Istraživanje i razvoj lijekova - od ideje do tržišta!

SAJAM IDEJA 2017

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Discovery of new drug!

Long and highly risky road!

How to decide what to work on?

Drug discovery & development process

10 - 15 years

Drug R&D

Clinical Trials

Target ID & Validation	Hit Generation	Lead Gen & Optimization	Pre Clinical Animal Studies	Phase 1: Safety	Phase 2: Efficacy Safety	Phase 3: Efficacy Safety	FDA Review & Approval
1-2 years	1-2 years	1-2 years	1 year	20-100 people 1-2 years	100-300 people 1-2 years	1,000-3,000 people 2-3 years	1-2 years
Link disease and target Biomarkers High-throughput screening Rational Design In silicon screening	Hits Confirmation Potency & cytotoxicity Prelim animal efficacy Initial SAR	Potency Studies Selectivity Studies PK/ADME-Tox properties SAR pharmacophore modeling	Pharmacological profile Administration route Drug interactions				

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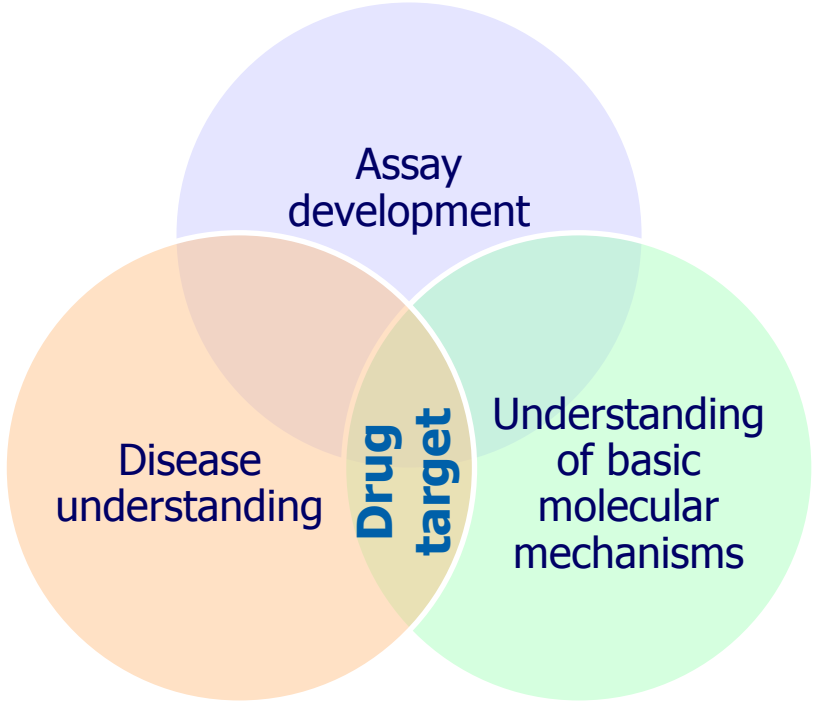
Target identification and validation

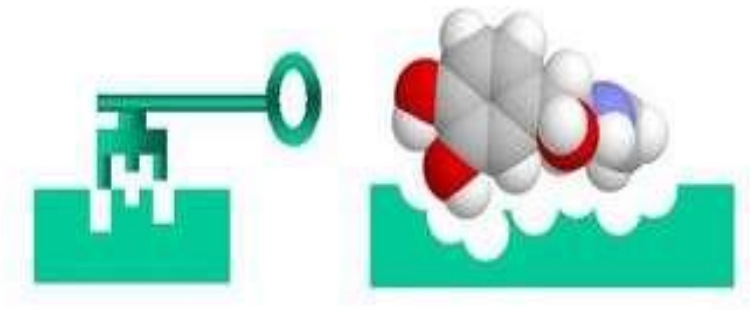
- Target identification: to identify molecular targets that are involved in disease progression
- Target validation: to prove that manipulating the molecular target can provide therapeutic benefit for patients (biochemical, cellular, or animal models)
- A target is never fully validated until a drug acting on it works on patient!

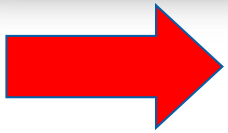


- Common receptors include proteins and enzymes
- Current drug therapies addresses around 500 biological targets.
- HG contains 12000-14000 encoding secreted proteins.

What is a drug?

