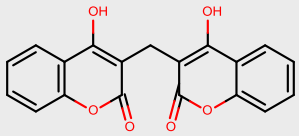
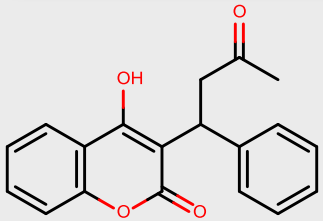
Accident (Decaying Hay)

Observation of a pharmacological effect

Link of the pharmacological effect to a substance



Chemical variation of the substance



Warfarin

Treatment of diseases

Modern Drug Discovery
From the Disease to the Drug

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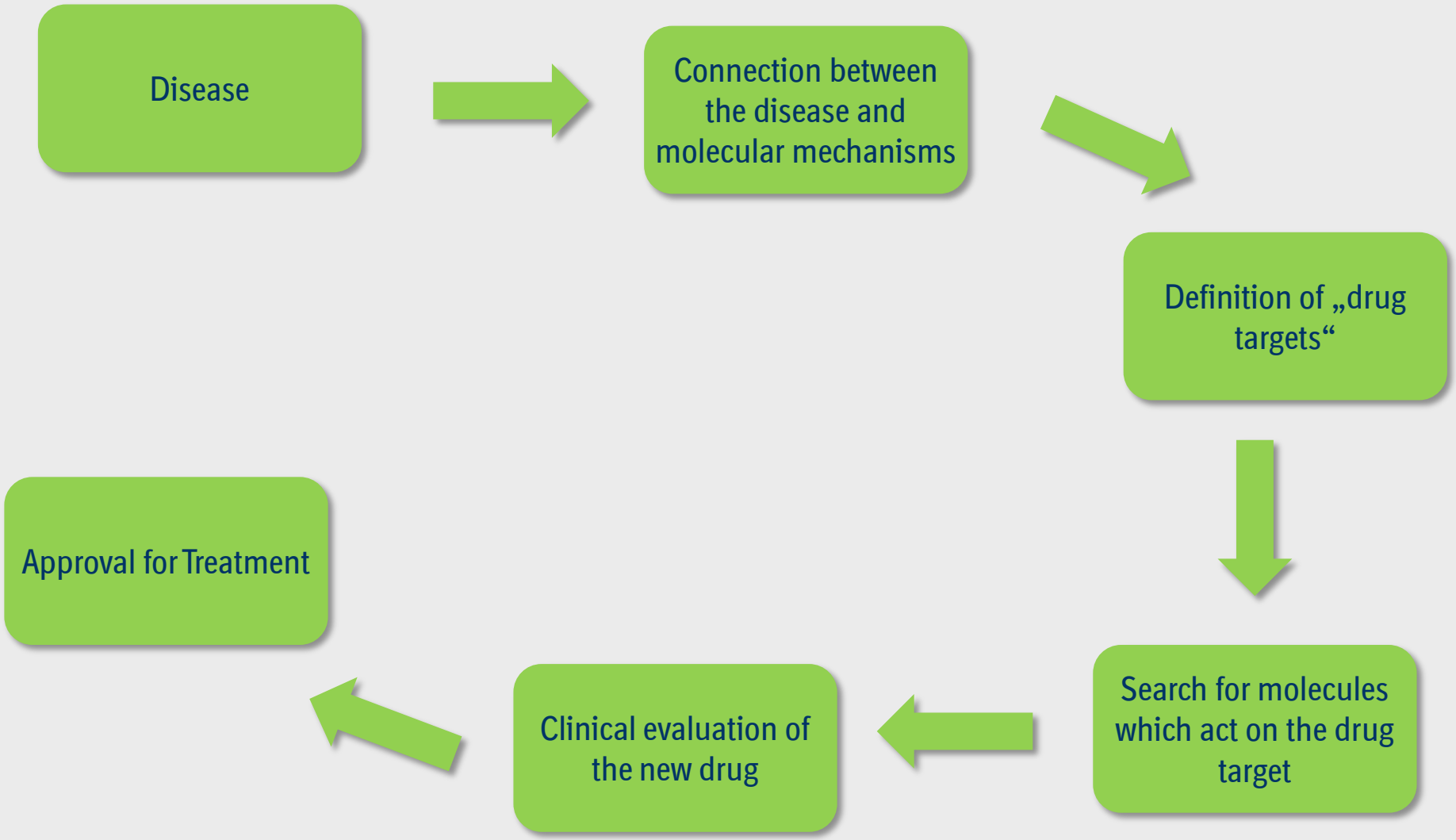

Drug Discovery and Development

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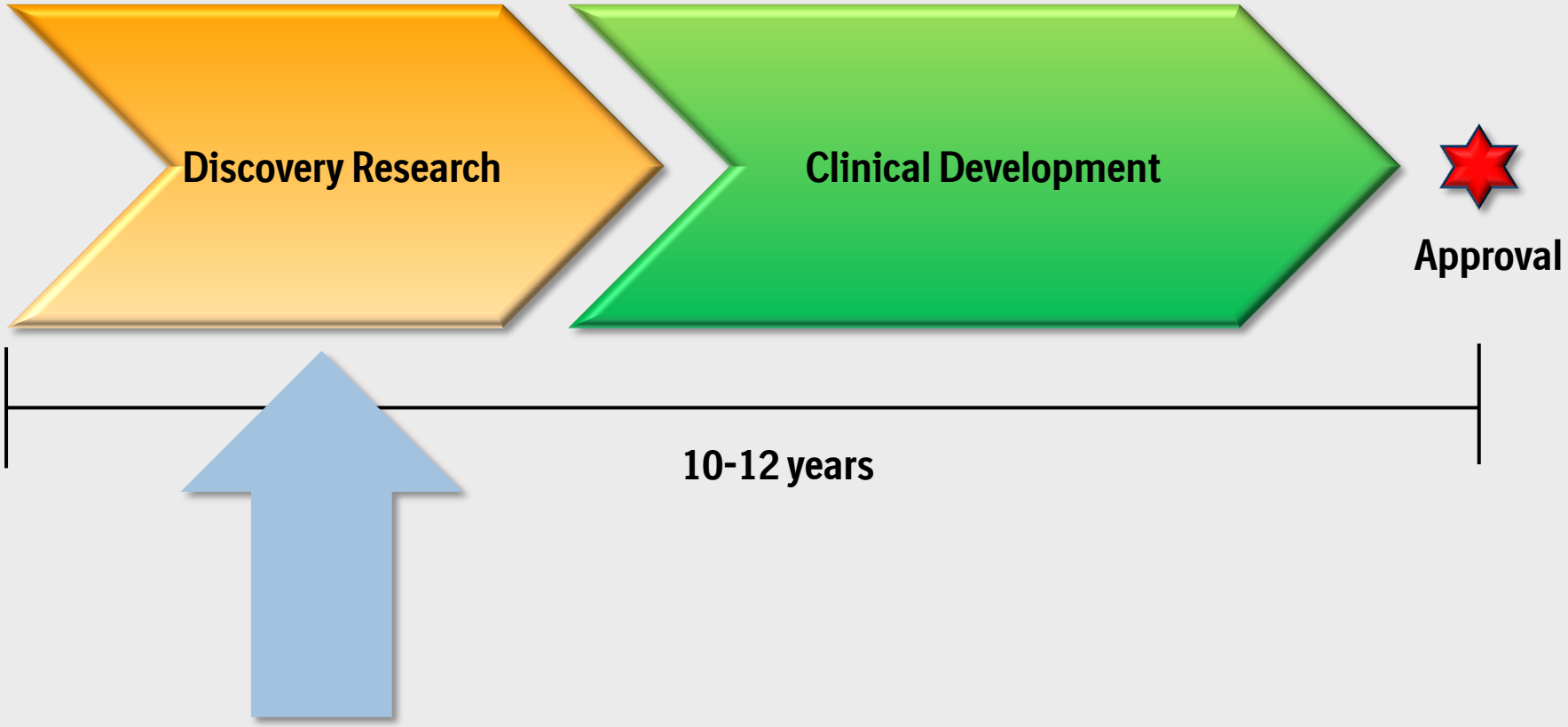

