Quo vadis Drug Discovery

Donatella Verbanac, Dubravko Jelić,

Sanja Koštrun, Višnja Stepanić, Dinko Žiher

PLIVA - Research Institute, Ltd.

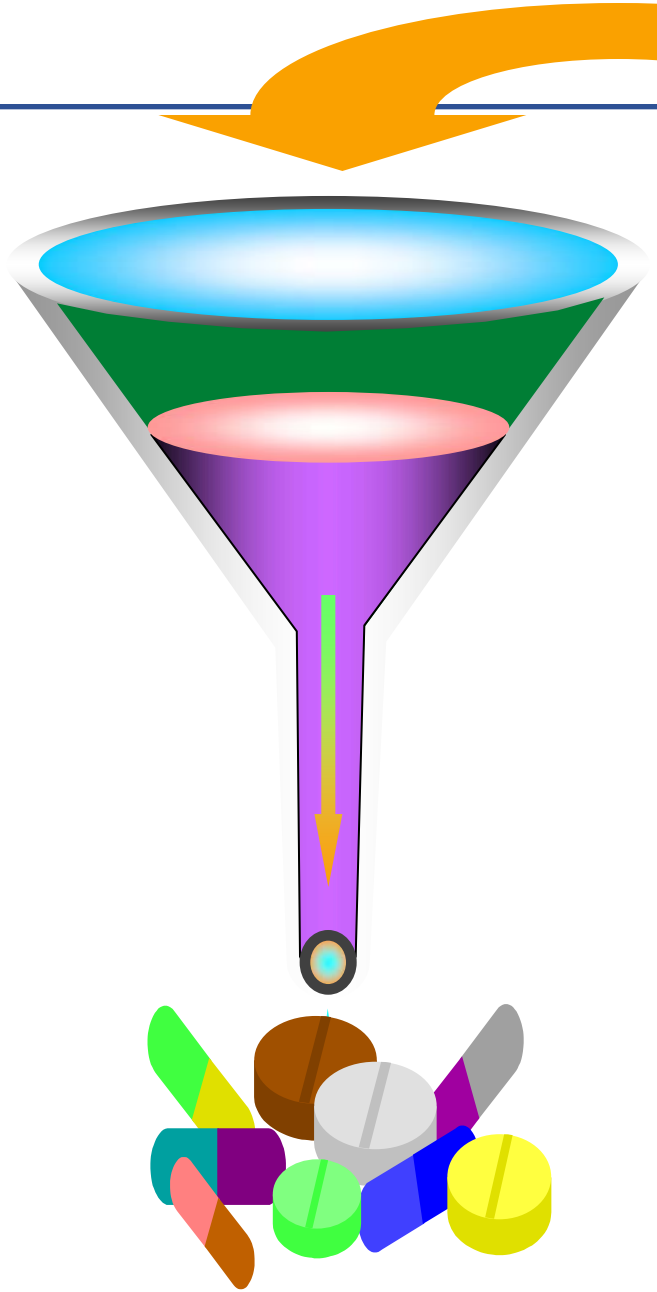
Prilaz baruna Filipovića 29, 10000 Zagreb, CROATIA

The Pharmaceutical Industry is Under Pressure !!!