- Any biologically active chemical *that does not occur naturally* in the human body that causes a physiological change in the body.
- Drugs are used for the treatment, prevention or alleviating the symptoms of disease.



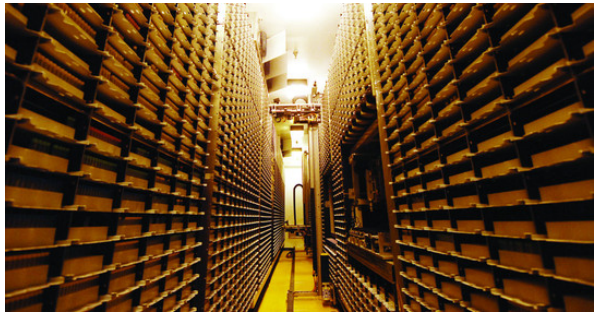


CELLULAR/BIOLOGICAL RESPONSE

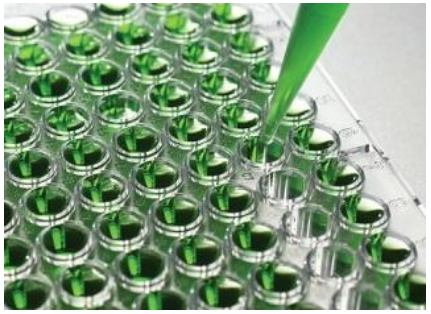
Searching for Compounds – HIT finding

- After target validation, next step is to find a chemicals that might modify the target or targets
- This sophisticated process can be divided into three distinct steps:

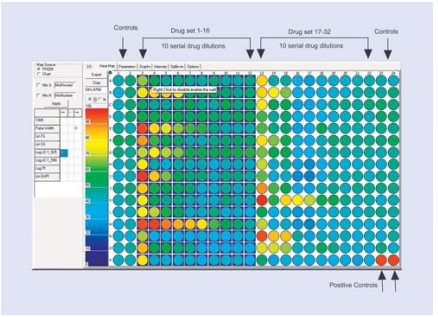
development and maintenance of large compound libraries → specific assay development → high-throughput screening (automated system)



- All compounds are stored in coded vials and organized in central bank so that they could be used on different biological targets.
- Some contains more than 5 million chemicals including products from natural sources.



- Assays are analyses that quantify the interaction of the biological target and the compound.
- They also might measure how the presence of the compound changes the way in which the biological target behaves.



- Identification of compounds with activity against biological targets.
- Fast and reproducible capable to perform screen on >1000 compounds per day.
- The purpose of this chemistry stage is to refine the compound.

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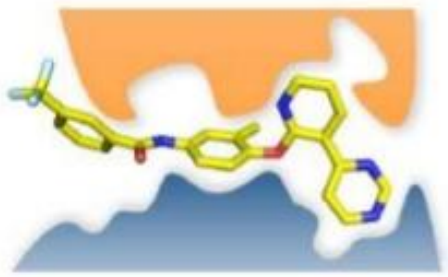
Fragment-Based Drug Discovery

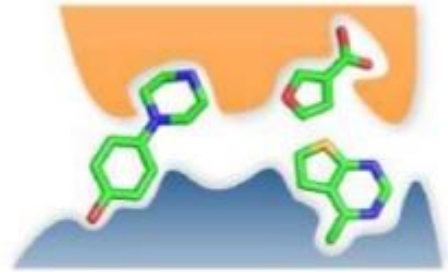
Alternative to HTS: Fragment-Based Drug Discovery (FBDD)



Typical compound hit from HTS screen

- Large molecule (MW between 250 – 600)
- Broad surface contact with no high quality interactions in key pockets
- May contain functional groups that contribute poorly to protein binding
- Emphasis on potency (30 µM – nM hit activity)

The idea that large molecules can be considered combinations of two or more individual fragments is a fundamental principle of fragment-based drug discovery



Typical compound hits from FBDD

- Smaller molecule (MW between 150 – 300)
- High proportion of the functional groups involved in binding
- Clearly interacts with pockets
- Potency in the range of mM to 30 µM
- Emphasis on efficiency and design

Rees, D.C.; Congreve, M.; Murray, C.W.; Carr, R. *Nature* **2004**, *3*, 660.
Scott, D.E.; Coyne, A.G.; Hudson, S.A.; Abell, C. *Biochemistry* **2012**, *51*, 4990.