Drug Discovery Project Phases

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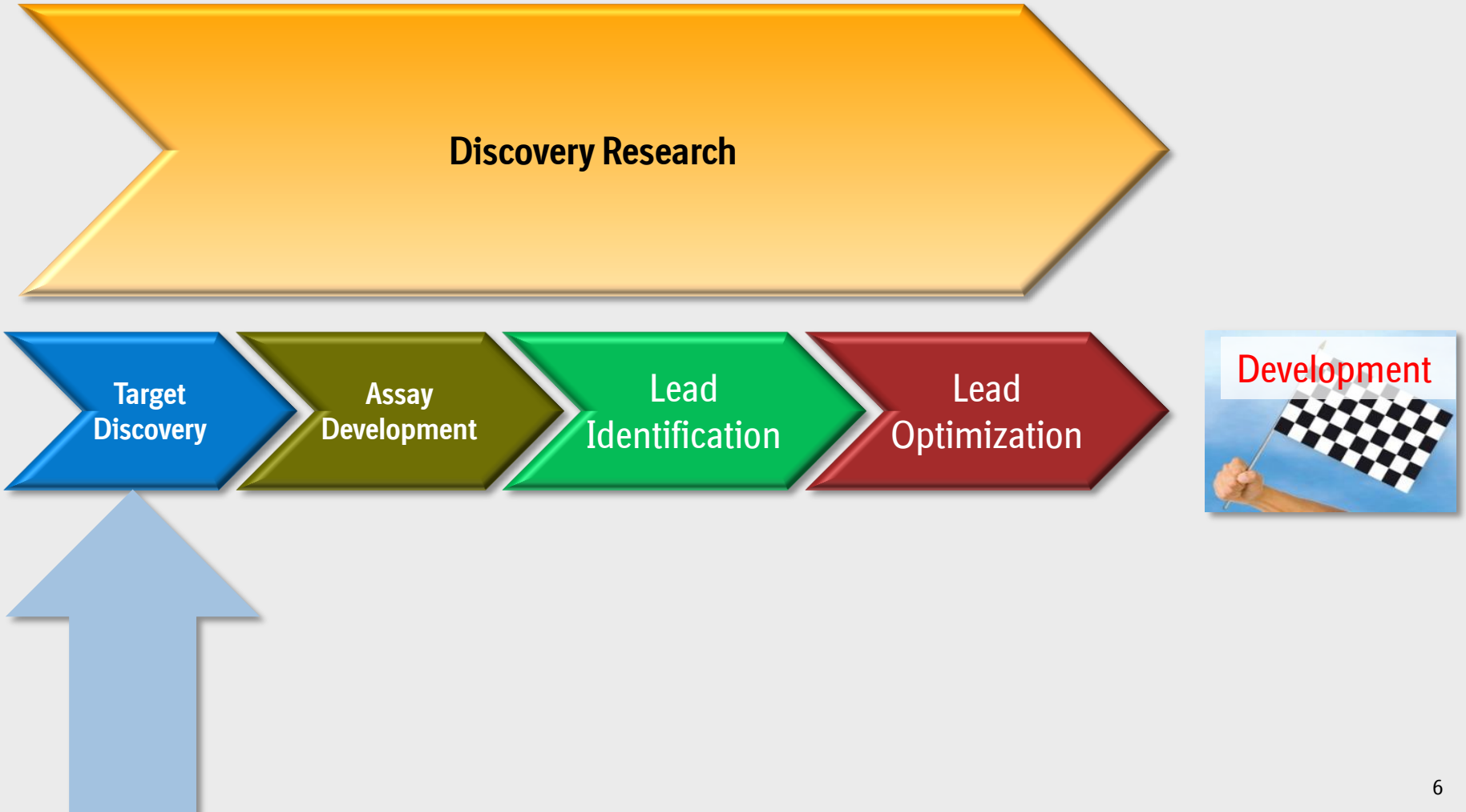
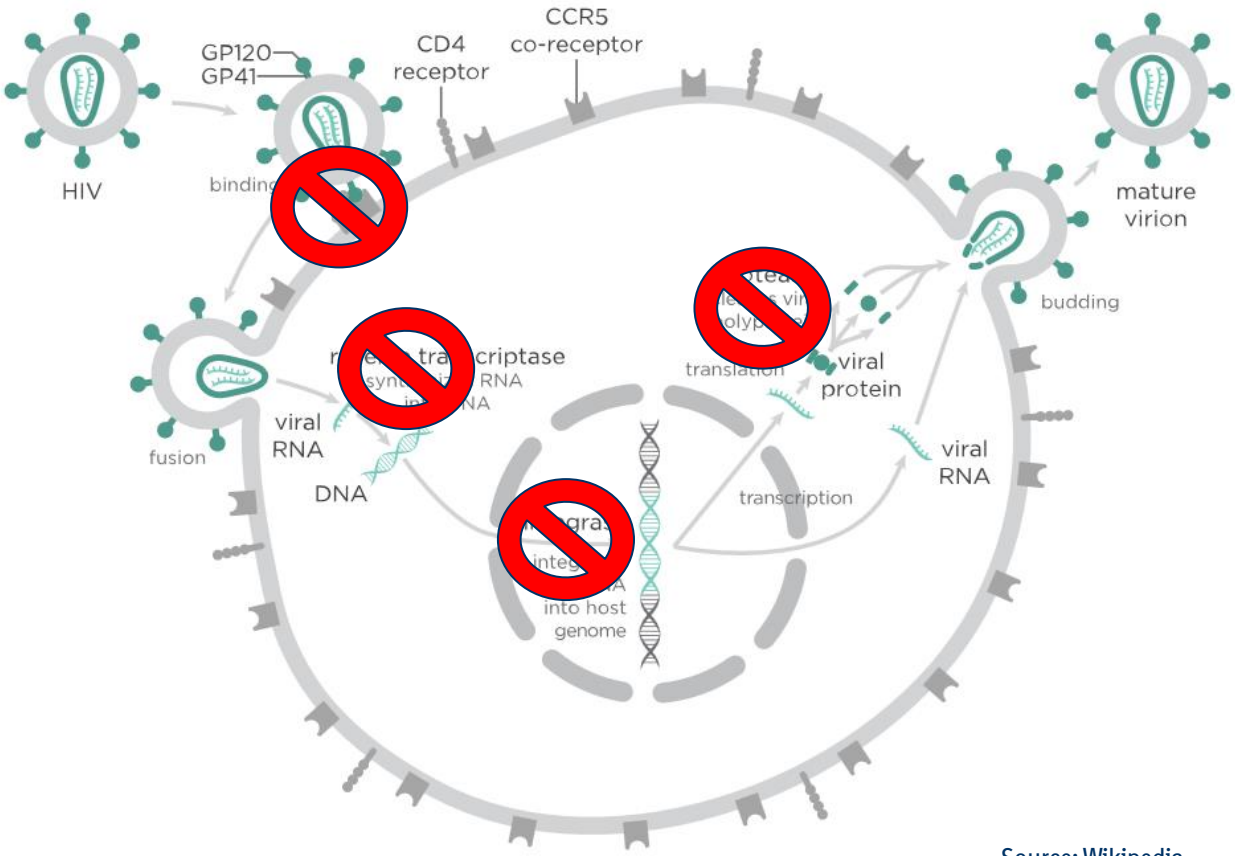


What are Drug Targets?
The Life Cycle of the HI Virus



Source: Wikipedia

Blocking a step in the virus life cycle stops viral reproduction

What are Drug Targets
The Link between a Target and a Disease

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Cleavage of the HIV poly-protein is essential for viral reproduction.

Understand the biology of the disease

Inhibition of the catalytic mechanism will prevent viral reproduction.

Propose drug target

Lower viral reproduction rate will slow down or even halt the progression to AIDS.

Postulate hypothesis of the link between a drug target and the disease.

Many drug discovery programs fail because the hypothesis about the target/disease link turns out to be wrong!

Inhibition of Drug Targets
HIV-1 Protease Inhibitors

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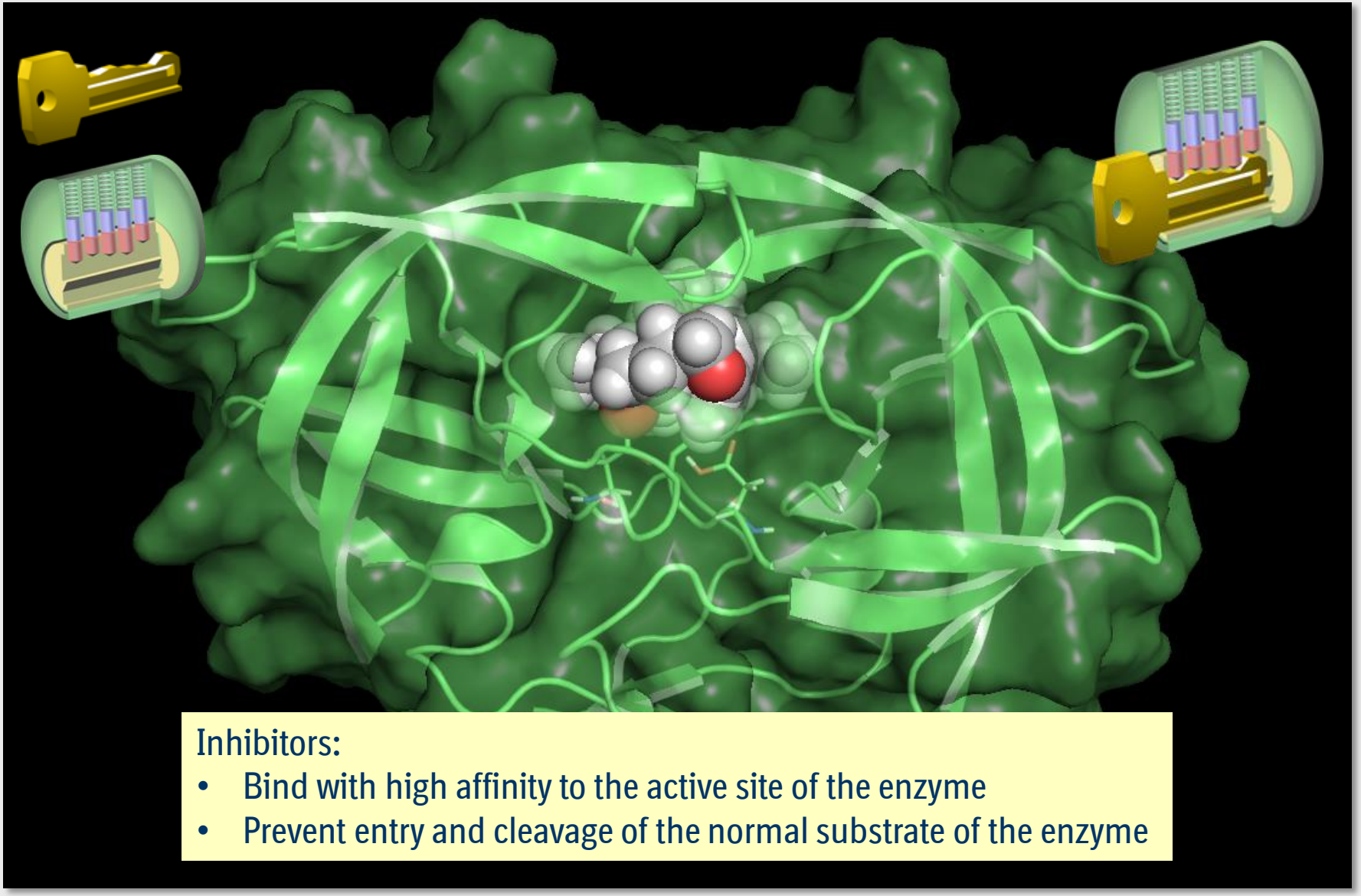

Inhibitors:

- Bind with high affinity to the active site of the enzyme
- Prevent entry and cleavage of the normal substrate of the enzyme