Success is now measured by the number of >$1 billion drugs you have

Pressure has increased due to investor expectations and competitors successes

Many drugs lost or are losing patent protection between 2001 and 2005



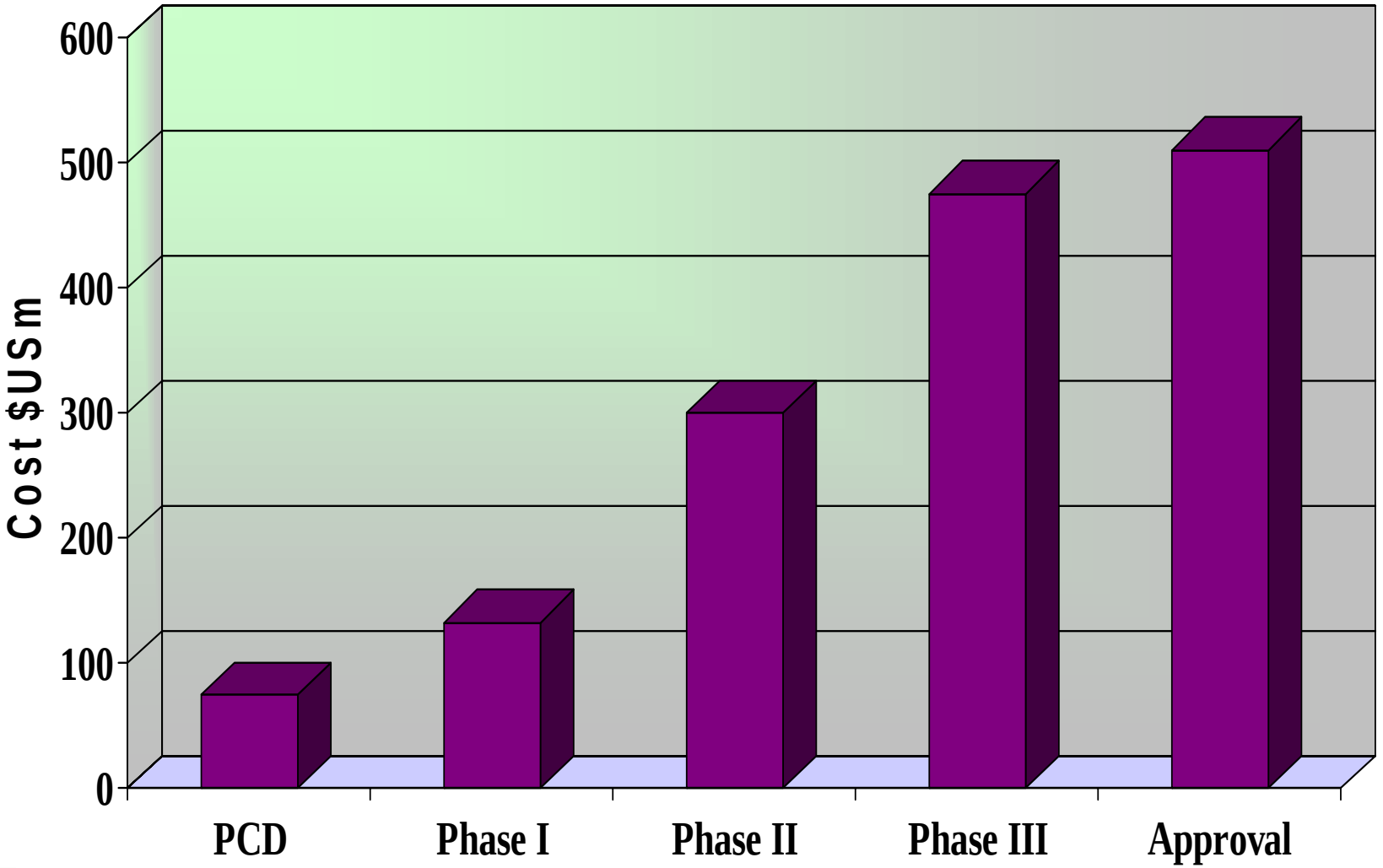
investment

3 NCEs/yr promised by leading companies

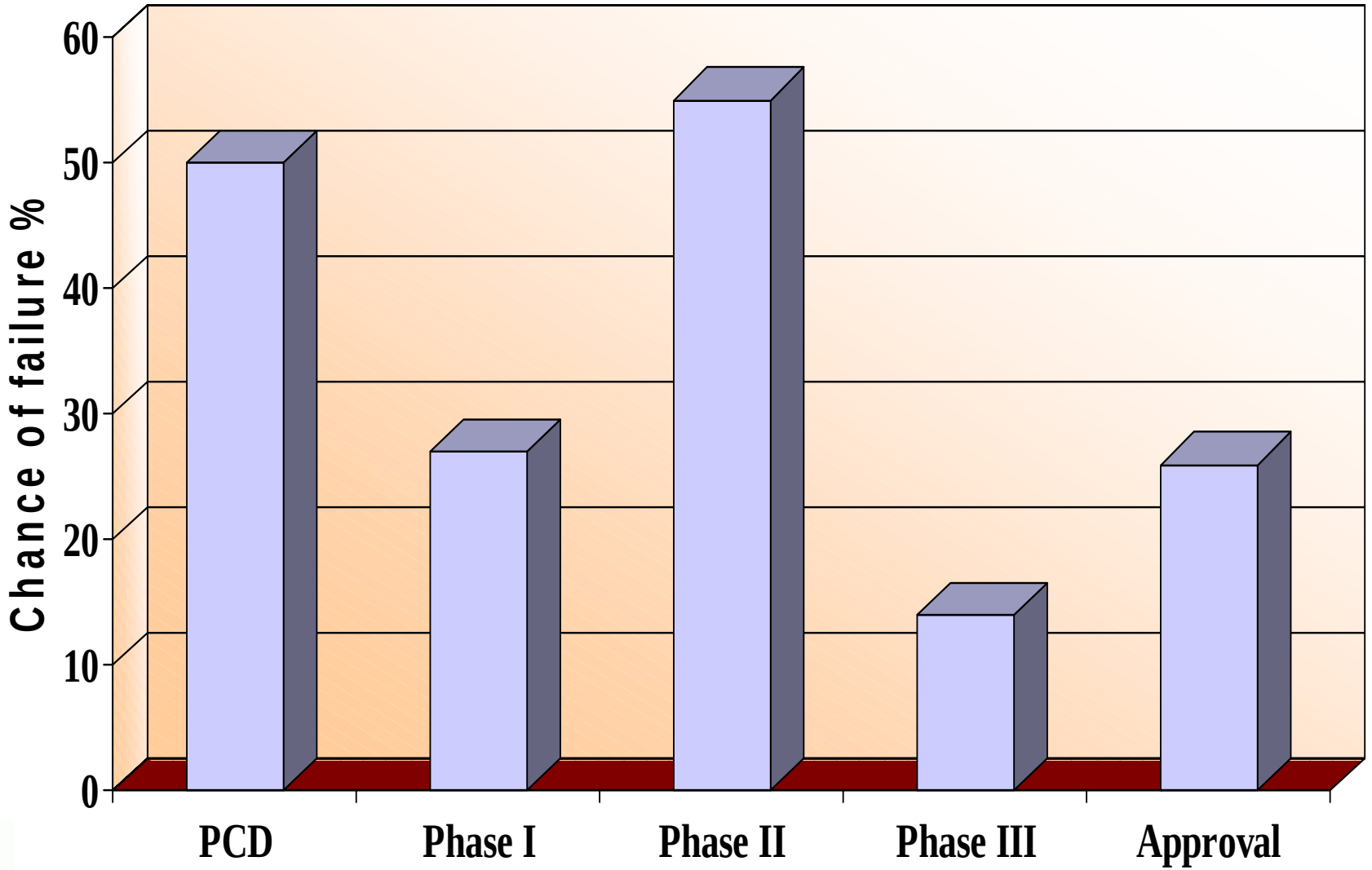
COST is >$600 MM/drug