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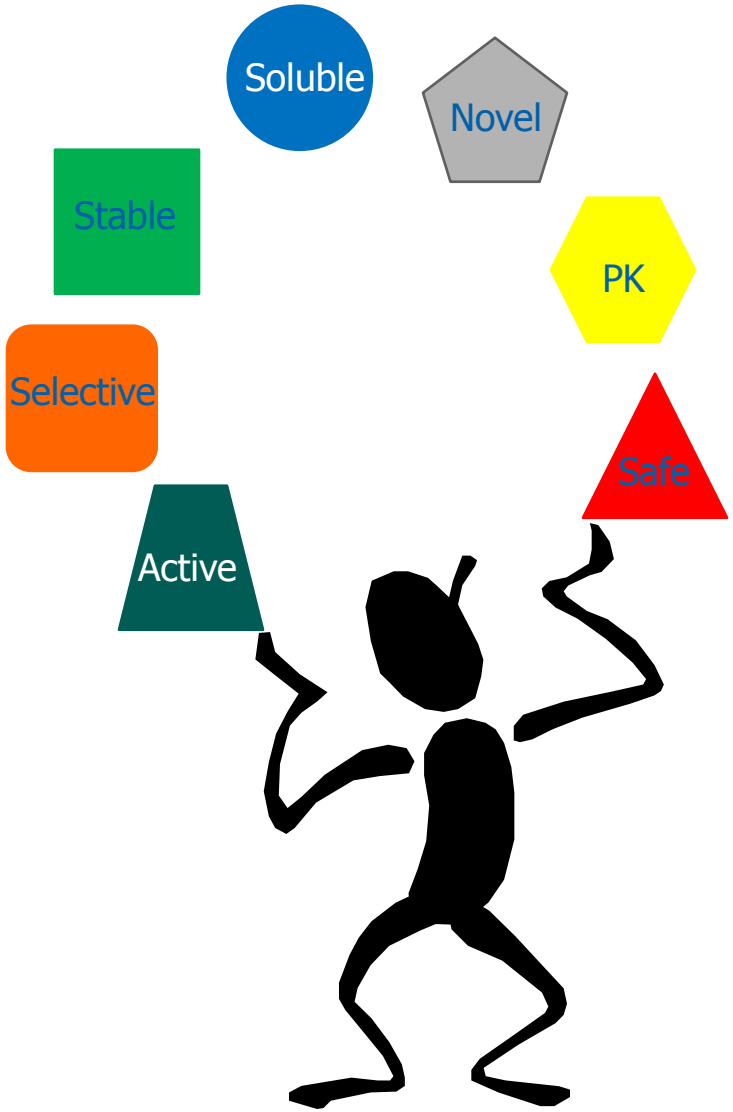
What when we found hit molecule?



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Drug for patients

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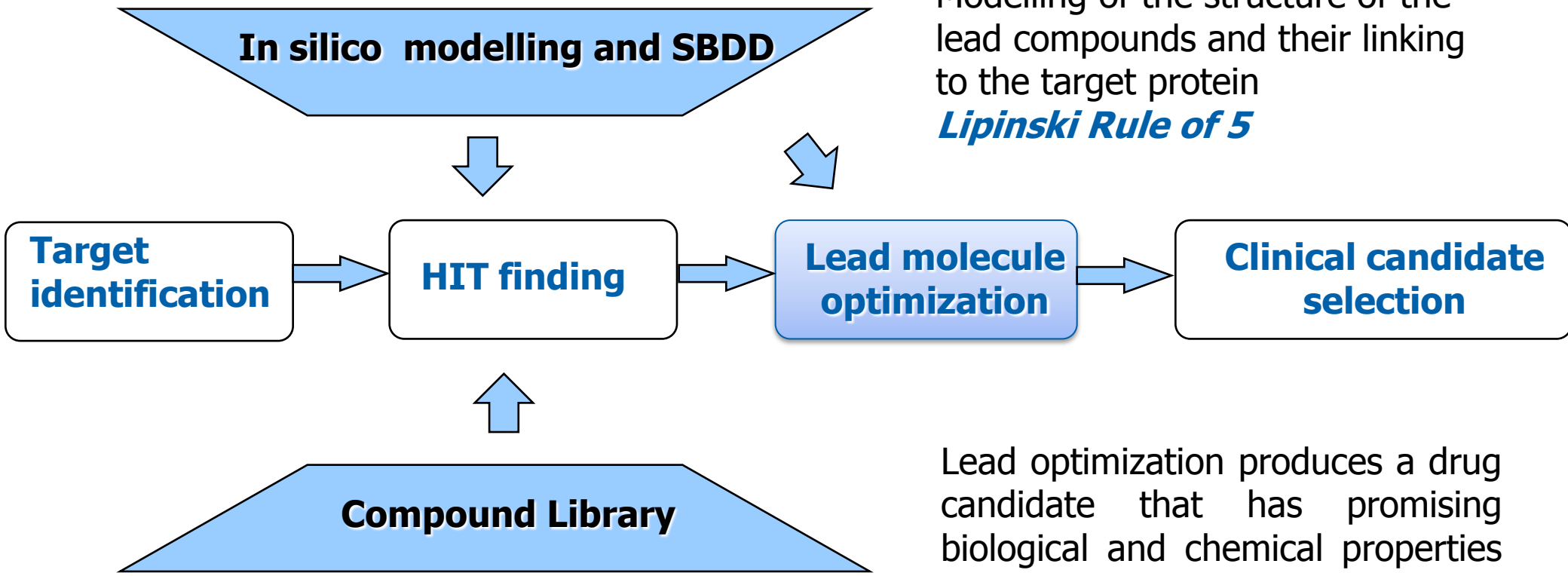
Modern rational approach