Inhibition of Drug Targets
Molecular Interactions

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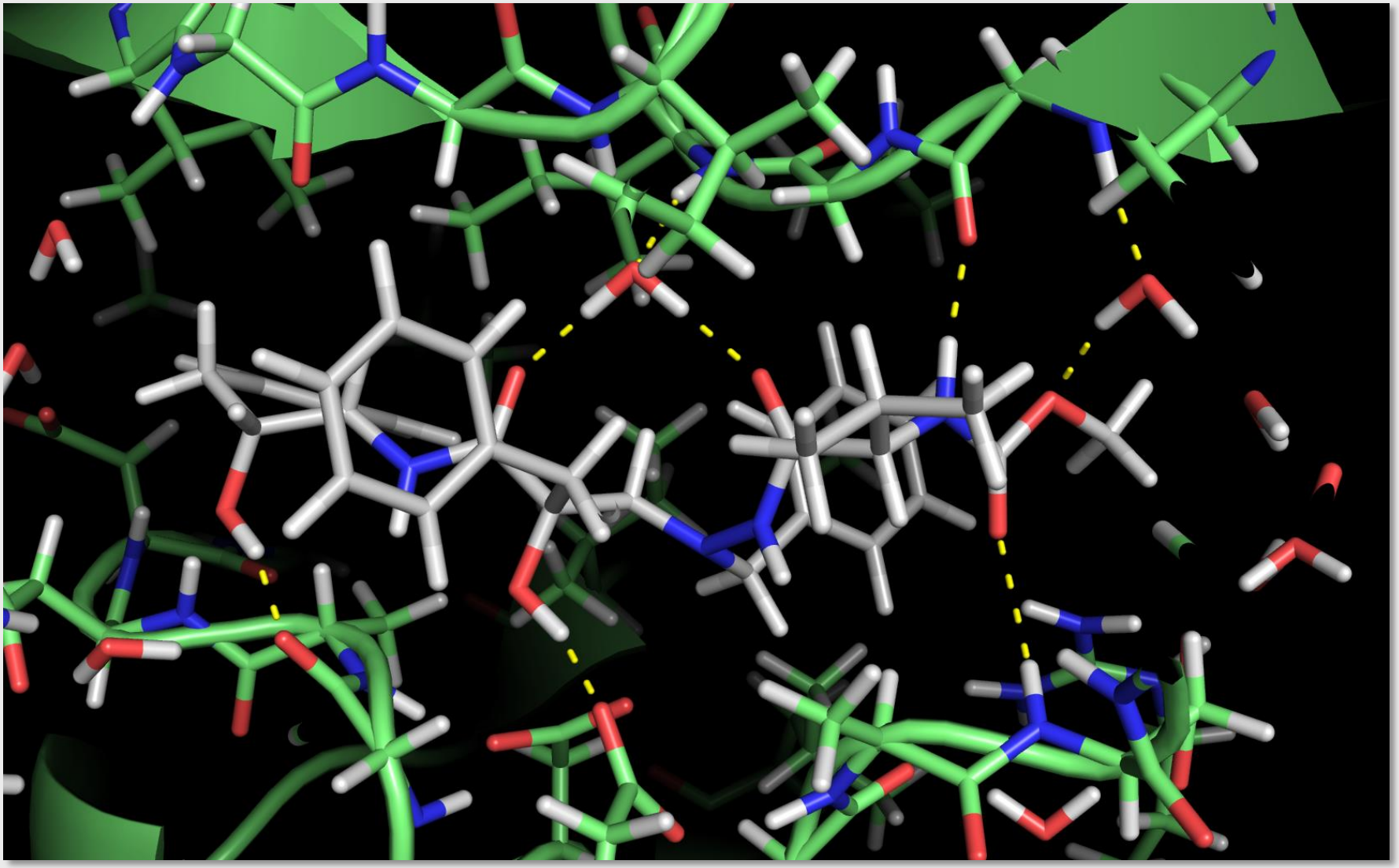

Inhibition of Drug Targets
Molecular Interactions

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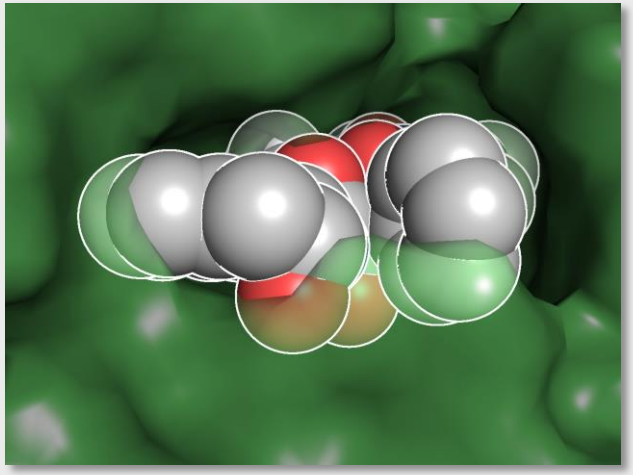

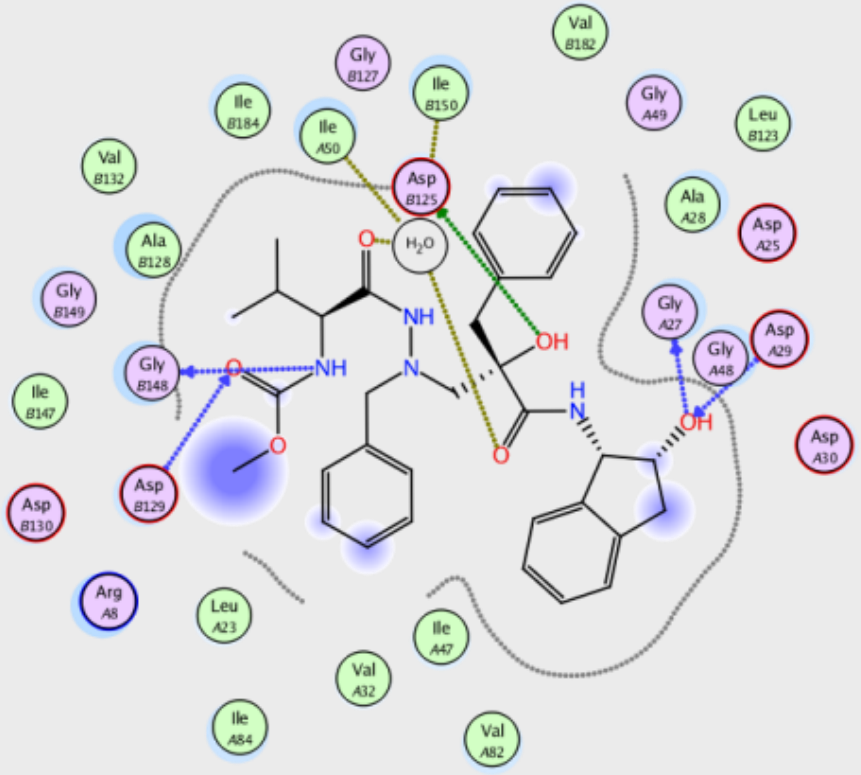

Principle of Drug Design:
Design molecules which are able to form multiple favorable interactions with the target and which are complementary in shape.

Drug Discovery Project Phases

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Discovery Research

Target Discovery → **Assay Development** → Lead Identification → Lead Optimization → Development

Assays in Drug Discovery
Assay Development

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- Develop a robust and reliable assay!
  - Reproducible results
  - Sufficient throughput
  - Physiologically relevant

No drug discovery program without reliable assay

Drug Discovery Project Phases

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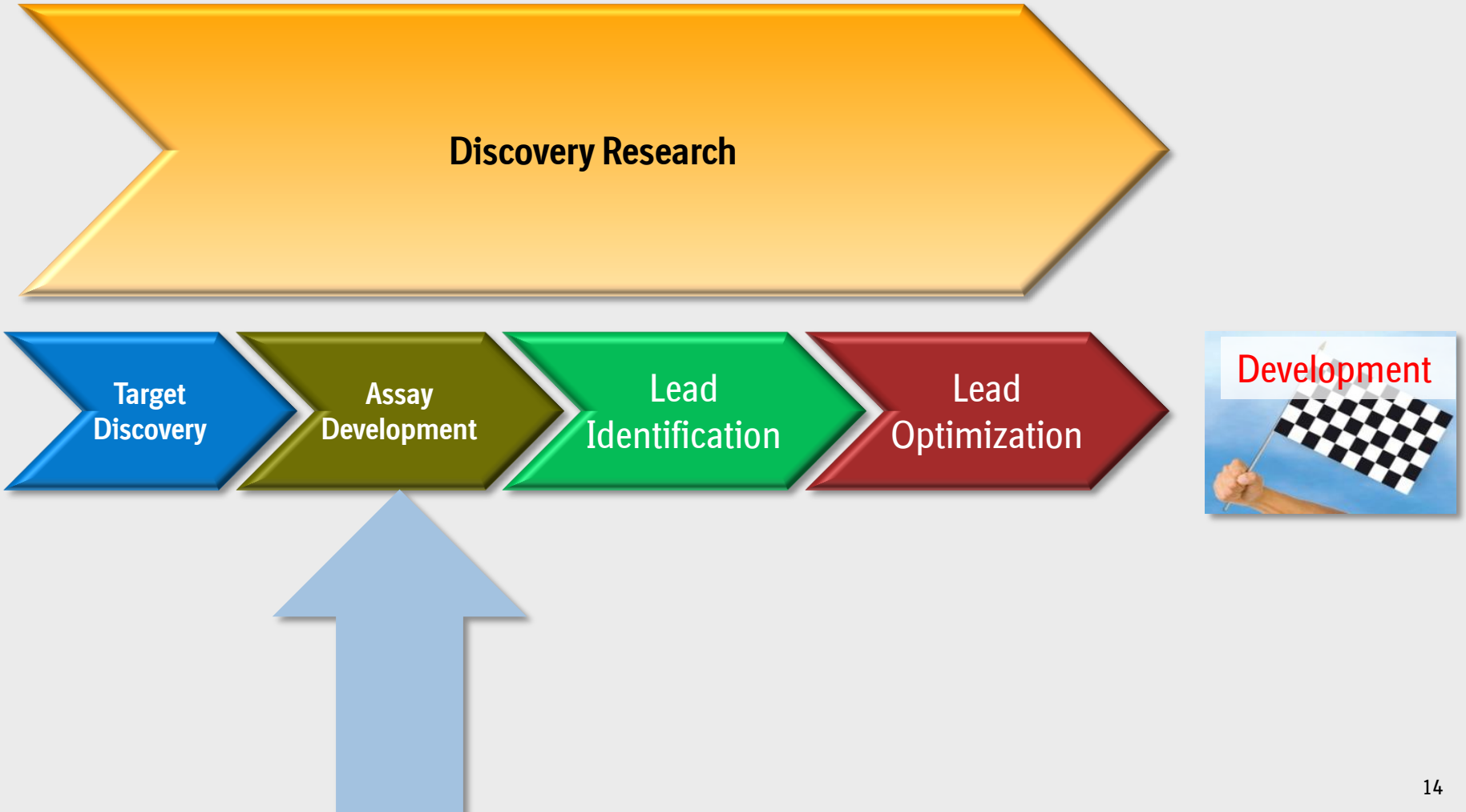

Lead Identification
High-Throughput Screening

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Big pharma companies have large compound collections

- Historically grown over decades of research
- Permanently updated with compounds from vendor catalogs
- Permanently updated through inhouse syntheses (combinatorial chemistry)

Boehringer Ingelheim has ~ **2 000 000** compounds registered in the central database

Boehringer Ingelheim‘s large screening pool currently contains ~ **850 000** compounds.