Only 1 of 3 drugs recoup development cost

Cumulative R&D Spend



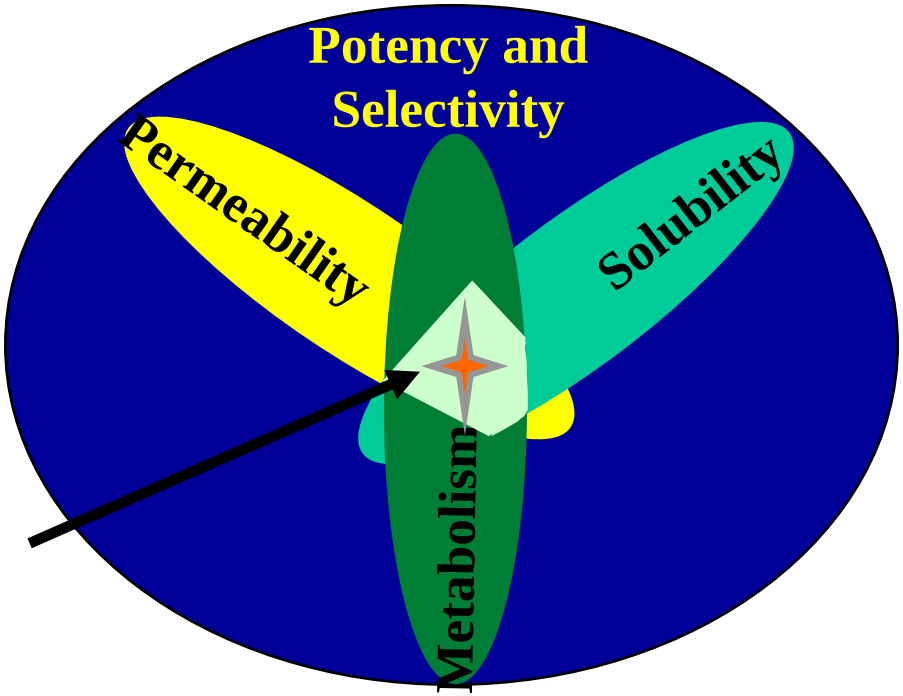
Attrition Rates



Why compounds fail in development

- Toxicity, permeability, solubility
- Pharmacokinetics
- Drug delivery
- Efficacy, adverse effects in humans
- Commercial
- Patent/ownership

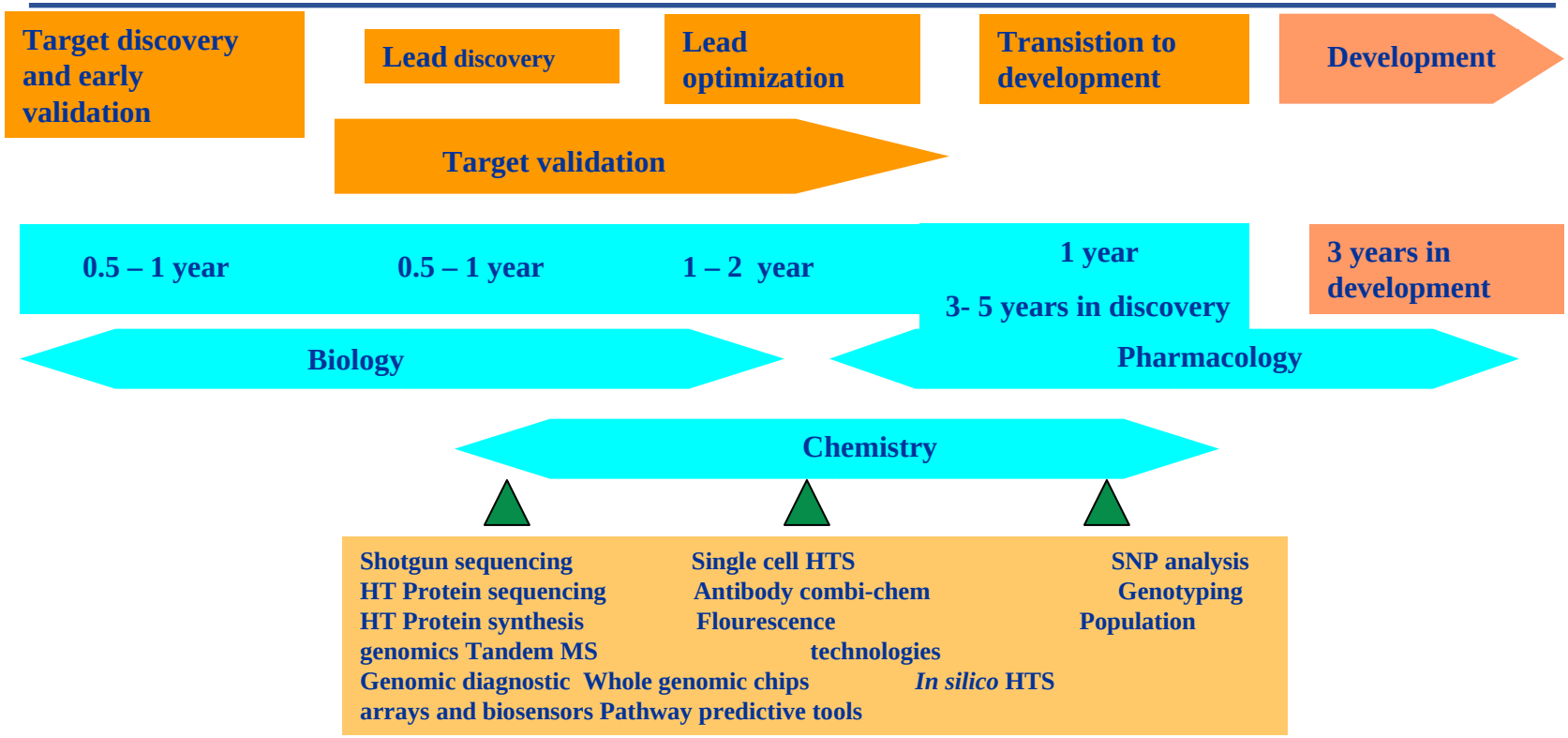
Generate data earlier to support decision making