Modelling of the structure of the lead compounds and their linking to the target protein

Lipinski Rule of 5

Lead optimization produces a drug candidate that has promising biological and chemical properties for the treatment of a disease!

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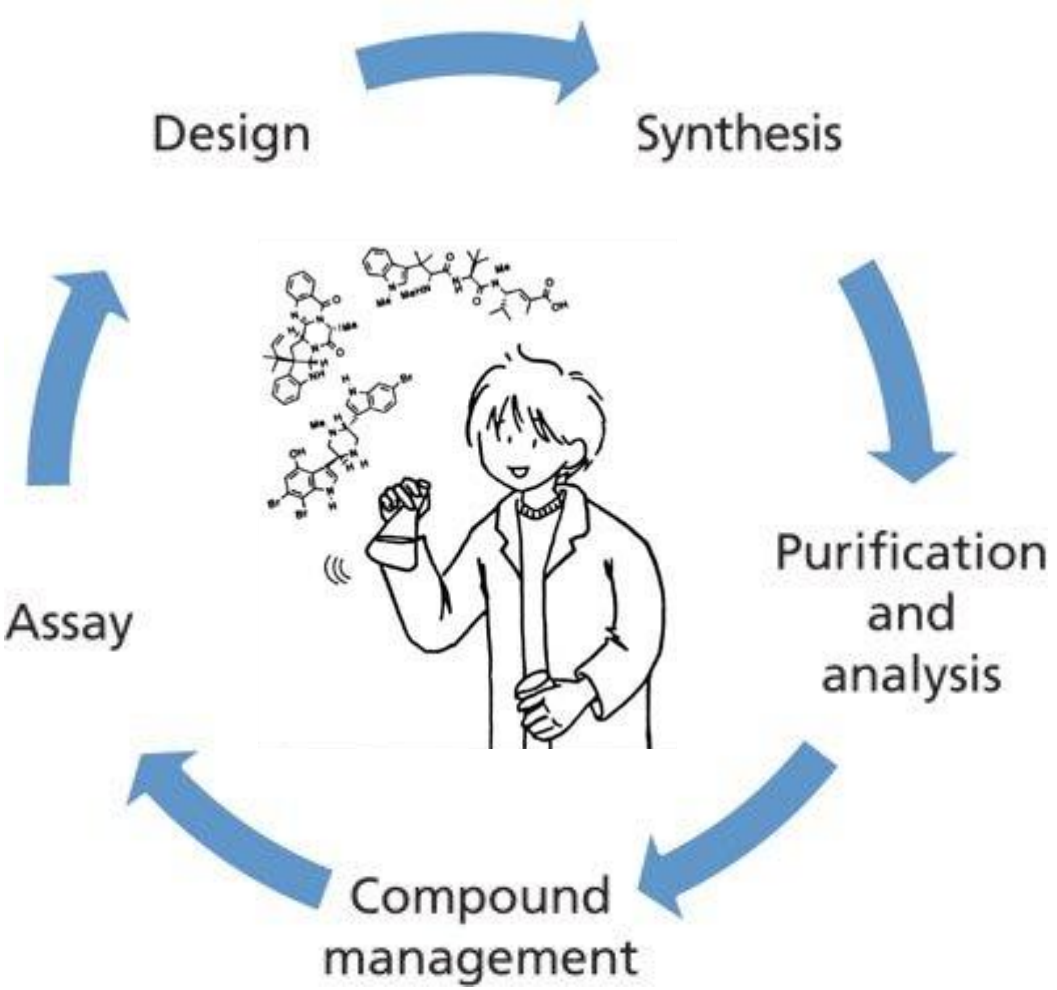
Drug discovery cycles in Fidelta



