Drug Discovery

Lecture 26

- **Drug:** A chemical substance of known structure (other than a nutrient or an essential dietary ingredient) which, when administered to a living organism, produces a biological effect.

- **Discovery phase:** Identification of a new chemical entity as a potential therapeutic agent.
- **Development phase:** Compound is tested for safety and efficacy for one or more clinical indications, and in suitable formulations and dosage form.

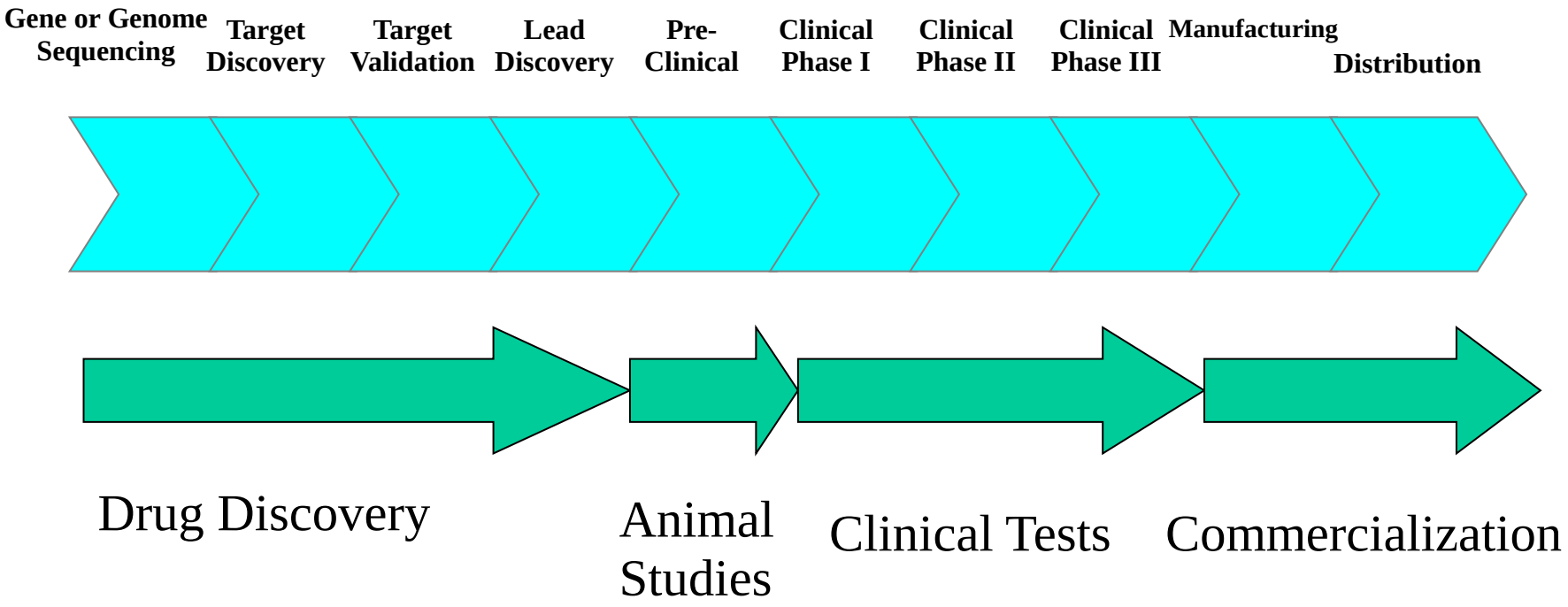
Major Stages of the New drug synthesis

- **Drug discovery:** Candidate molecules are chosen on the basis of their pharmacological properties.
- **Preclinical development:** Non-human studies (e.g. toxicity testing, pharmacokinetic analysis and formulation) are performed.
- **Clinical development:** The selected compound is tested for efficacy, side effects and potential dangers

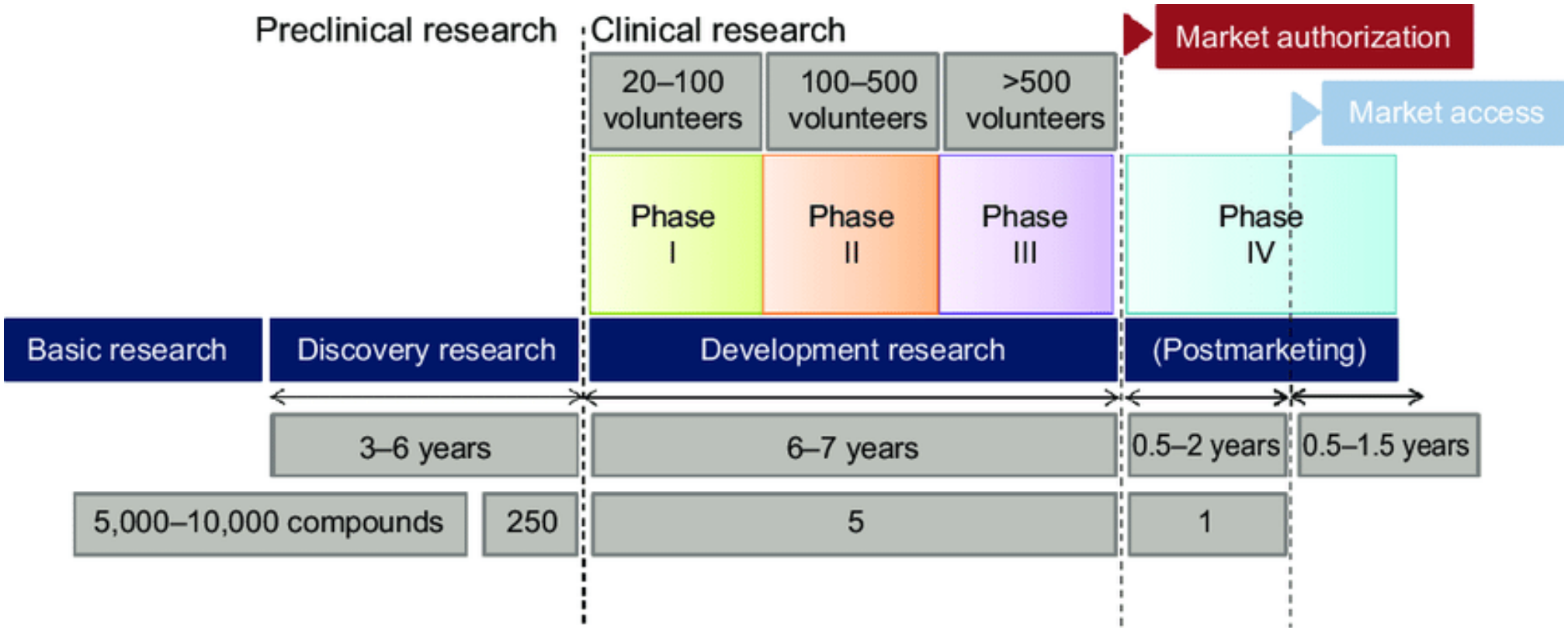
Drug discovery

- Drug discovery is the process through which potential new medicines are identified.
- It involves a wide range of scientific disciplines, including biology, chemistry and pharmacology.