Efficacy
Selectivity
ADME
Toxicity

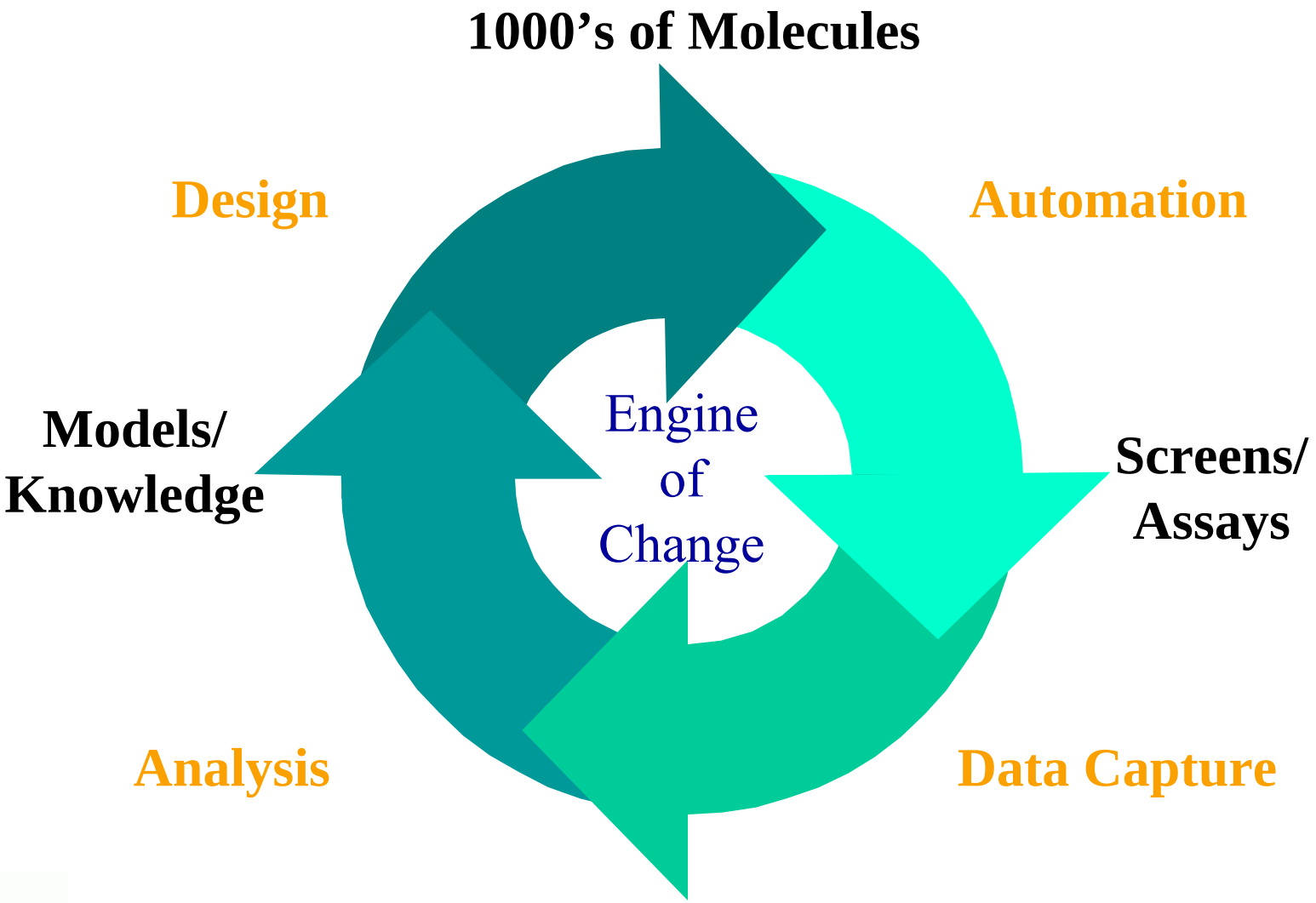
Target selection → **Lead identification** → **Lead optimization** → **Pre-clinical** → **Full development**