Lead Identification
High-Throughput Screening

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Throughput ~ 50 000 cpds/day

Lead Identification
From Data to Information – HTS Analysis

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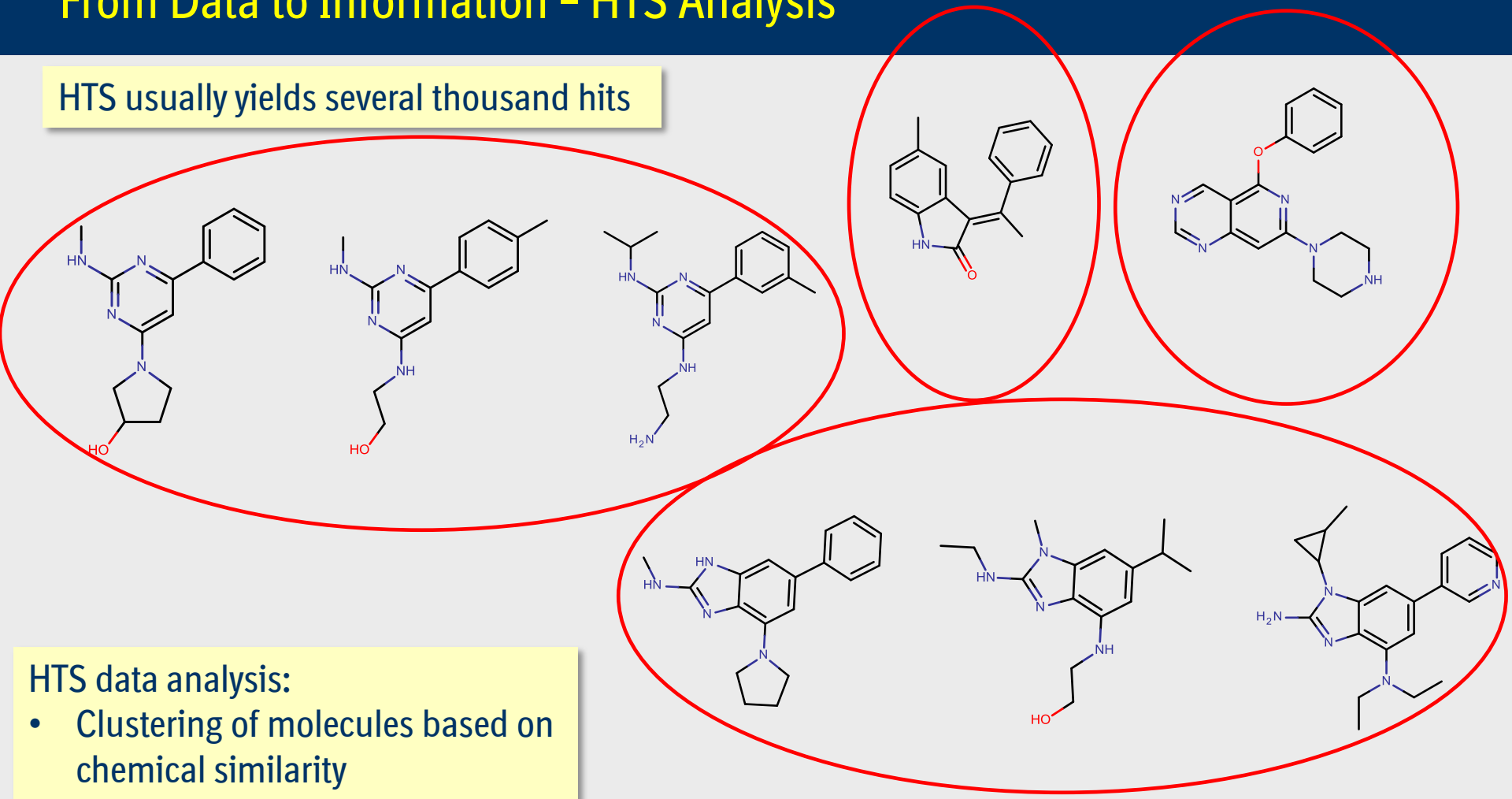
HTS usually yields several thousand hits



HTS data analysis:

- Clustering of molecules based on chemical similarity
- Identify common patterns among hits (structure-activity relationships, SAR)

Lead Identification
From Data to Information – HTS Analysis

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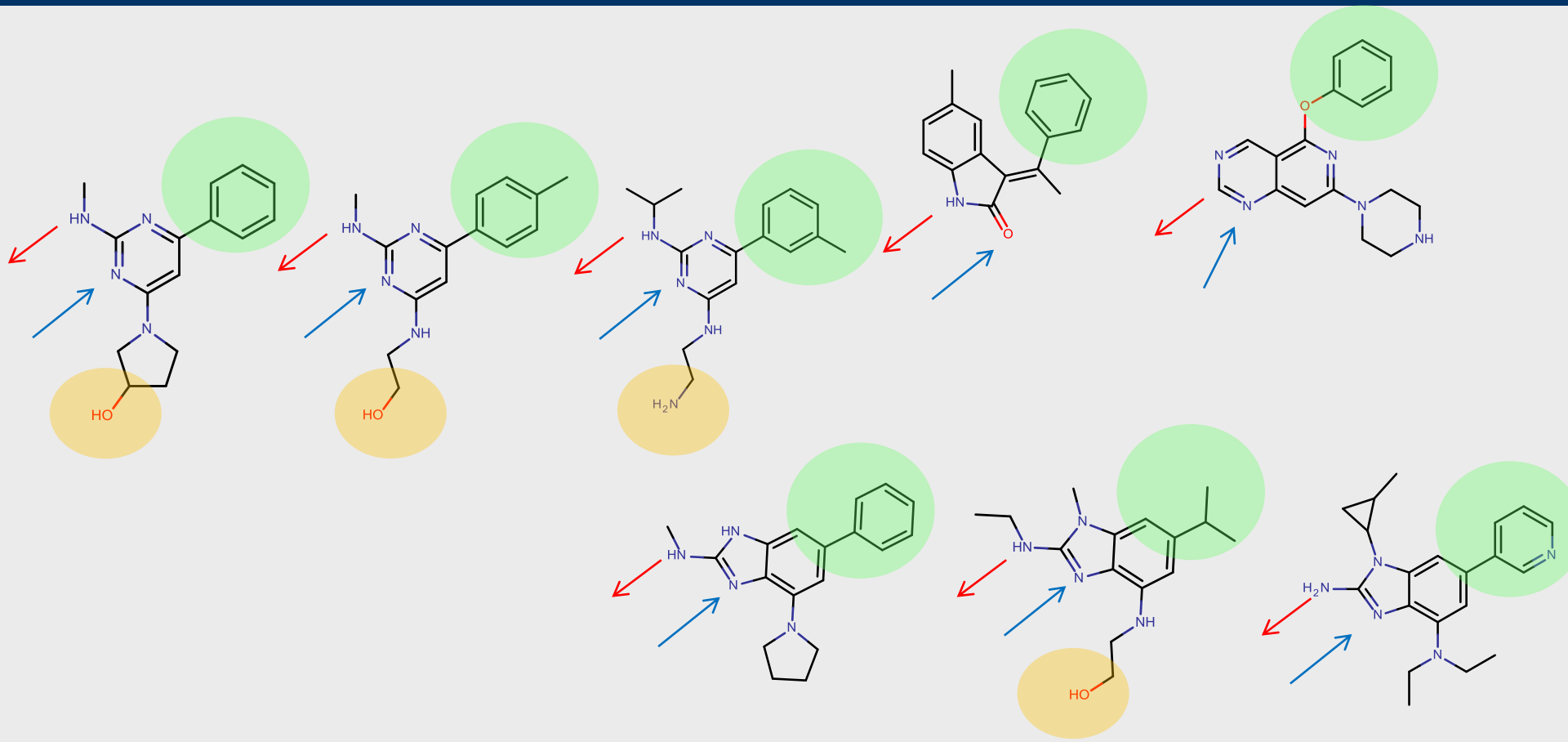

Find Attractive Starting Points for Optimization **-> Lead Classes**

Drug Discovery Project Phases

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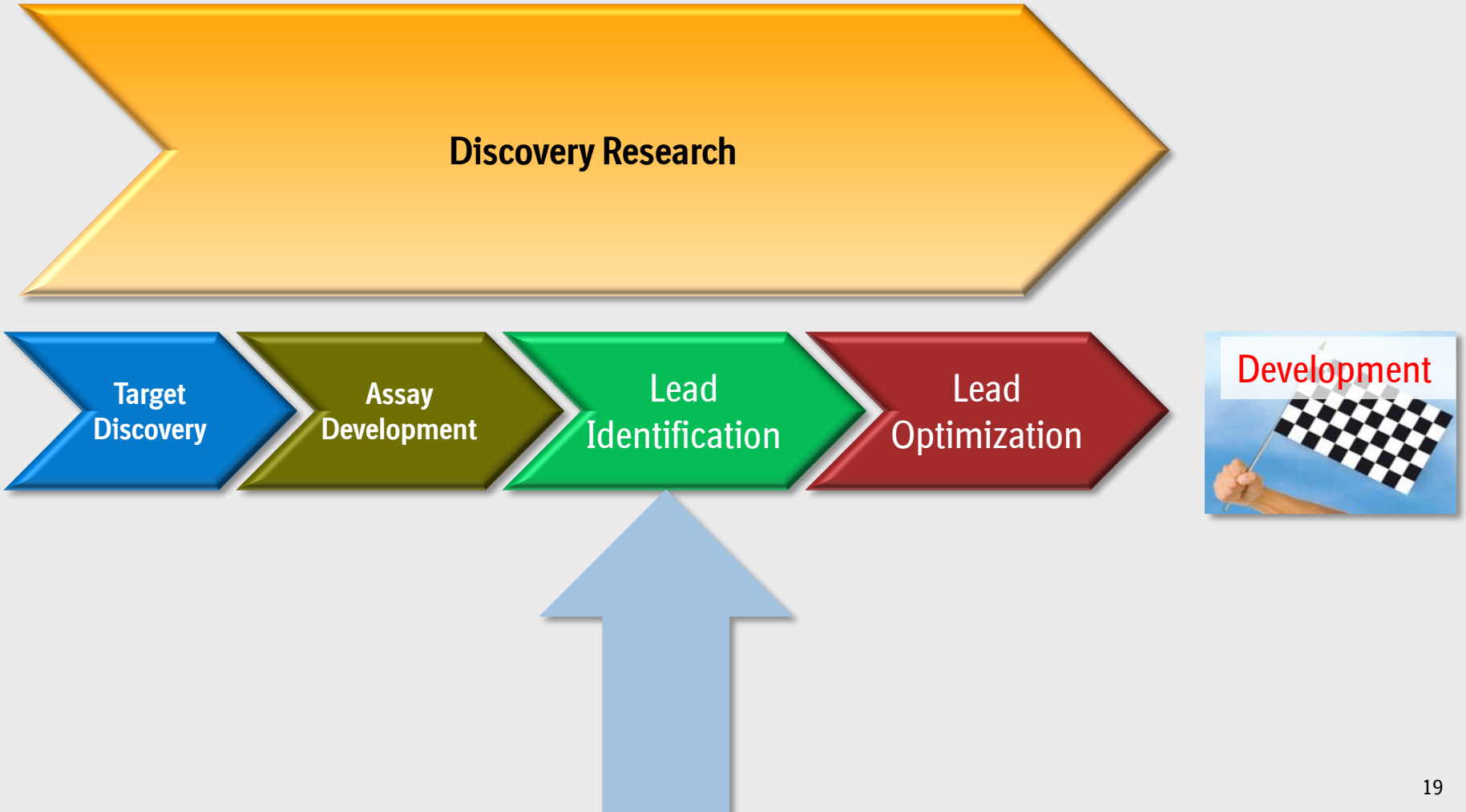