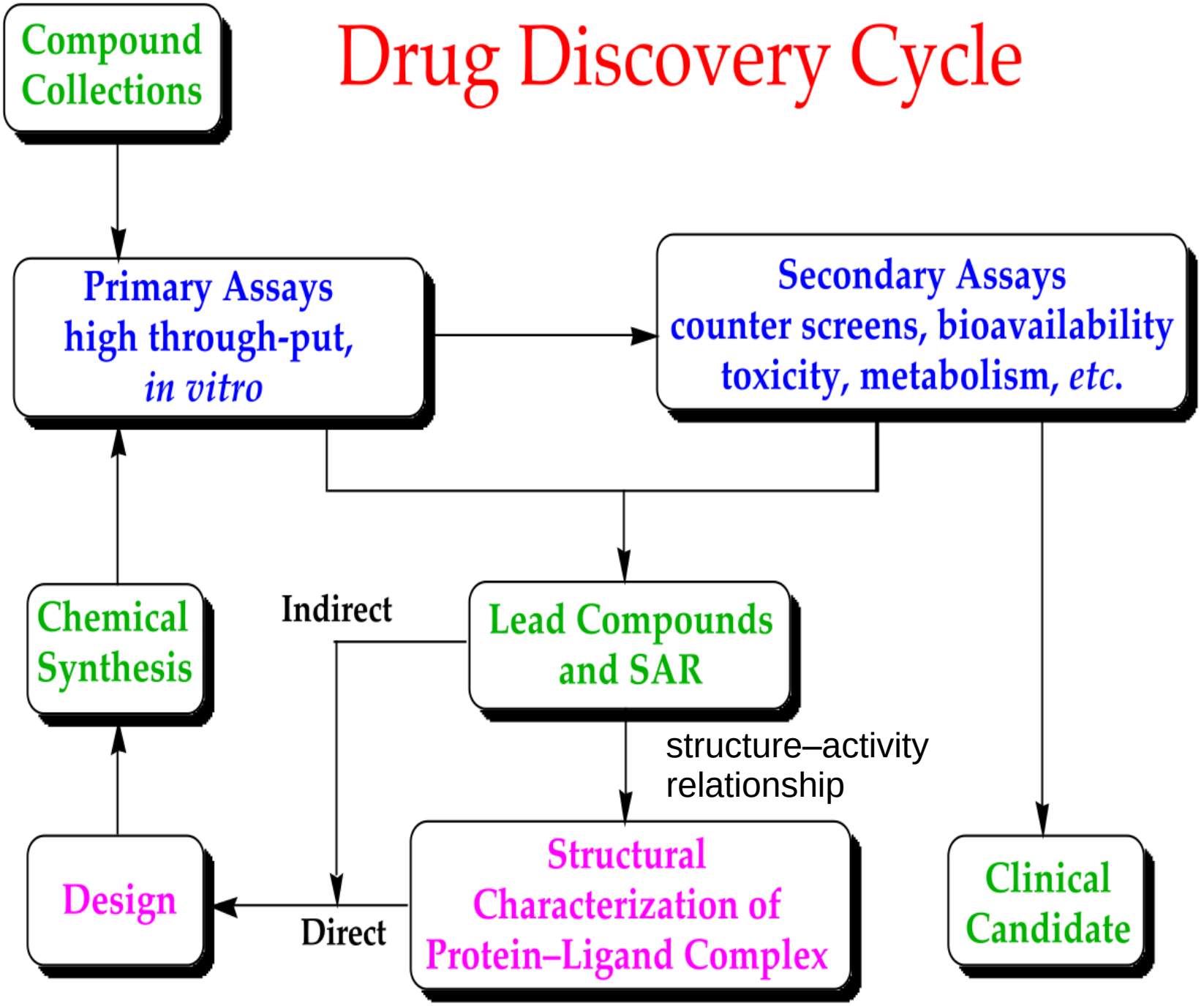
Drug development process



Schematic representation of the drug development process with timeline



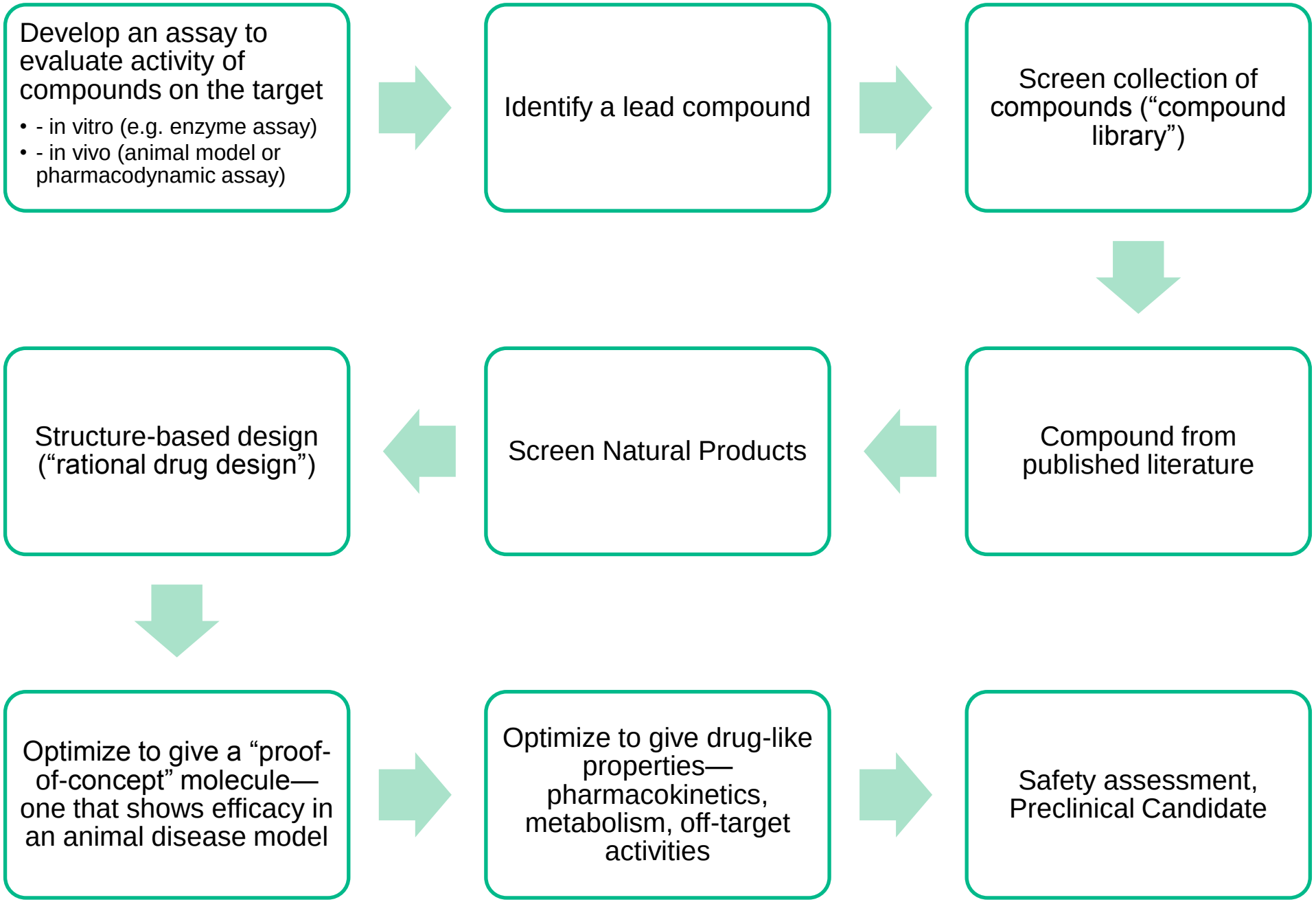
Drug Discovery Cycle



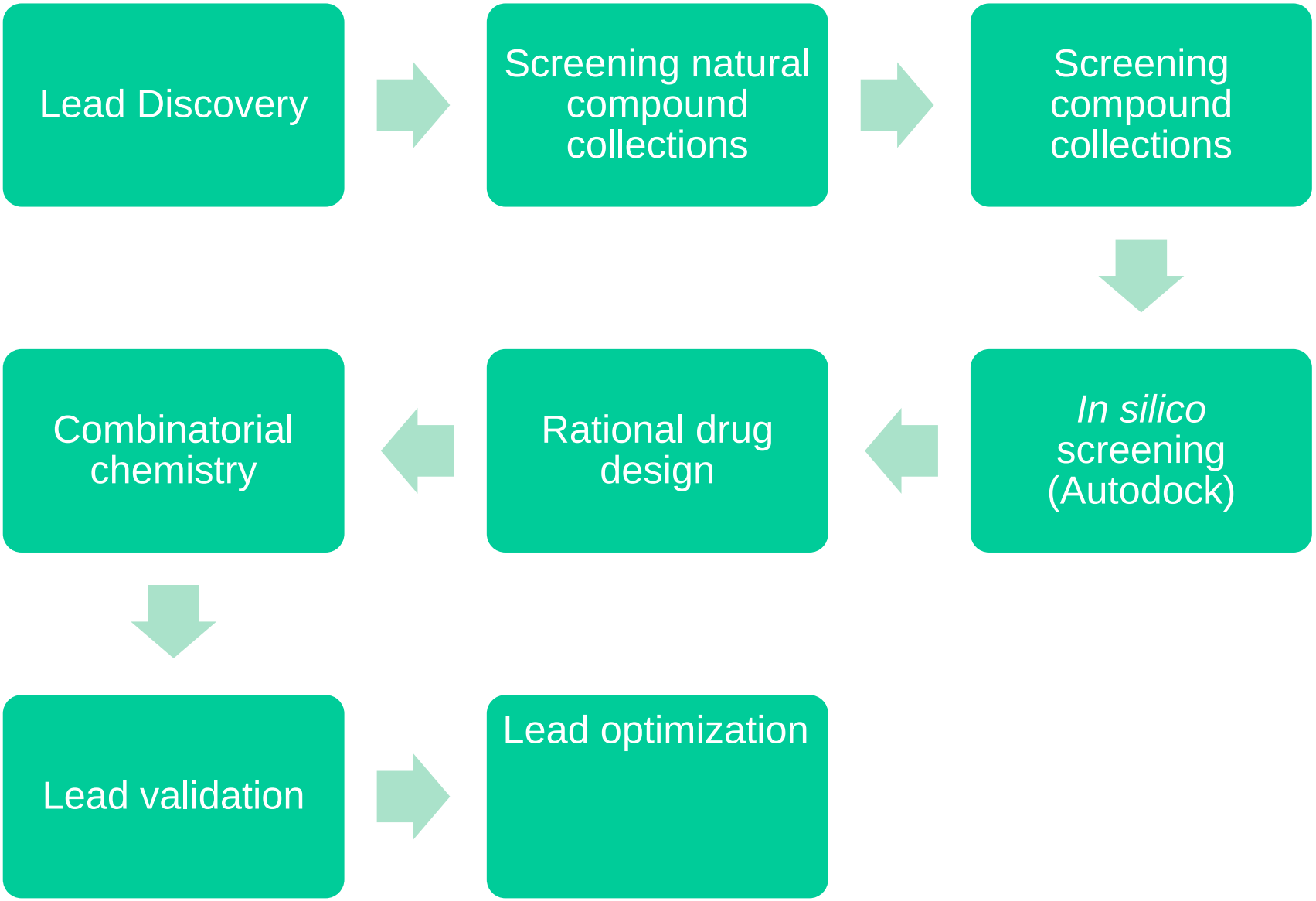
Target Selection & Validation

- Define the disease
- Understand the molecular mechanism of the disease
- Identify a therapeutic target in that pathway (e.g gene, key enzyme, receptor, ion-channel, nuclear receptor)
- Demonstrate that target is relevant to disease mechanism using genetics, animal models, lead compounds, antibodies, RNAi, etc.