Evolving approach

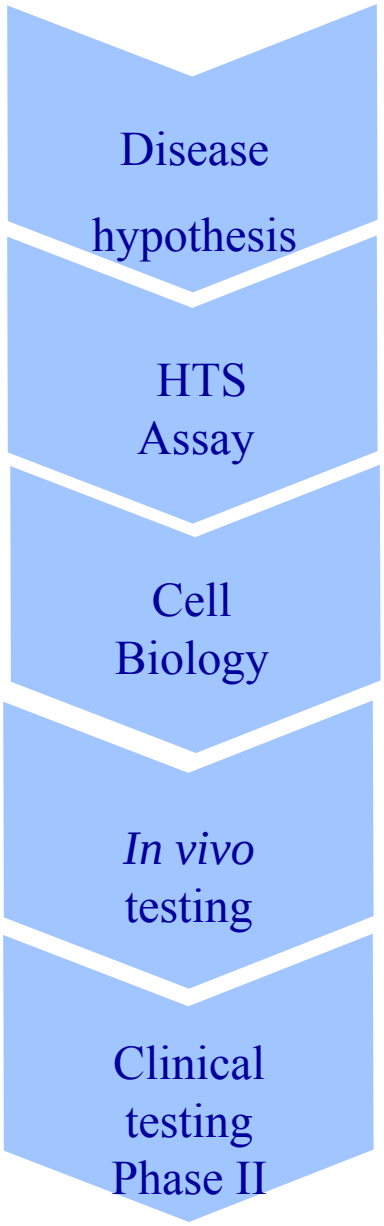


Traditional approach

The Discovery of New Medicines

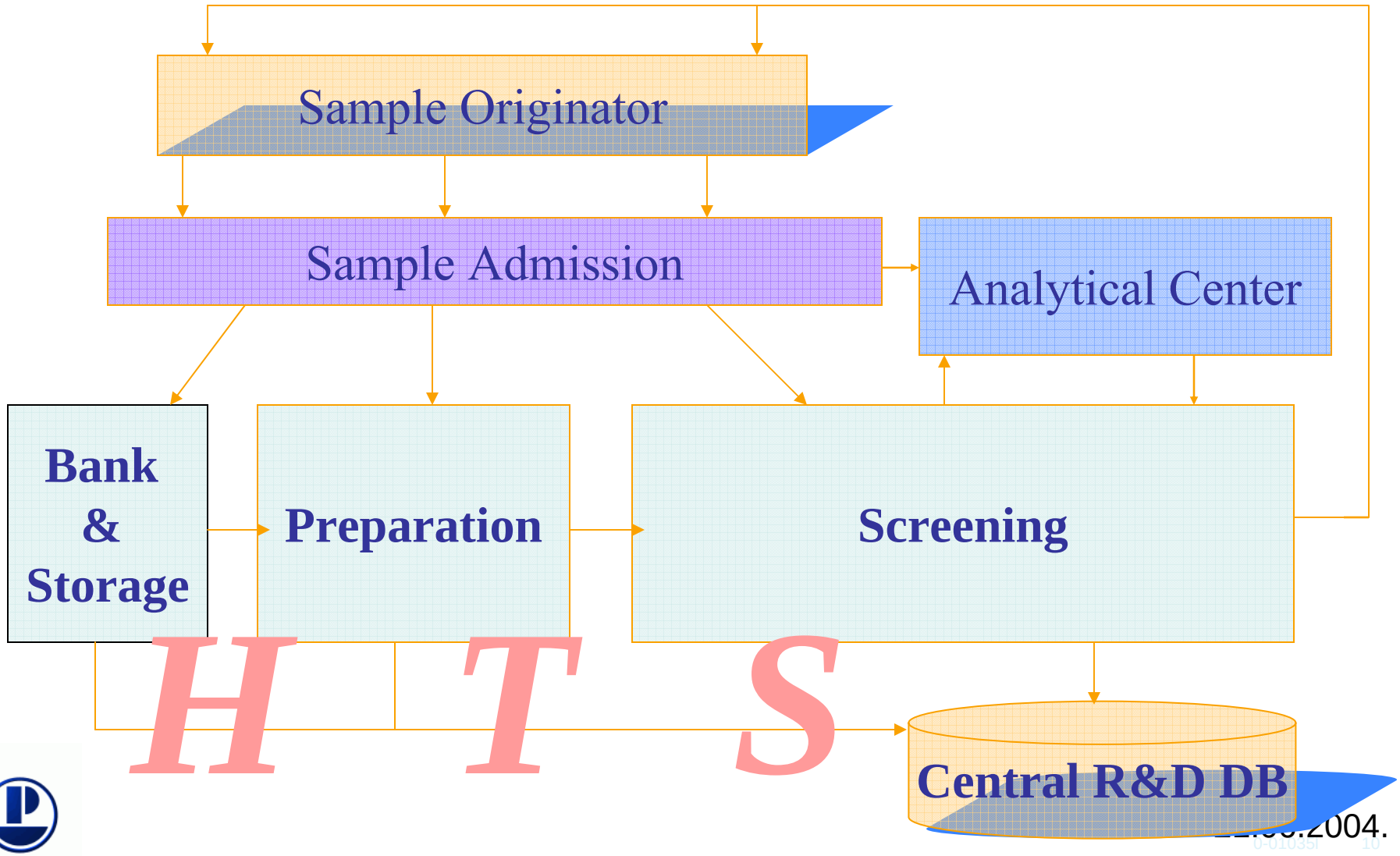


Biological assays as gateways - increasing sophistication and cost