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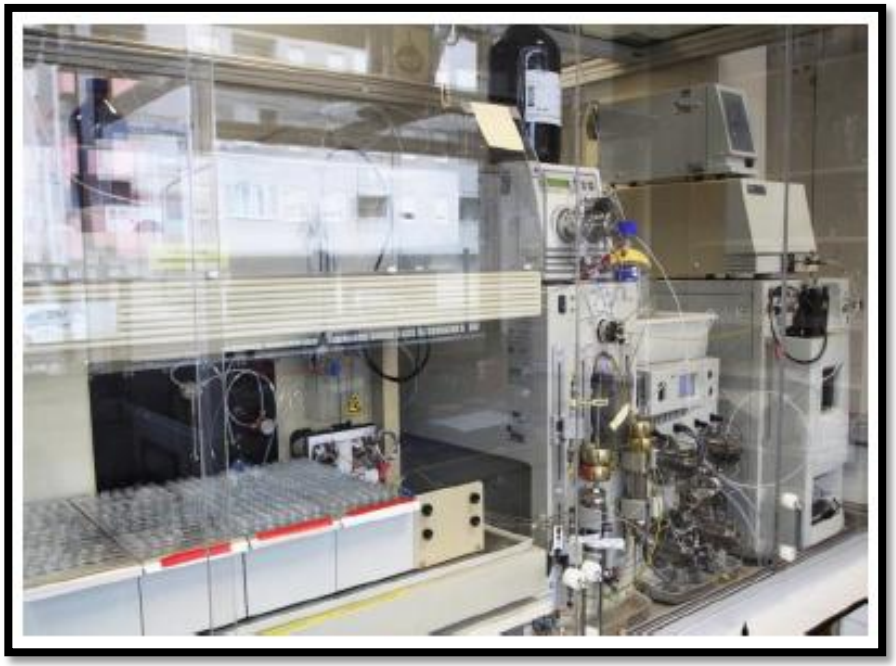
Synthetic and medicinal chemistry



- Synthesis (traditional, flow, libraries, MW, scale up)
- Purification
- Identification and structure, characterization

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Biological activity

- Biochemical assays on various protein classes delivered by different screening technologies (absorbance, radioactivity, luminescence and fluorescence) supported by assay development, optimization and validation

- Disease relevant *in vitro* assays

(in biochemistry, cell biology, microbiology, molecular biology)

- Access to and assays in human disease tissue
- *In vivo* animal models (models of inflammation, infection, metabolic diseases and oncology)
- Translational approaches and biomarker discovery and evaluation.