Discovery

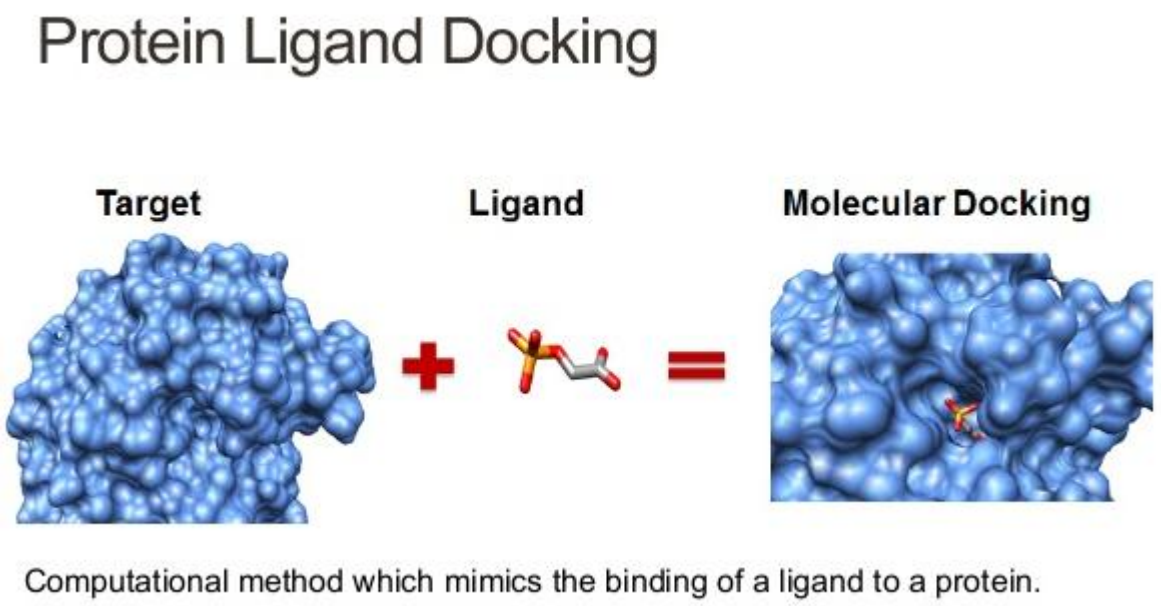

Develop an assay to evaluate activity of compounds on the target
- in vitro (e.g. enzyme assay)
- in vivo (animal model or pharmacodynamic assay)
Identify a lead compound
Screen collection of compounds (“compound library”)
Compound from published literature
Screen Natural Products
Structure-based design (“rational drug design”)
Optimize to give a “proof-of-concept” molecule—one that shows efficacy in an animal disease model
Optimize to give drug-like properties—pharmacokinetics, metabolism, off-target activities
Safety assessment, Preclinical Candidate