Lead Optimization
Multiple Challenges for a Molecule

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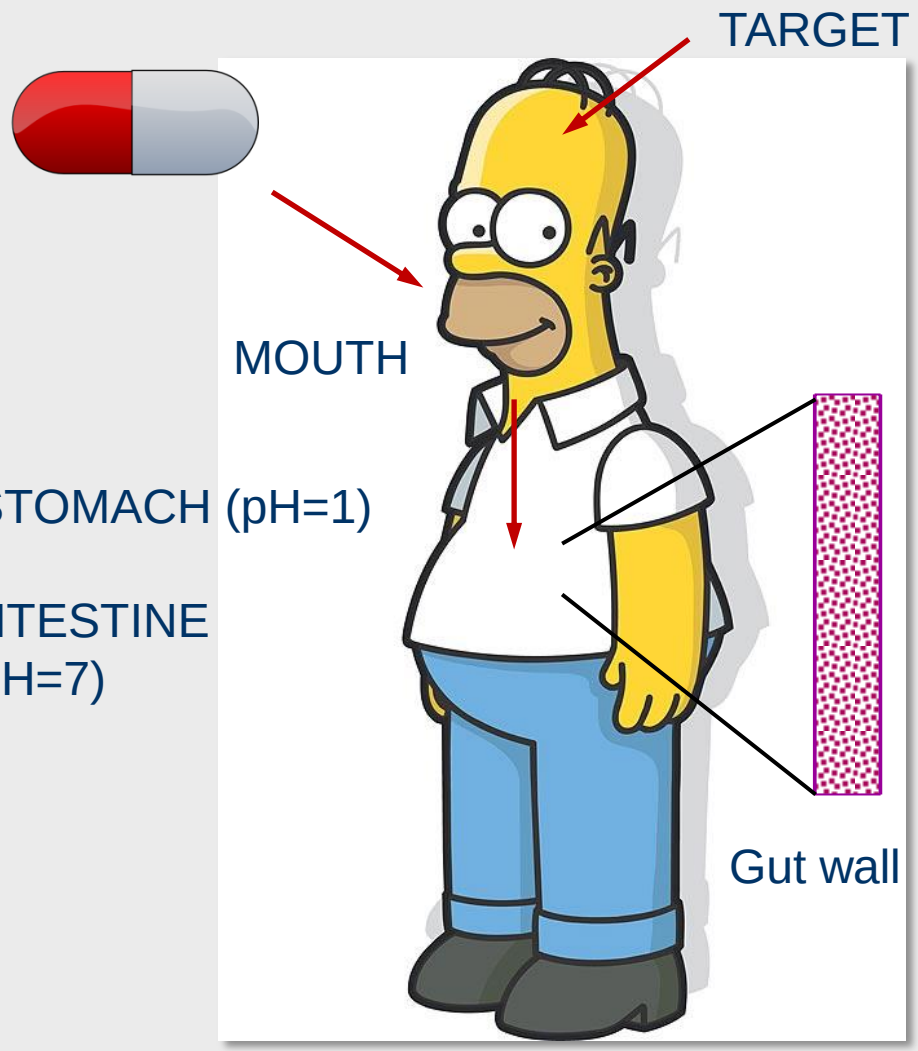

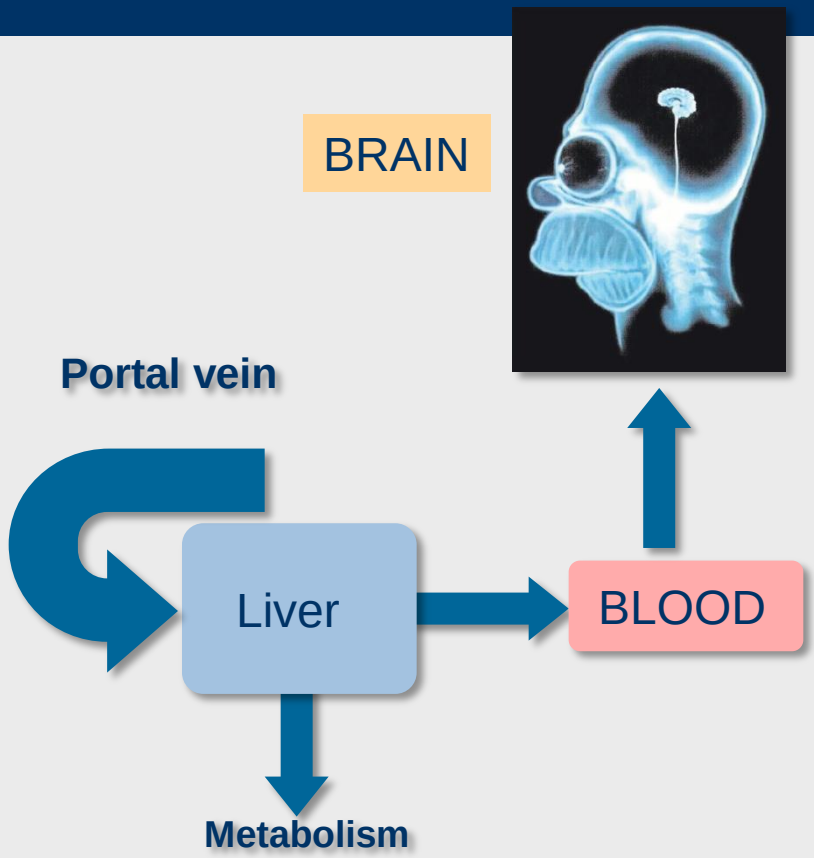

Lead Optimization
Optimization Parameters

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Drug Design is a Multi-Parameter Optimization

- Potency
- Selectivity
- Bioavailability
- Solubility
- Metabolic Stability
- Plasma Protein Binding
- Cytochrome Inhibition (Drug/Drug Interactions)
- Brain Permeation
- Toxicity
- Pharmacokinetic
- .....

Lead Optimization
From a Lead to a Drug Candidate

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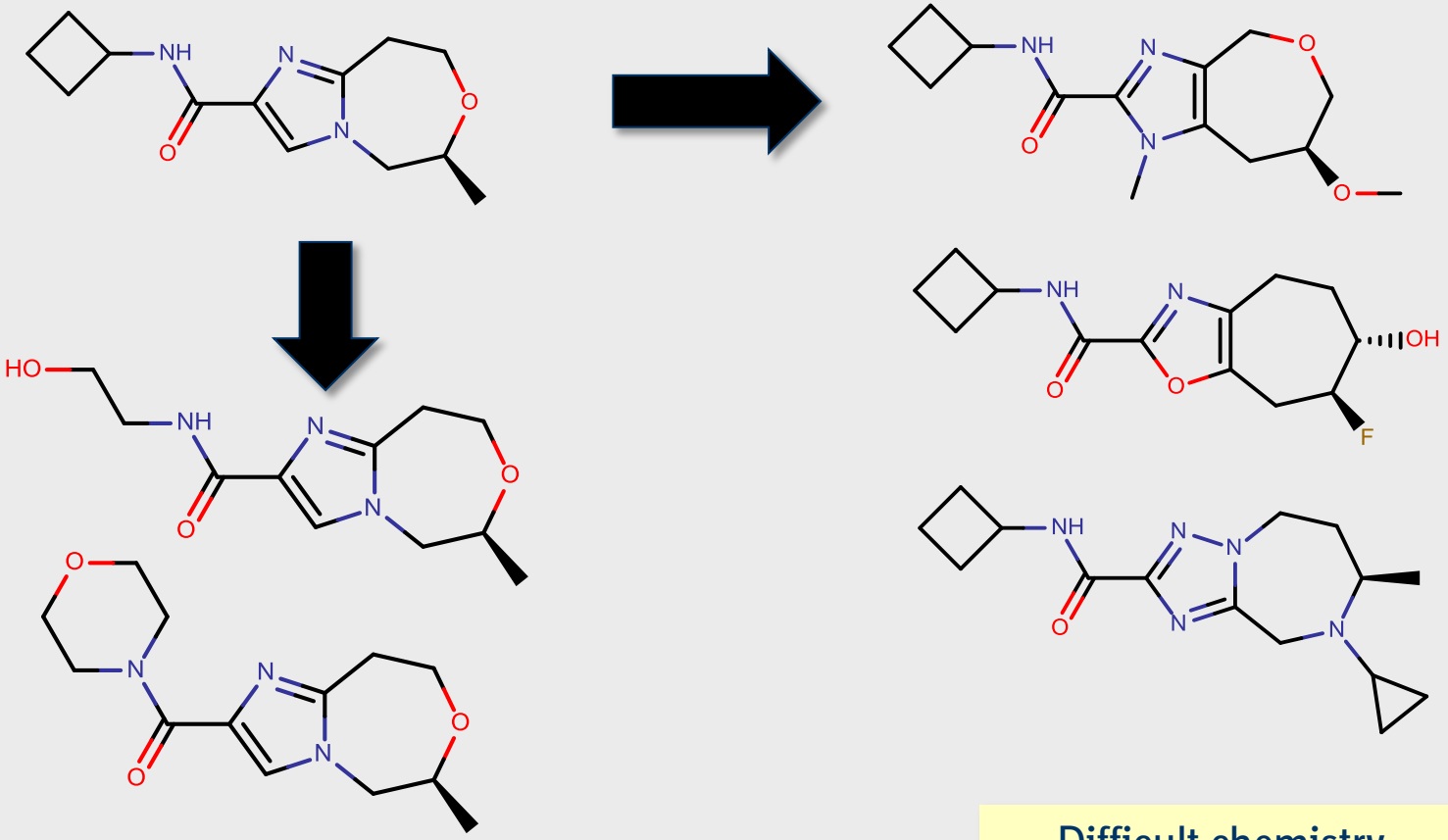
Lead Optimization essentially means synthesis of close analogs of an active molecule.



- „Easy“ chemistry -> Variation straightforward
- **Cheap!**

- Difficult chemistry
- Different synthetic routes
- **Expensive!**

Lead Optimization
Prediction of Molecule Properties

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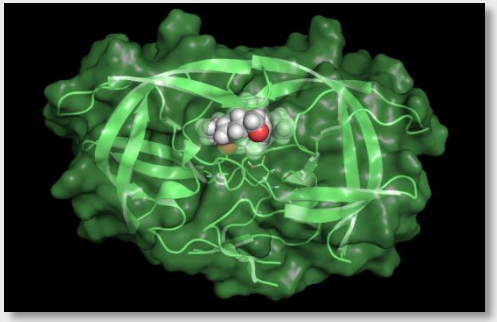
- Synthetic Chemistry can be very expensive (on average 2000€/molecule)

→ Make Predictions of Molecule Properties!