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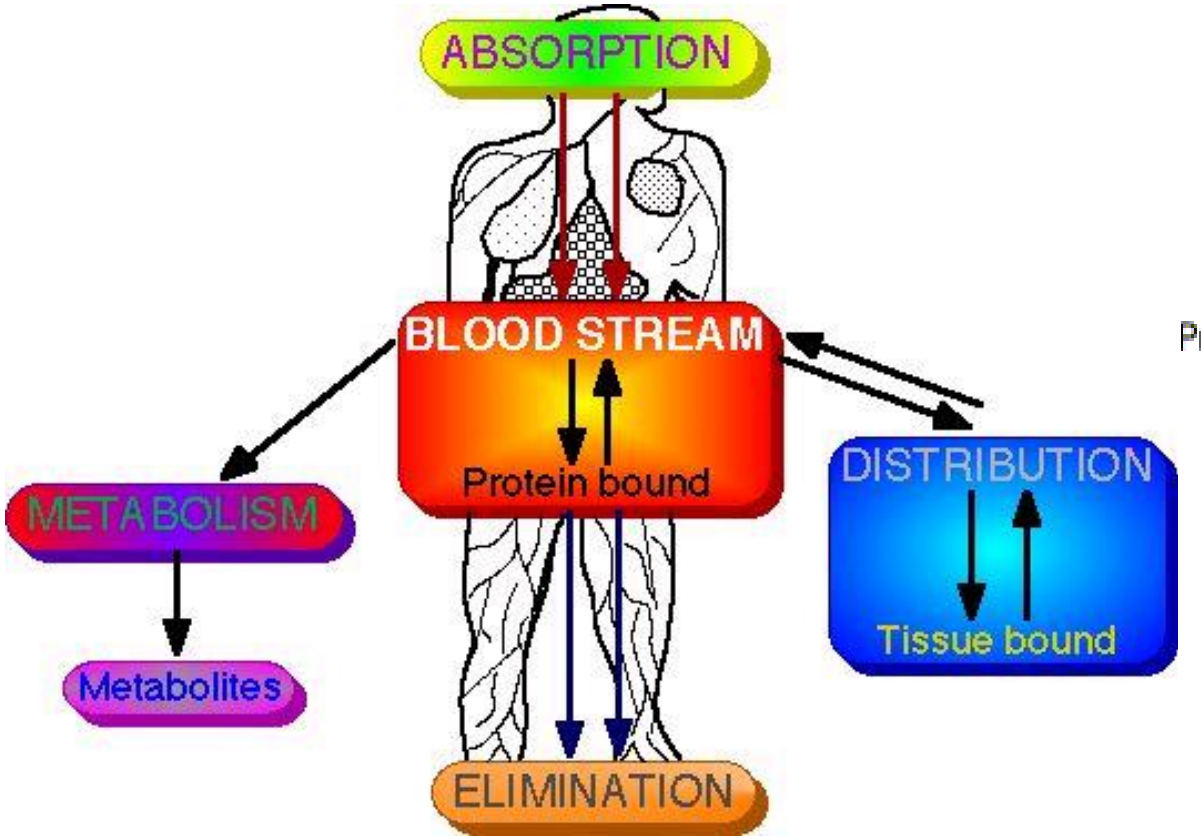
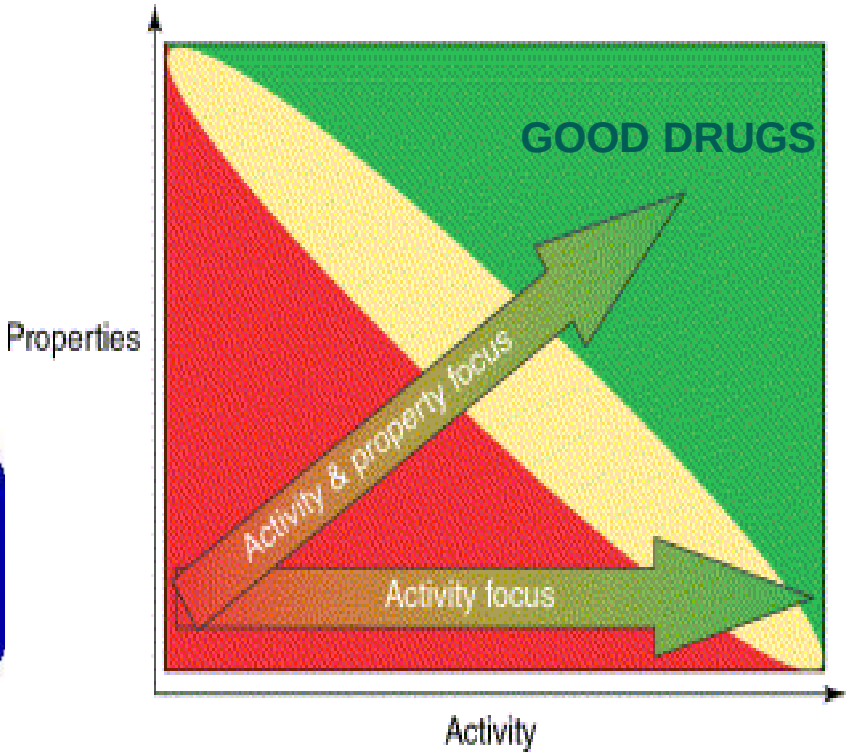
Pharmacokinetics
What is ADME? Where it happens?