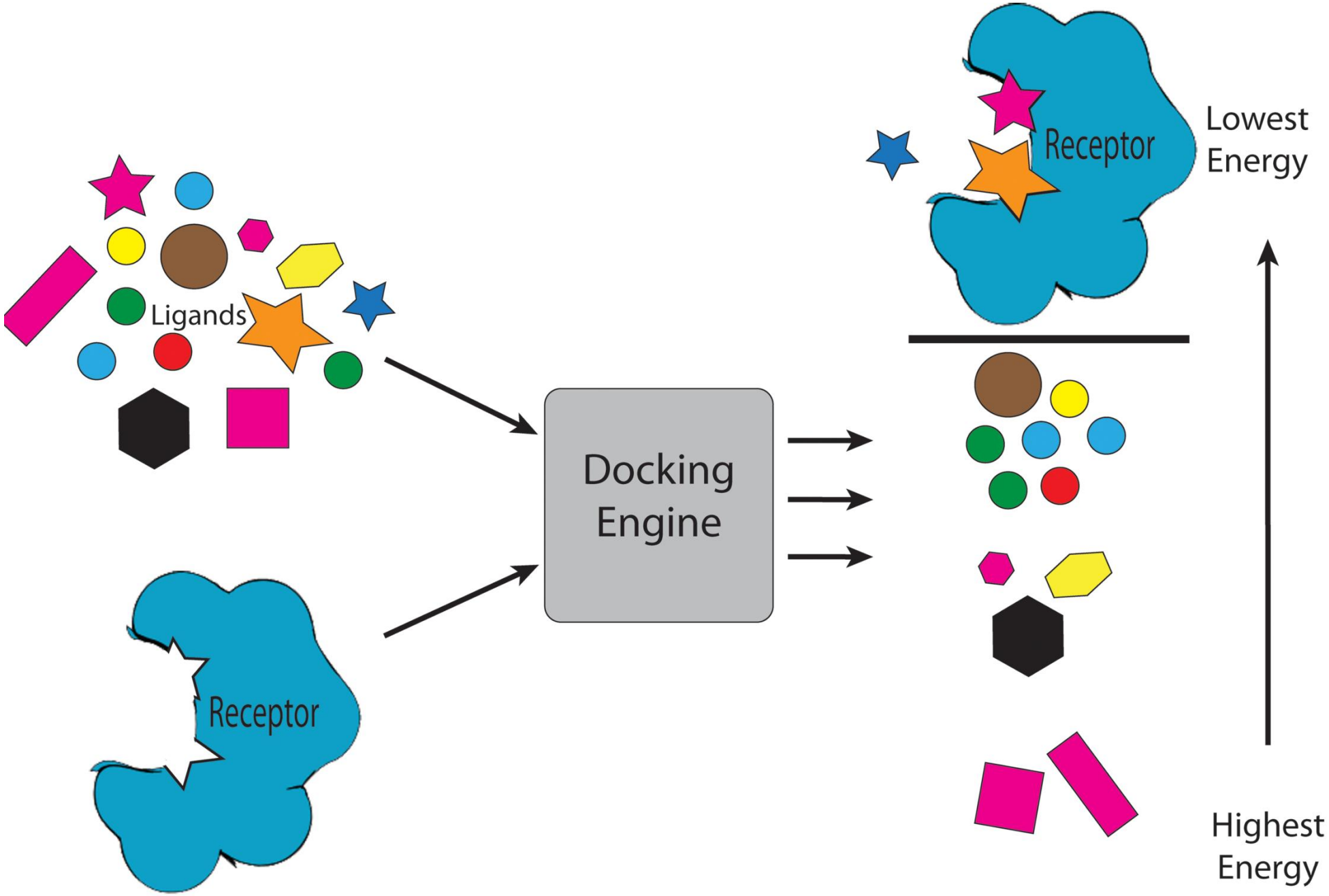
Drug Discovery Methods

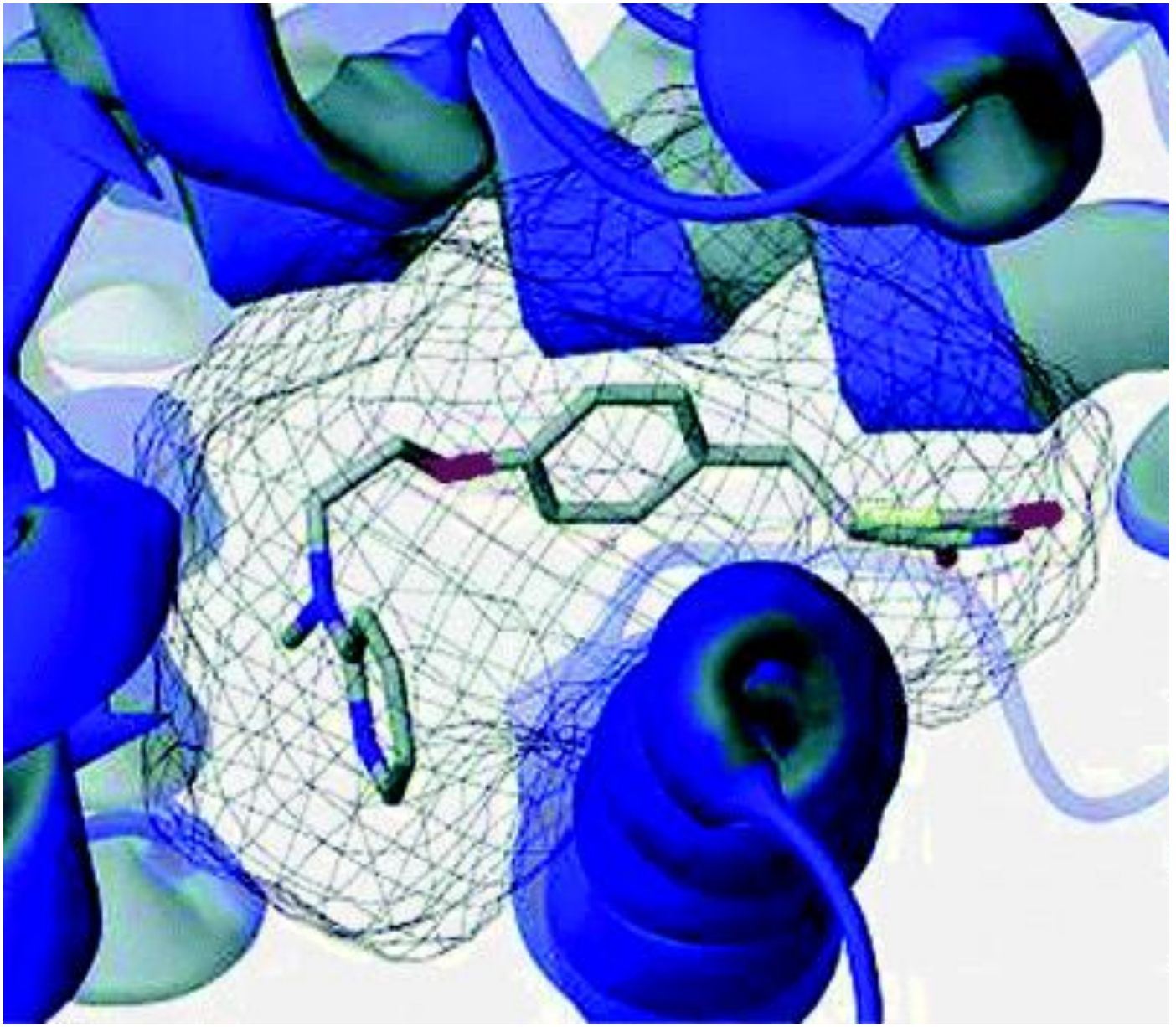


Docking

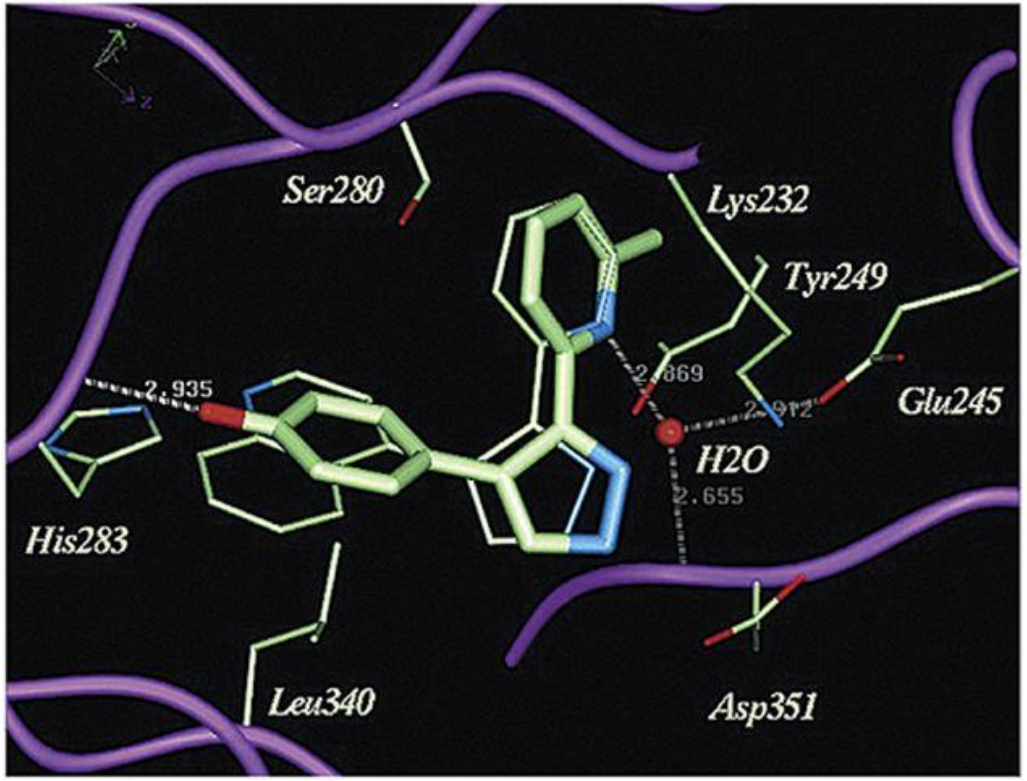
- A method which predicts the preferred orientation of one molecule to another when bound to each other to form a stable complex.
  - Ex: Autodock