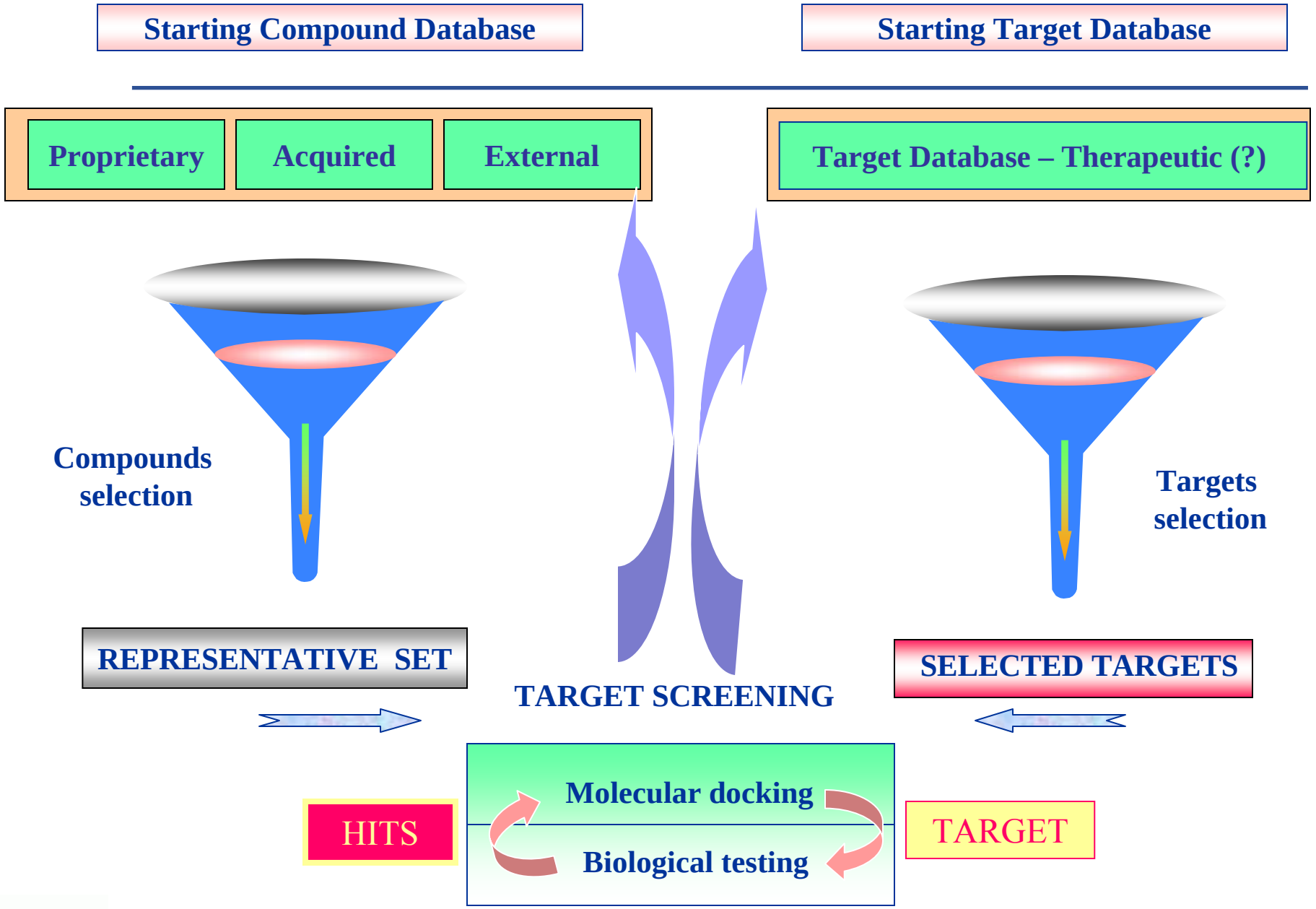


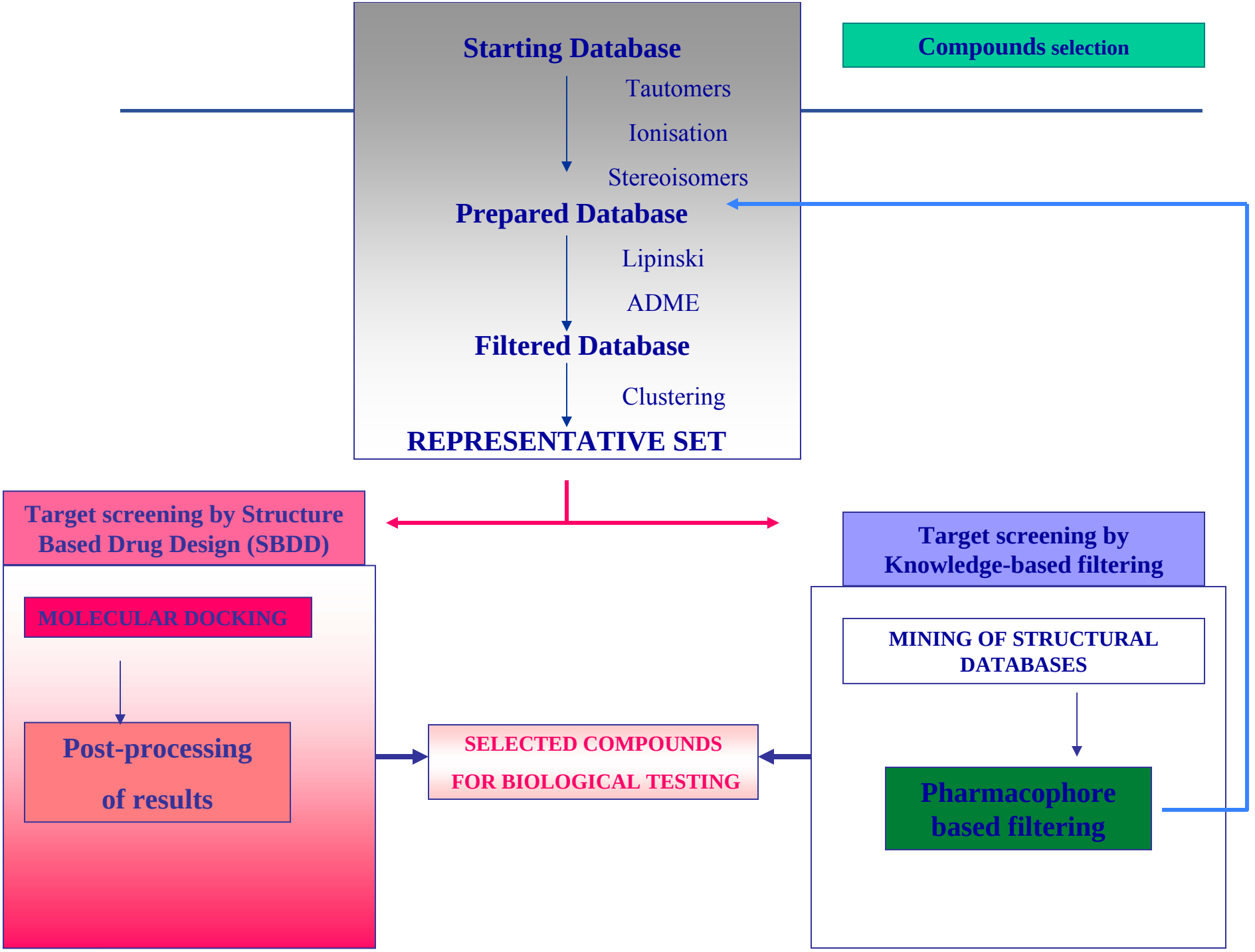
	Cost	Stage	Success?
Disease hypothesis			
HTS Assay	$ 3	Positives	?
Cell Biology	$ 300	Hits	1/3
In vivo testing	$ 30’000	Leads	1/3
Clinical testing Phase II	$ 3’000’000	Candidates	1/3