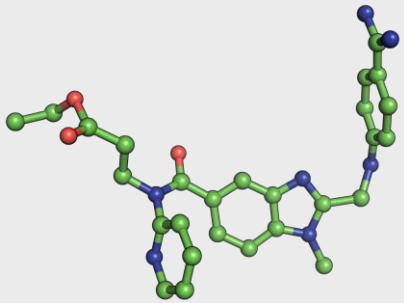
„Predictions are difficult, especially about the future“ (Niels Bohr)

Structure-based design



- Xray structure(s) required
- Physics-based approaches

Ligand-based design



- Known ligand required
- Physics-based approaches
- Chemoinformatics

Data-driven design

- Lots of data required
- Chemoinformatics
- Machine Learning

Lead Optimization
Structure Based Design

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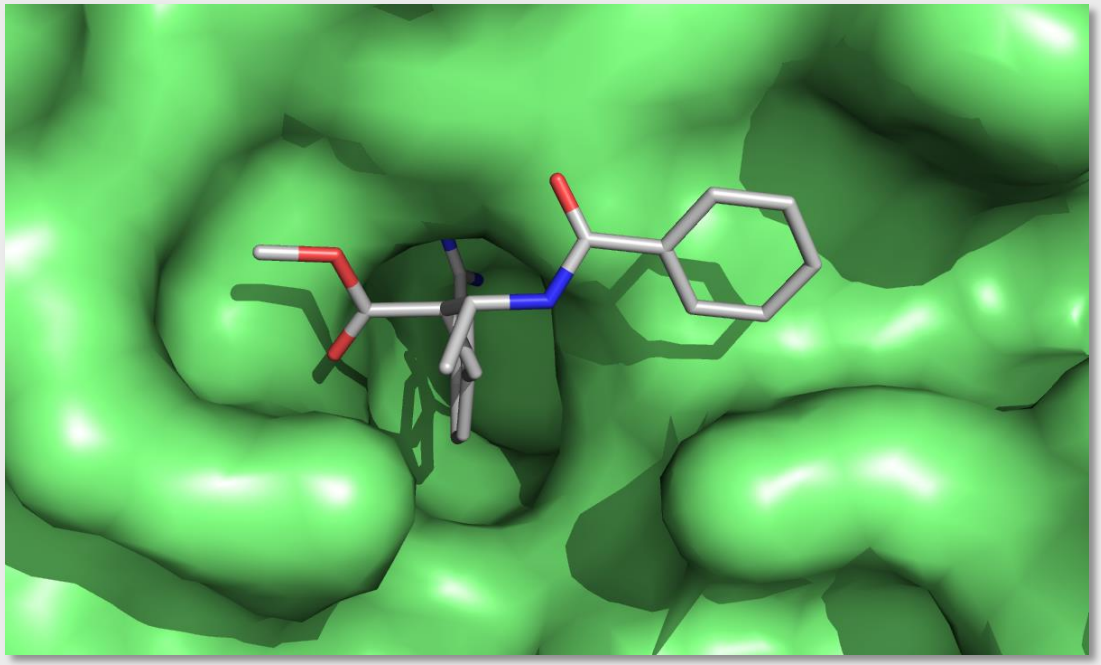

Xray Crystallography is a key technology for potency optimization, but....

Free Energy of Binding is an ensemble property -> Cannot be computed from a single structure

Lead Optimization
Computing Binding Free Energies

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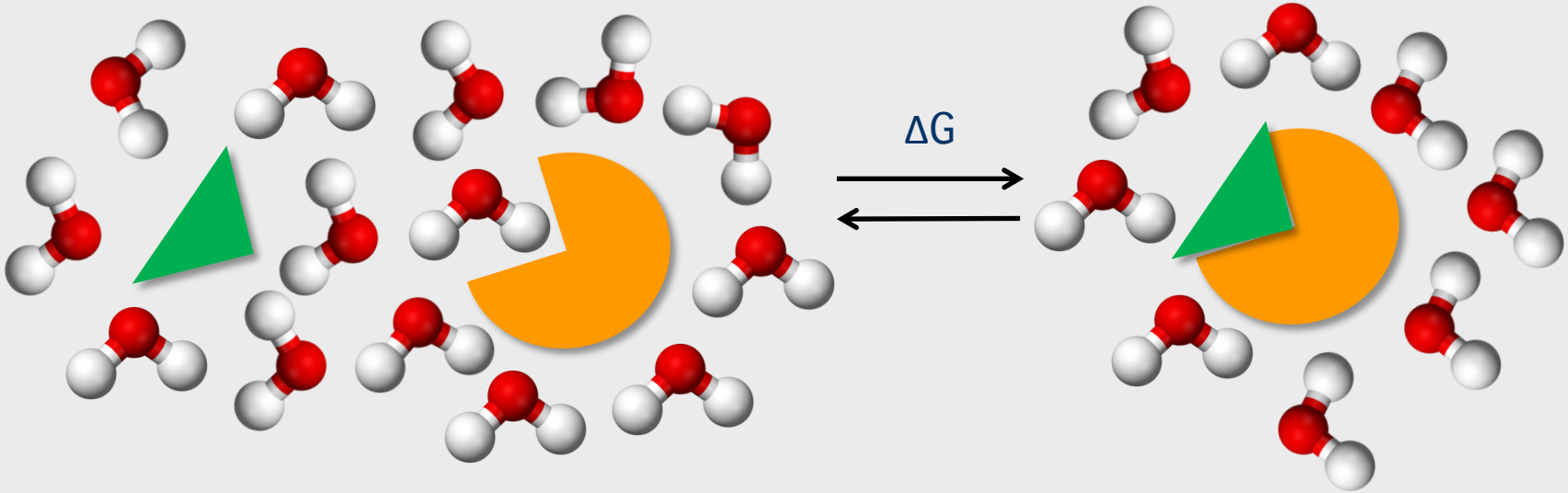
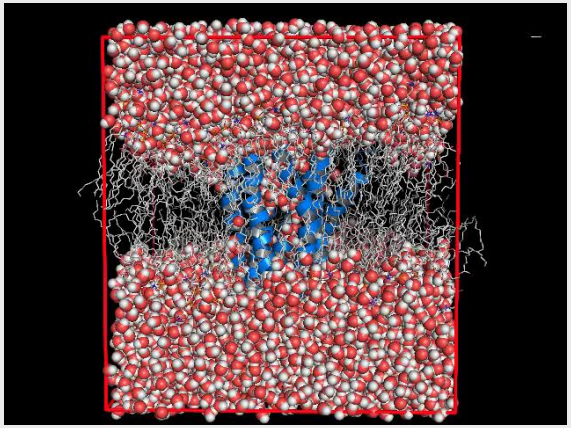


$$\Delta G = -RT \ln \left(\frac{1}{8\pi^2} \frac{C_P C_L}{C_{PL}} \frac{\int e^{-(U(r_{PL})+W(r_{PL}))/RT} dr_{PL}}{\left(\int e^{-(U(r_P)+W(r_P))/RT} dr_P\right)\left(\int e^{-(U(r_L)+W(r_L))/RT} dr_L\right)} \right)$$

- Molecular Dynamics Simulations
- Alchemical Free-Energy calculations



Lead Optimization
Ligand-Based Design

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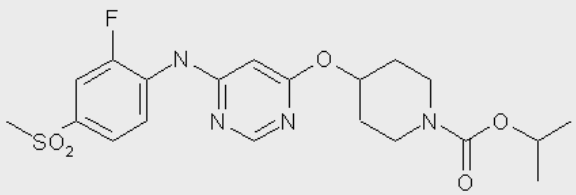
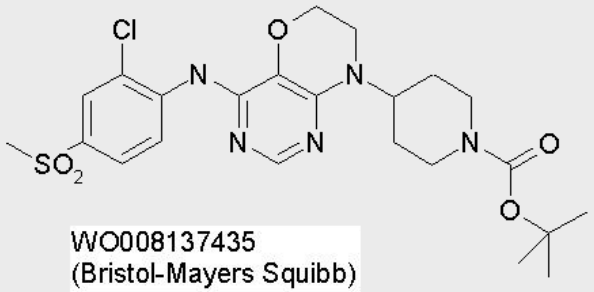
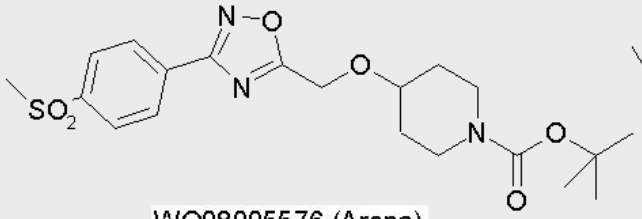
Activity of a molecules against a target is determined by their 3-dimensional structure



WO05121121 (Arena)



WO008137435
(Bristol-Mayers Squibb)



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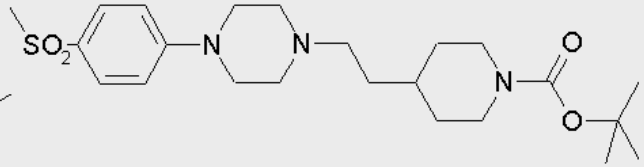

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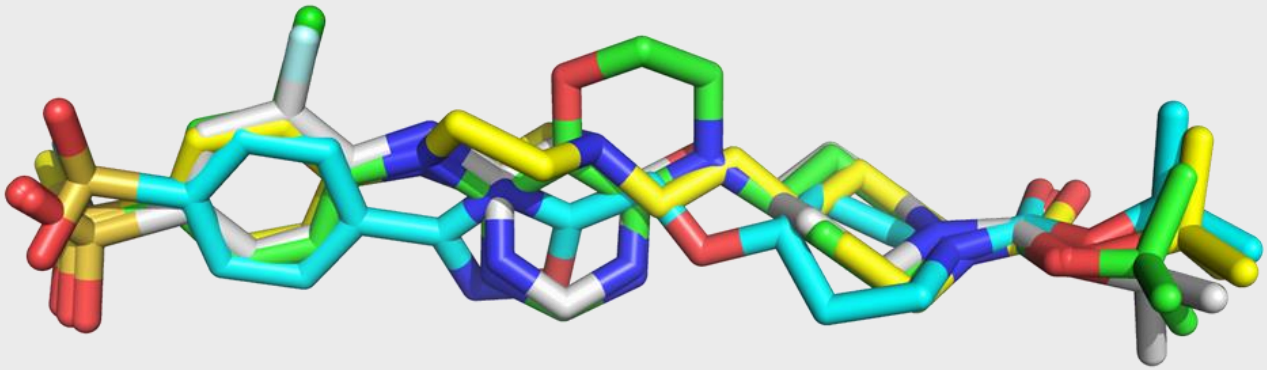

Ligand-based design: Search for molecules which are **similar** to a template molecule