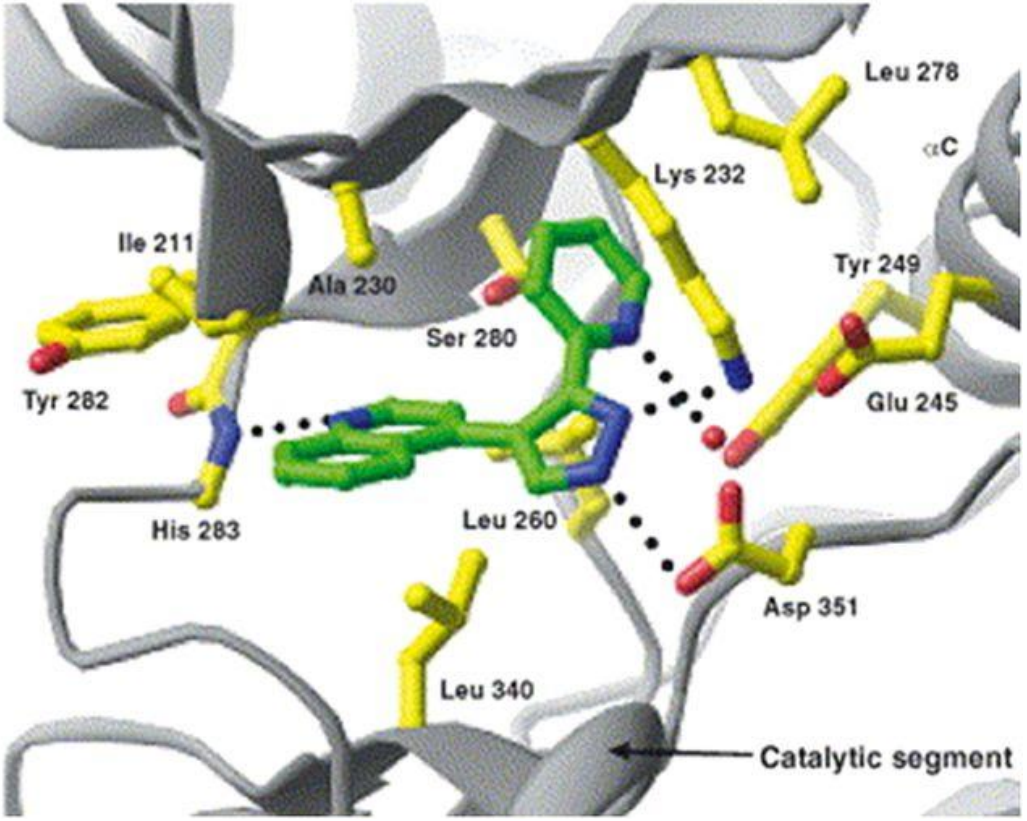

Ligands
Receptor
Docking
Engine
Receptor
Lowest
Energy
Highest
Energy



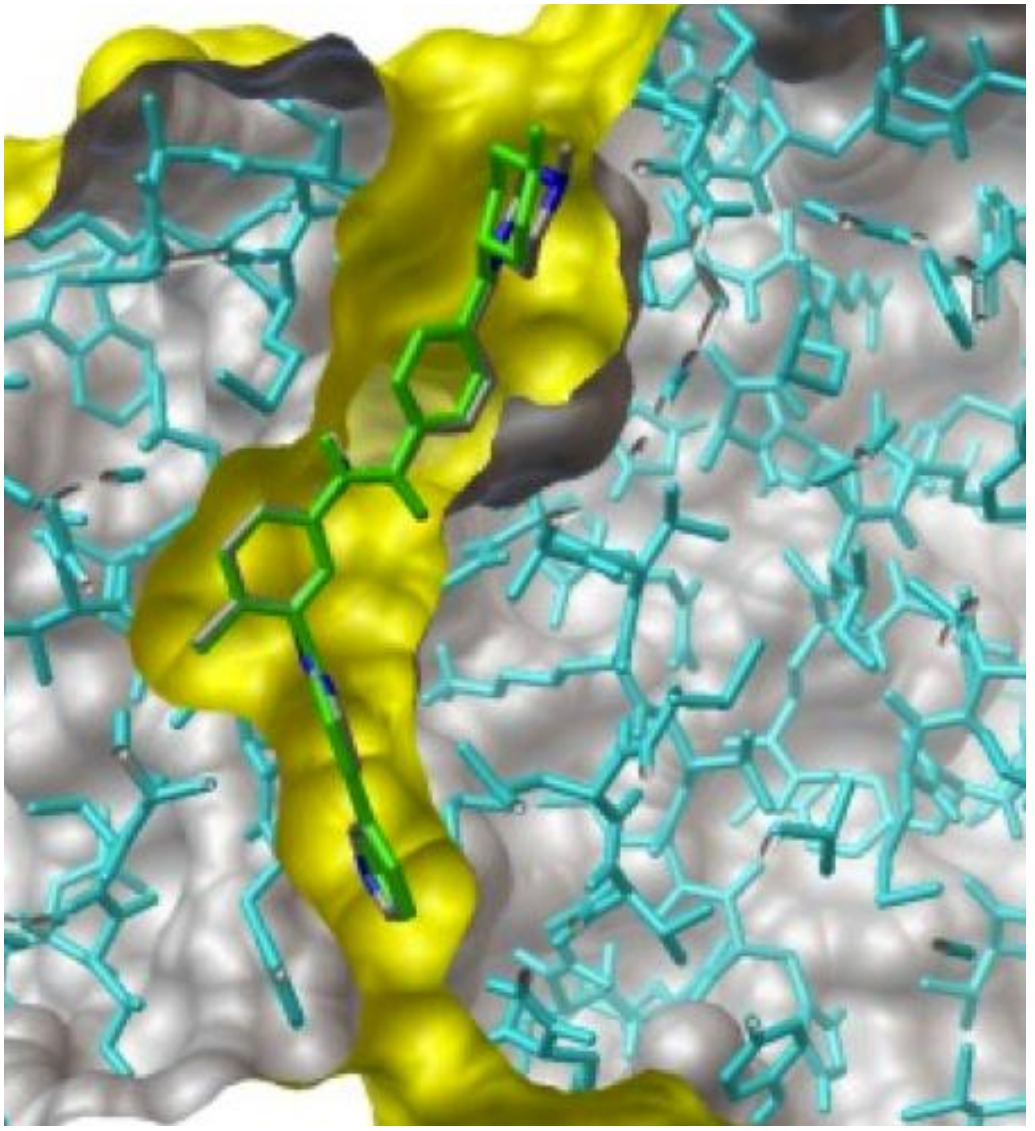
I)