HTS Unit – a central part of the process

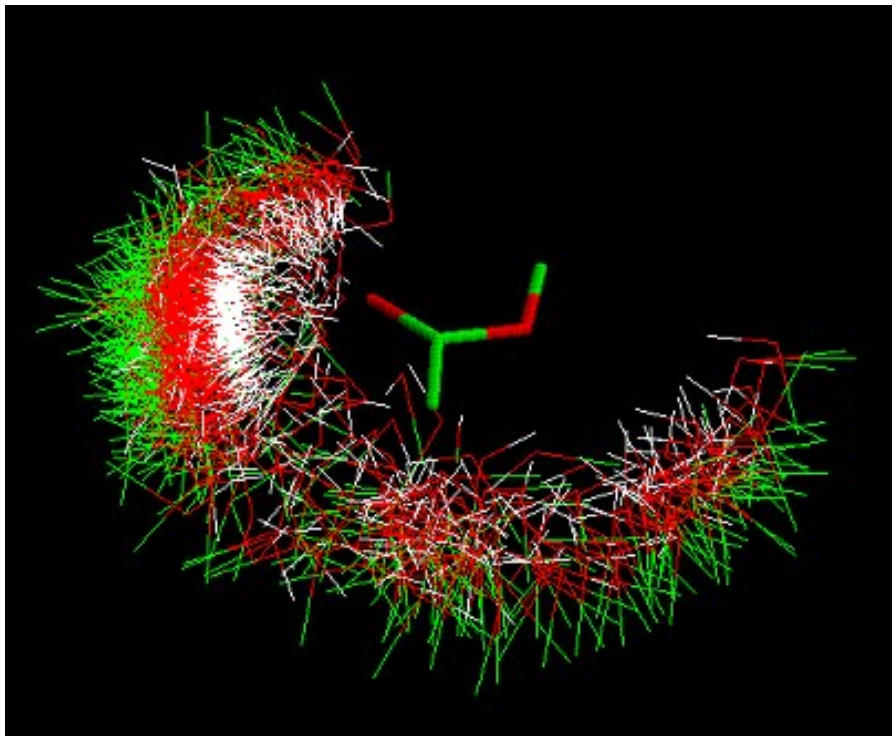


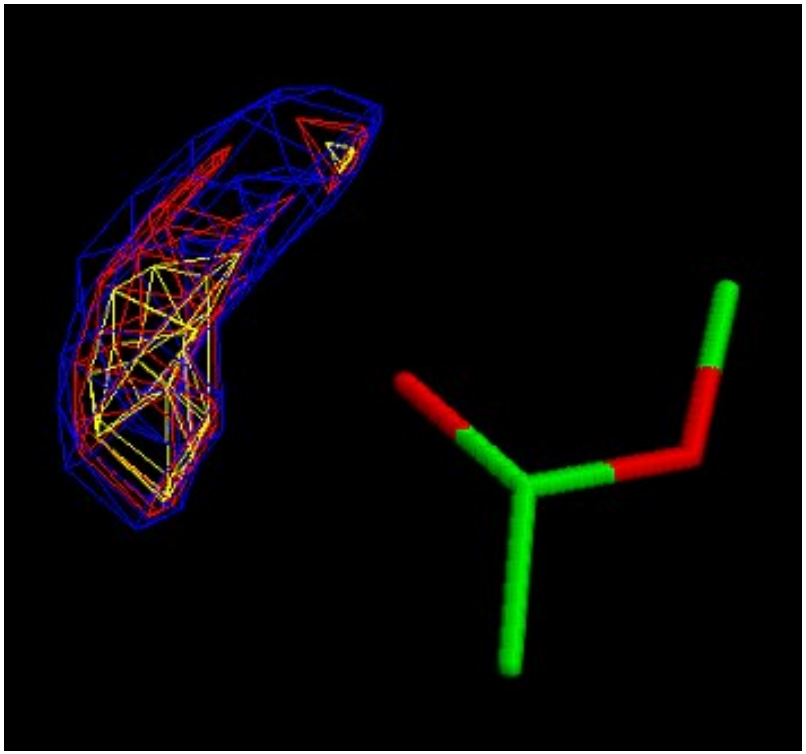
Computer modeling


Starting Compound Database
Starting Target Database
Proprietary
Acquired
External
Target Database – Therapeutic (?)
Compounds selection
Targets selection
REPRESENTATIVE SET
TARGET SCREENING
SELECTED TARGETS
Molecular docking
Biological testing
HITS
TARGET


Starting Database
Tautomers
Ionisation
Stereoisomers
Prepared Database
Lipinski
ADME
Filtered Database
Clustering
REPRESENTATIVE SET
Compounds selection
Target screening by Structure Based Drug Design (SBDD)
MOLECULAR DOCKING
Post-processing of results
Target screening by Knowledge-based filtering
MINING OF STRUCTURAL DATABASES
Pharmacophore based filtering
SELECTED COMPOUNDS FOR BIOLOGICAL TESTING