Lead Optimization
Ligand-Based Design

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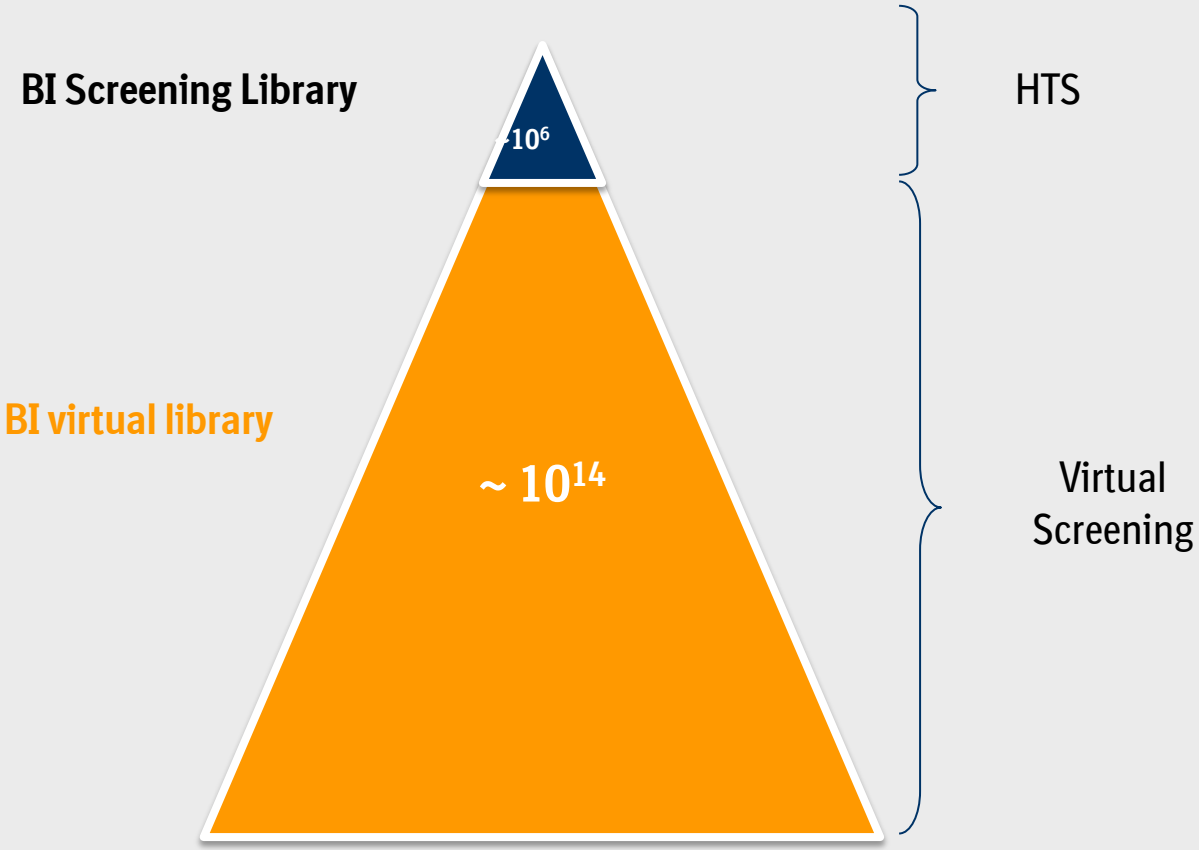
Search for similar molecules in a virtual chemical space



Lead Optimization
Virtual Libraries

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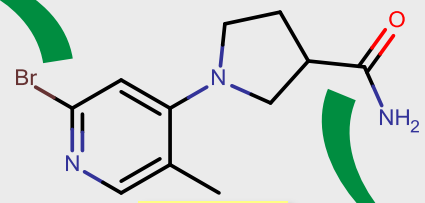
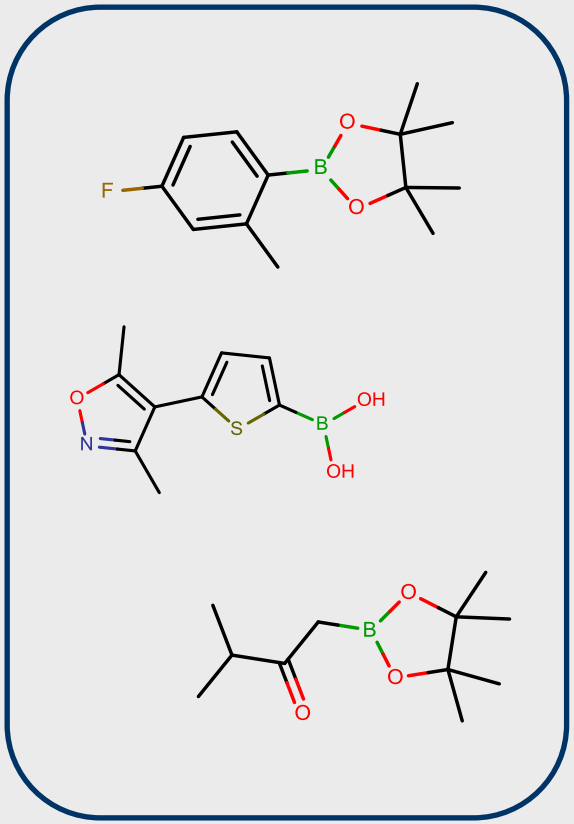
BI's virtual library consist of molecules which can be easily synthesized

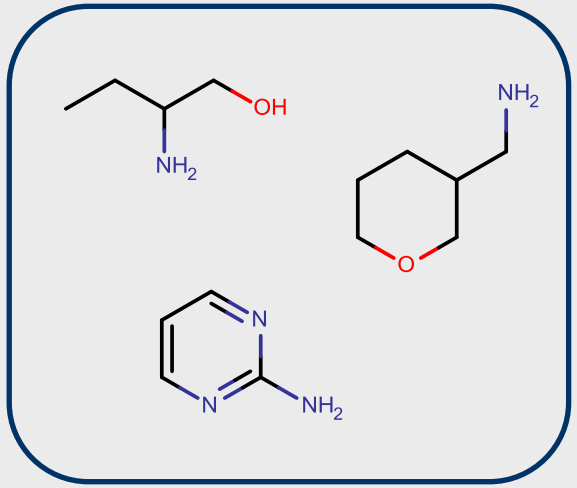


Core

- Suzuki Coupling (boronic acids)
- Buchwald-Hartwig (anilines, amines)



Amid-coupling
- amines
- anilines



BI in house

prim Amines (4000)
prim. Anilines (3500)
sec. Amines (6000)
sec. Anilines (2000)
boronic acids (2500)

Millions of possible combinations for each core.

Lead Optimization
Ligand-Based Design

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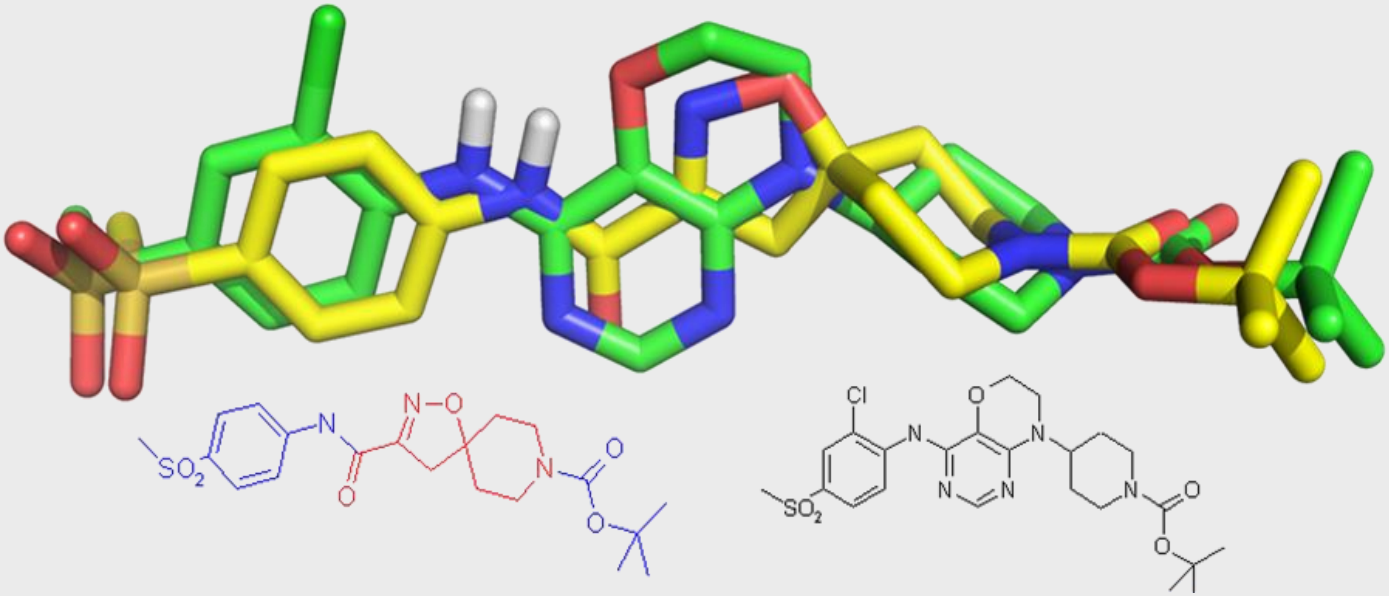

Lead Optimization
Ligand-Based Design

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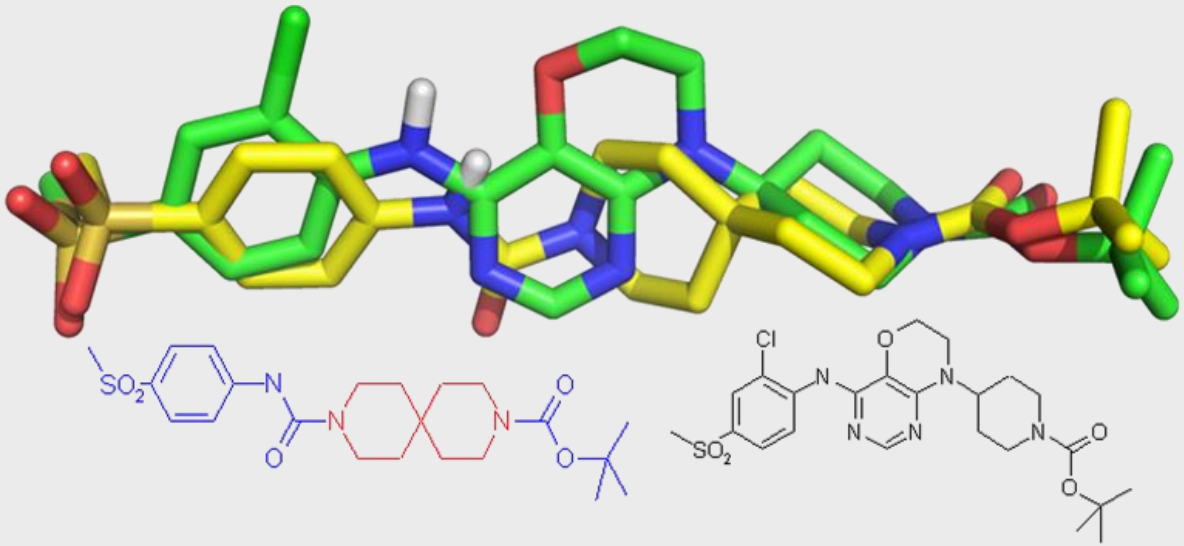

Lead Optimization
Optimization Parameters

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Drug Design is a Multi-Parameter Optimization

- Potency
- Selectivity

Structure/Ligand-based Design (target-specific)

- Bioavailability
- Solubility
- Metabolic Stability
- Plasma Protein Binding
- Cytochrome Inhibition (Drug/Drug Interactions)
- Brain Permeation
- Toxicity
- Pharmacokinetic
- .....