Ser280
Lys232
Tyr249
Glu245
H2O
His283
Leu340
Asp351
2.935
2.655

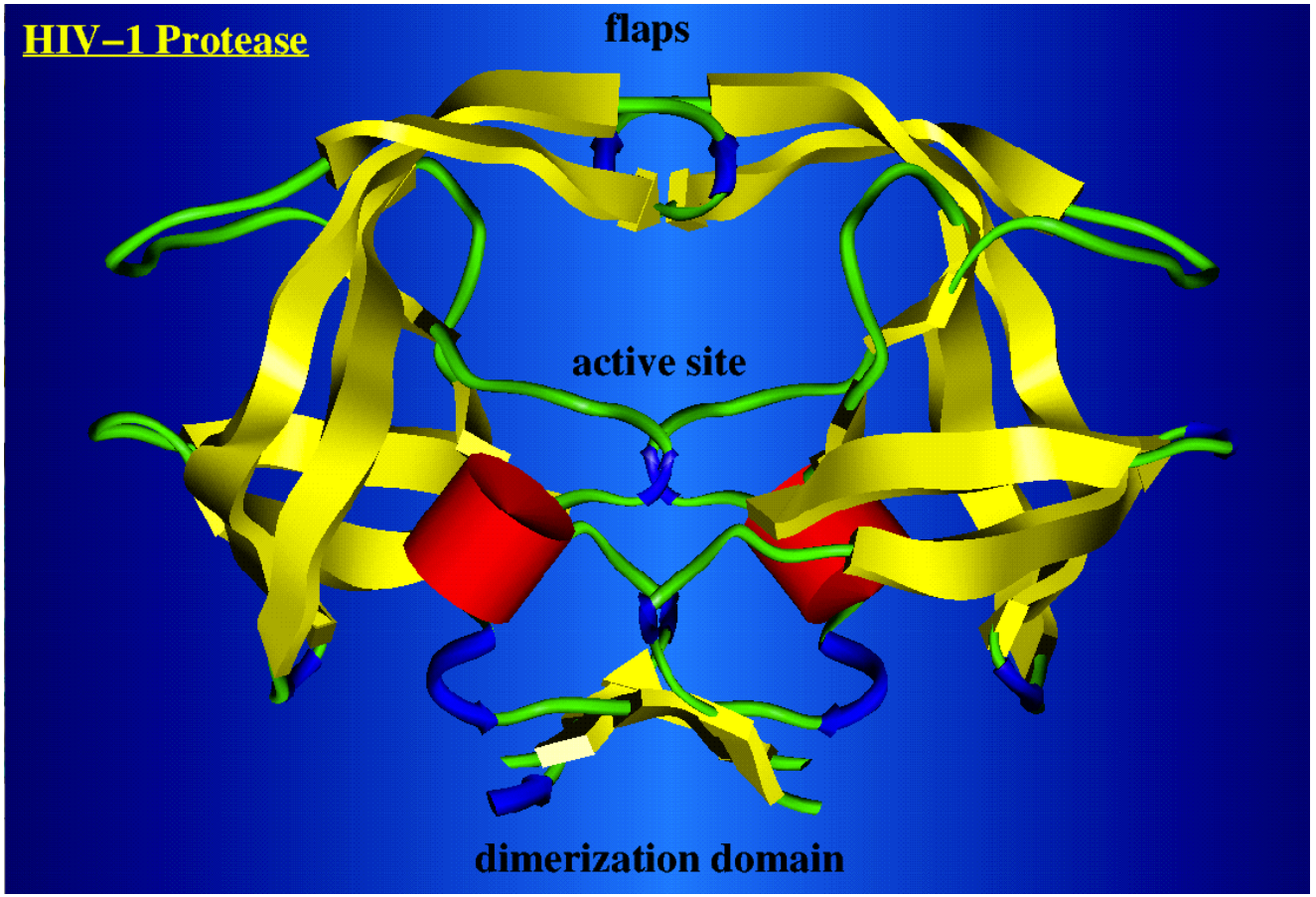
II)


Leu 278
αC
Lys 232
Ile 211
Ala 230
Tyr 249
Ser 280
Tyr 282
Glu 245
His 283
Leu 260
Asp 351
Leu 340
Catalytic segment

In silico screening with Autodock
Gleevec (Imatinib) bound to BCR-Abl Protein



Rational Drug design for HIV Protease



Rational drug design refers to the **development** of medications based on the study of the structures and functions of target molecules.