Kerns EH, Di L., Drug Discovery Today. 2003 Apr 1;8(7):316-23.

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In vitro ADME

Permeability

- Cellular permeability
  - MDCK, MDCK-MDR1
  - Caco-2
- Artificial membranes
  - PAMPA
  - Skin PAMPA

Binding

- Plasma protein binding
  - Equilibrium Dialysis
  - Ultrafiltration
- Blood Partitioning
- Tissue Binding
- Microsomal binding

DDI

- Inhibition
  - CYP450 direct inhibition & MDI (recombinant, HLM)
- Reactive metabolites
  - Glutathione trapping

Solubility

- Kinetic solubility
- Thermodynamic solubility
  - pH
  - SGF, FeSSIF

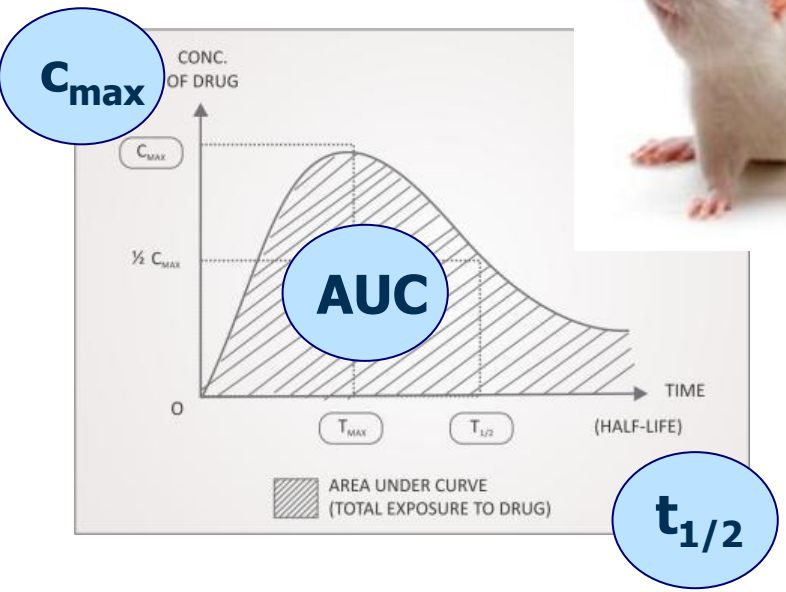
Metabolic Stability

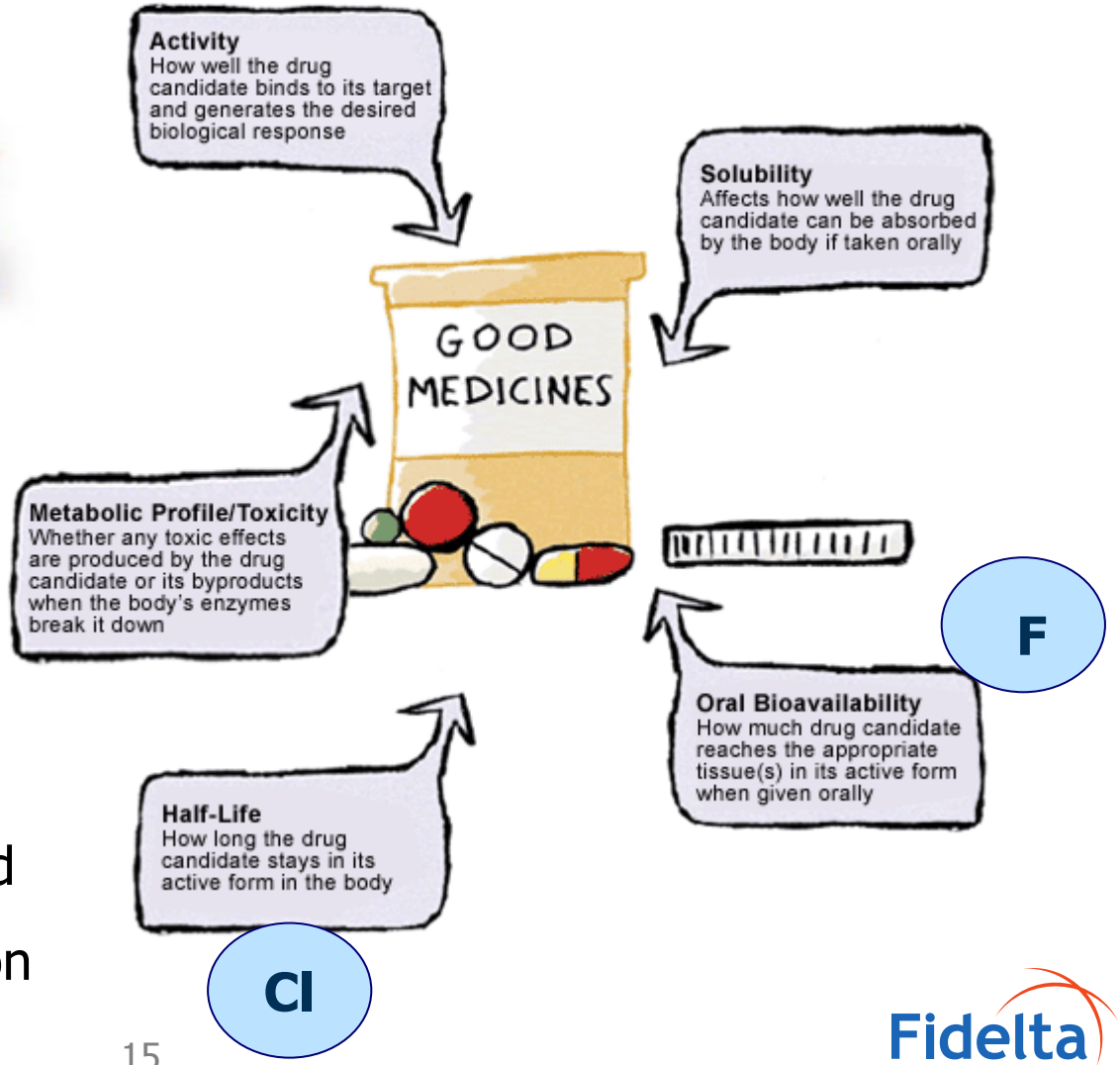
- Microsomes, S9, Hepatocytes
- Recombinant enzymes
- Plasma and blood
- SGF, FeSSIF

Metabolite Profiling & ID

- Aldehyde Oxidase
- Reaction Phenotyping
- Metabolite Identification
  - Interspecies Profiling

In vivo pharmacokinetics





- In house:
  - >50 *in vivo* models established
  - various routes of administration

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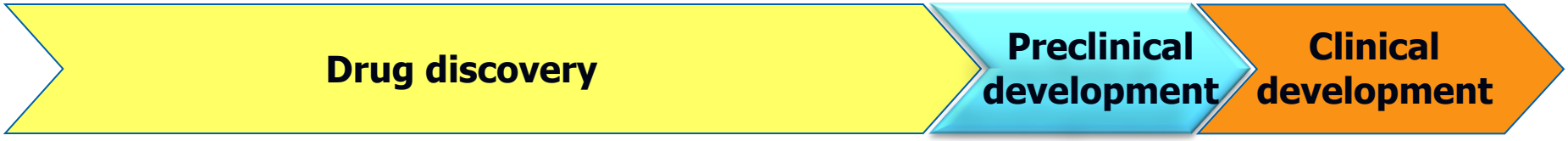
Preclinical development



- Usual time duration: 1.5 years
- Performed on animal models
- The aims of preclinical testing:
  - to evaluate a drug's safety, efficacy, and potential toxicity in animal models
  - to prove that a drug is not carcinogenic, mutagenic or teratogenic
  - result of work at this stage is a pharmacological profile of the drug
  - PK / PD model
  - Formulation

Clinical development

	Phase 1	Phase 2	Phase 3
Years	1-1.5	2	3-3.5
Test population	20-80 healthy volunteers	100-300 patients	1000-3000 patients
Purpose	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reaction for long term use

Regulatory approval

- Usual time duration: 1-2 years
- Submission of full date and review by regulatory agencies

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Finally
How to decide what to work on?

Differentiate your product

Differentiated positioning begins on factors established in clinical trials

- **Efficacy** and **safety**
- **Unmet needs** (no effective therapy available, current drugs sub-optimal)
- **Target patient population** (personalised medicine, gene therapy)