Data-driven Design (often target-independent)

Lead Optimization
Prediction of Molecule Properties with Machine Learning

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What is Machine Learning?

Data (Big Data)

Artificial Intelligence

Prediction

Prediction of Molecule Properties
Machine Learning

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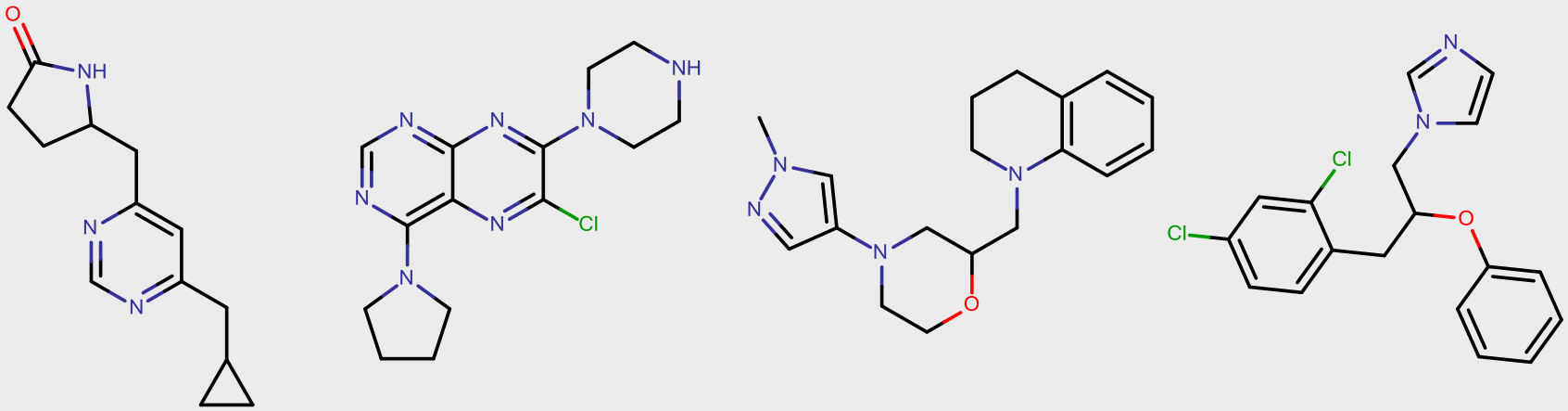
Prediction of Molecule Properties
Machine Learning

Boehringer Ingelheim



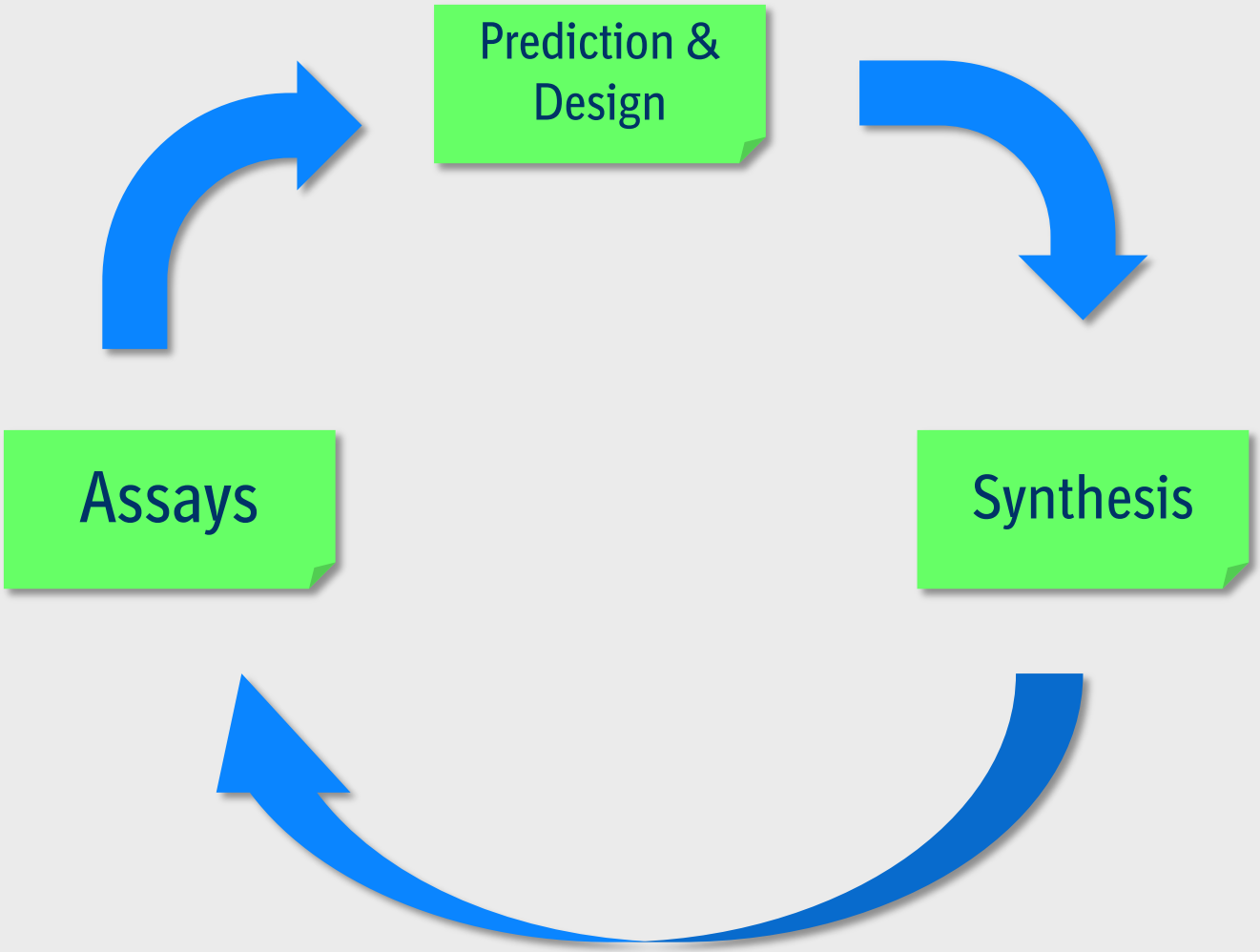
- Solubility?
- Metabolic Stability?
- hERG inhibition?
- CYP inhibition?
- Plasma Protein Binding?

Project (Target)-independent properties

- Solubility: **> 50 000 data points**
- Metabolic Stability: **> 80 000 data points**
- hERG inhibition **> 8 000 data points**
- CYP inhibition **> 40 000 data points**
- Plasma Protein Binding **> 4 000 data points**

Large data sets assembled over years and different research projects

Lead Optimization
Optimization Cycle



Drug Discovery Project Phases

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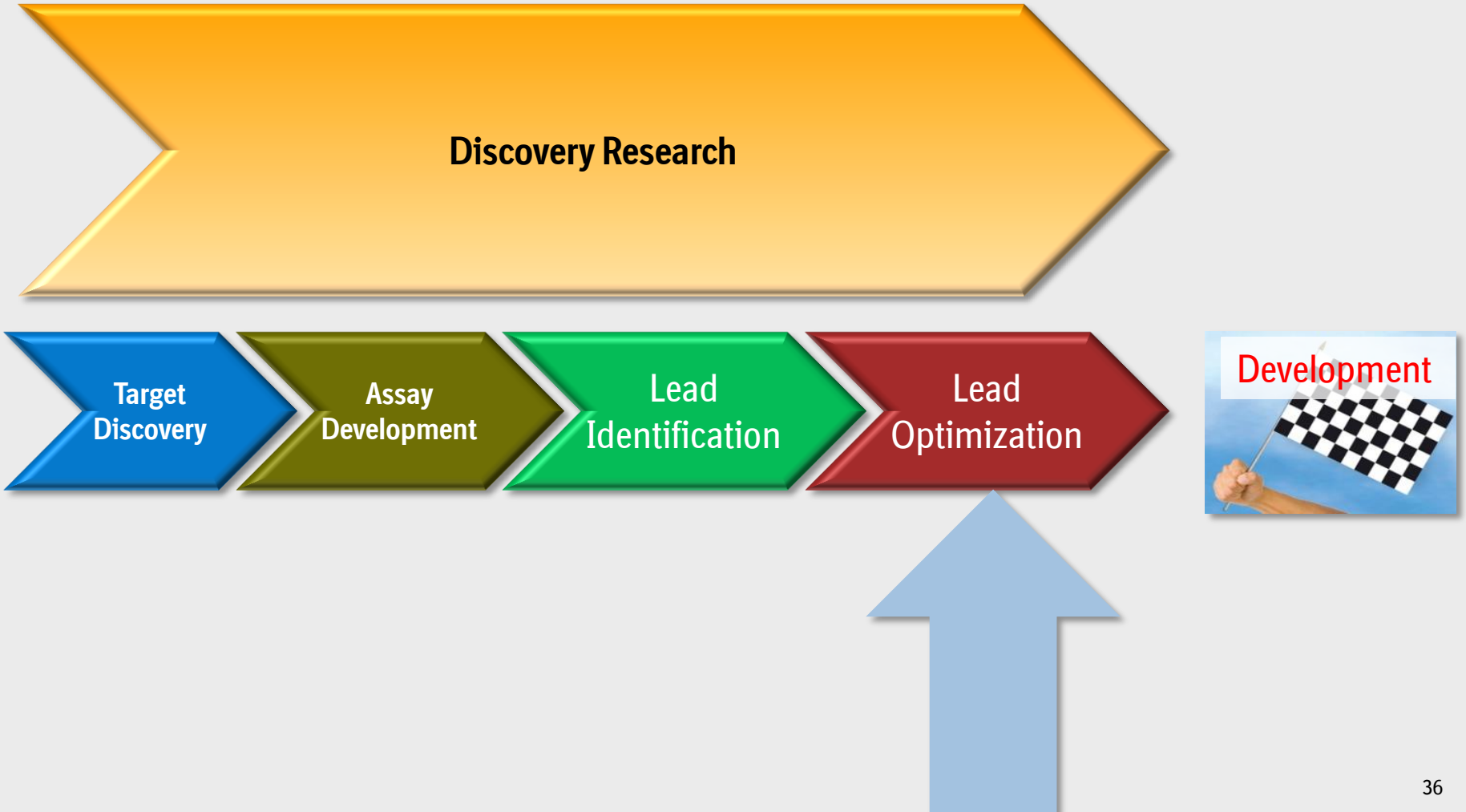

Summary

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- The paradigm of modern drug discovery is to connect diseases and symptoms to molecular mechanisms
- Drug discovery programs are target centric
- Drug design is a multi-parameter optimization
- Modern computational technologies and hardware developments allow reasonable predictions of activity and other molecular properties
- Drug discovery is a very interdisciplinary field of science