ADMET: Ideal Properties of Drugs

Absorption – From GI track into blood stream

Distribution - Gets to target tissue (blood brain barrier)

Metabolism – Not readily metabolized

Excretion – Not readily secreted

Toxicity – Not toxic to other cells or tissues

Chris Lipinski's Rule of Five

- H-bond donors <5.
- Molecular weight <500.
- Partitioning coefficient (Log P) <5. (The **partition coefficient** is the measure of the lipophilicity of a **drug** and an indication of its ability to cross the cell membrane.)
- H-bond acceptors <10 (=5×2).
- The "rule of five"name came from the cutoffs all being multiples of five.

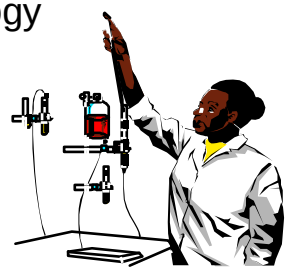
Development

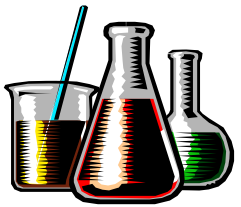
Pre-Clinical

Safety Assessment
Toxicology

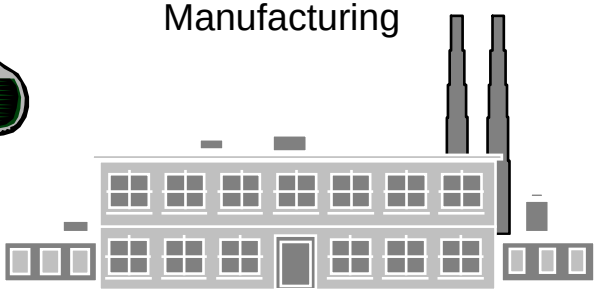
Drug Metabolism
(ADME)

Pharmacology

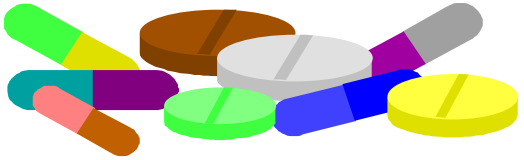




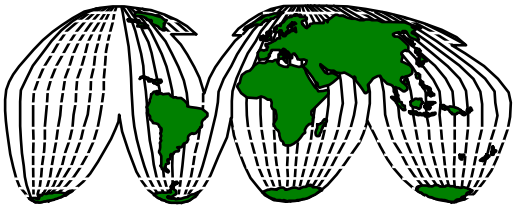
Process R&D
Chem Eng. R&D
Manufacturing

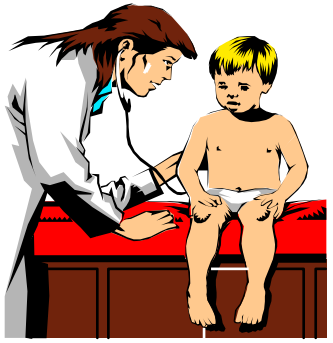


Pharmaceutical R&D
Formulation



Bio Process R&D





Clinical Investigator
& patient

Clinical Pharmacology
Clinical Research

Regulatory Affairs
Project Planning & Management
Marketing

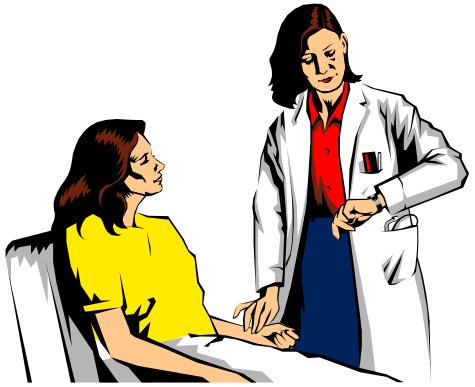
Statistics & Epidemiology
Data Coordination
Research Information Systems
Information Services

Clinical

Investigational New Drug application

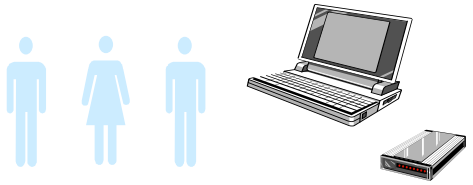
IND

Clinical Trials



Phase I

20 - 100 healthy volunteers take drug for about one month



Remote data entry

Product Profile ———➚ **Marketing SOI**

Information Learned

1. **Absorption and metabolism**
2. **Effects on organs and tissue**
3. **Side effects as dosage is increased**

Phase II

Several hundred health-impaired patients

Treatment Group Control Group

Information Learned

1. **Effectiveness in treating disease**
2. **Short-term side effects in health -impaired patients**
3. **Dose range**

Phase III

Hundreds or thousands of health-impaired patients

Information Learned

1. **Benefit/risk relationship of drug**
2. **Less common and longer term side effects**
3. **Labeling information**

Compassionate Use

Clinical Trials Continued

Advisory Committee

Regulatory Review Team

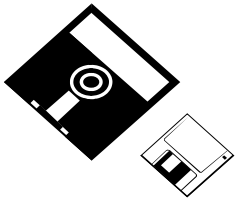
APPROVAL PROCESS
(Ex. FDA)

Reviews, comments, and discussions

Submit to Regulatory Agencies

Drug Co./Regulatory liaison activities

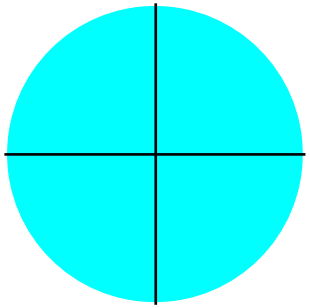
New Drug Application (NDA)



APPROVAL

Worldwide Marketing Authorization (WMA) in other countries

Drug Discovery—Convergence of Disciplines



Combinatorial Chemistry

Synthetic Chemistry

Patent Law

Modelling

Novel Molecule

Intellectual Property

Physiology

Information Technology

Design

Structural Activity

Biochemistry

Physiology

Metabolism

Safety

Pharmaco-dynamics

Physiology

Pharmacology

Safety Assessment

In Vivo activity

Pharmacokinetic Properties

Immunology

DMPK

Pharmacology

Behavior

Pathology

Physiology

Physical Chemistry

Physiology

Enzymology

Genetic and Biomarker Followup

But why stop learning when the drug is on the market ? A proposal to create larger safety and efficacy databases, assess biomarkers