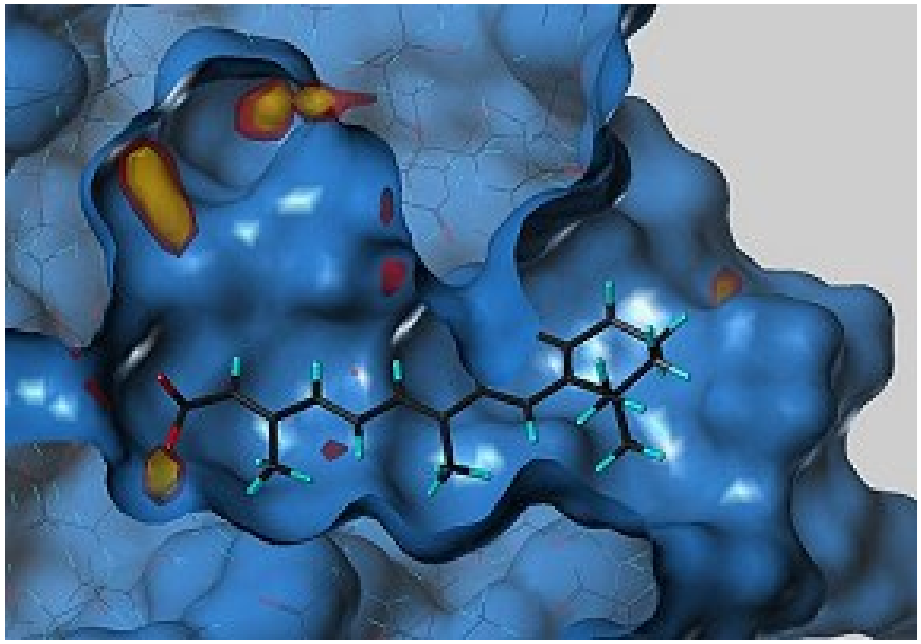
IsoStar

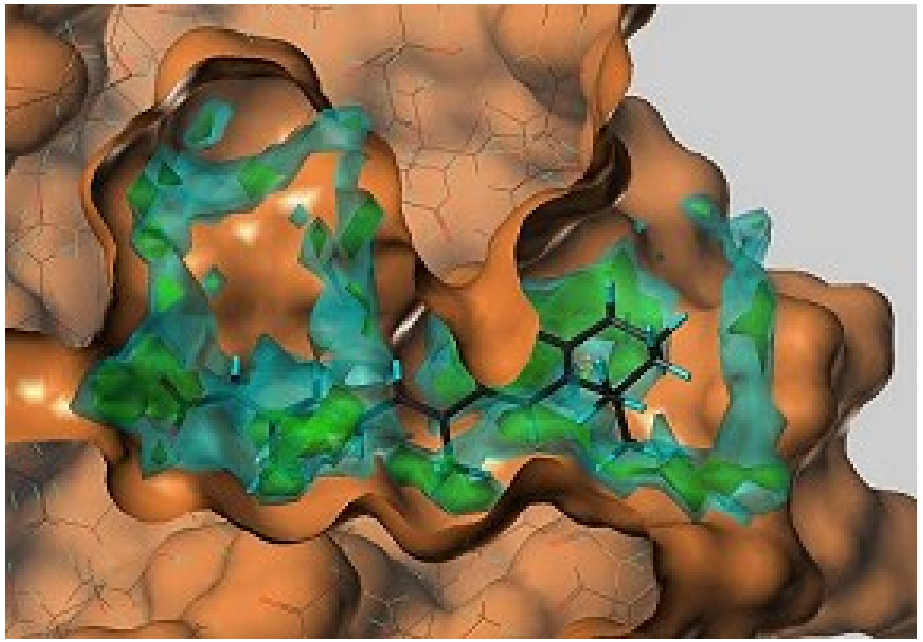




IsoStar shows intermolecular interactions.
Developed from CCDB & PDB.
Exploring the most probable interactions for selected molecules.

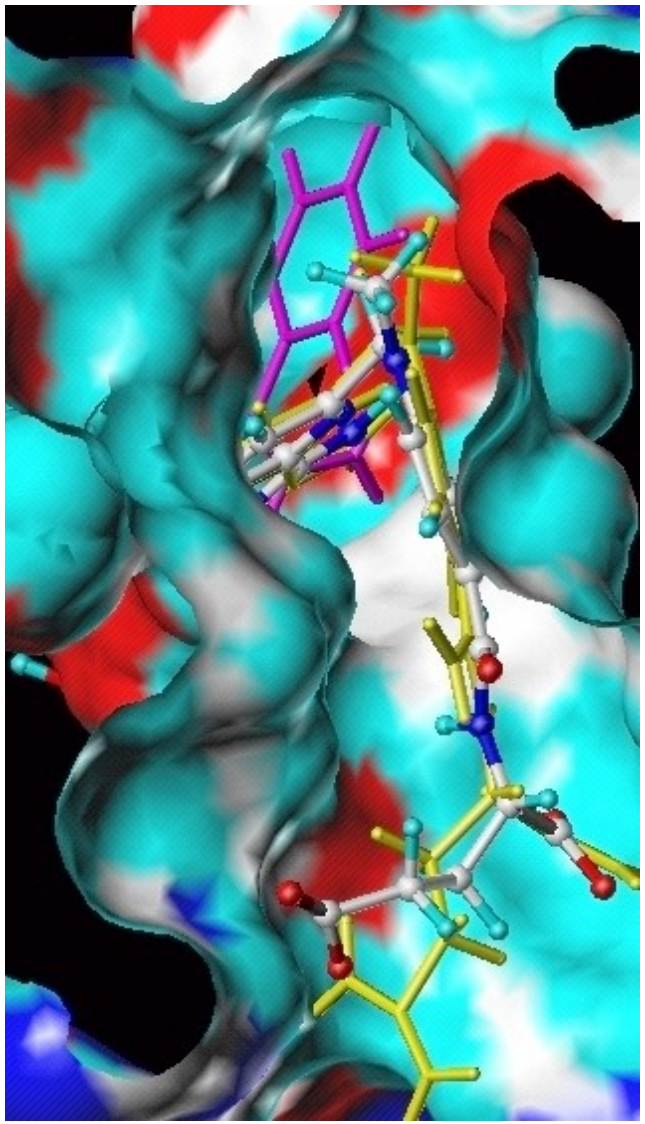
SuperStar





SuperStar PDB can provide insight look into the binding site.
Useful for the pharmacophore definition.
Important tool for the preparation of 3D virtual screening.

Structure based virtual screening



- Standard docking-example in computational biology.
- DHFR with methotrexate as ligand.
- Prediction of the way of binding.
- Cost reduction, time saving …

Biological screening

Primary and secondary screening

antibacterial (MIC)

enzymatic (EC_{50})

cytotoxicity (IC_{50})

- **Assay design/assay development**
- ***In vitro* assays for activity**
- **Gene expression technology - Microarrays**

Screening request form

PLIVA — *High Throughput Screening Unit* — Research Division

REGISTRATION FORM

SCREENING

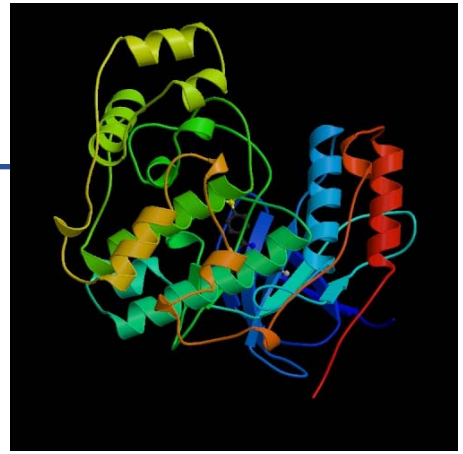
RESEARCHER:	**Phone:**	**Date:**
SIN:	**MT:**	**NO. OF COMPOUNDS:**

PL (SampleID)	BatchID	MW	m/mg	Solvents	Type of testing	Comments

Signature:

CONFIDENTIAL

HTS - Compounds Bank



- Registration of newly synthesized compounds and batches in PLIVA
- Central Depository for all samples
- New compounds acquisition
- Sample preparation for 1º or 2º screening.
- One sample is tested more than once

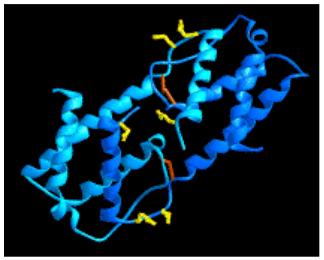
Compounds Bank

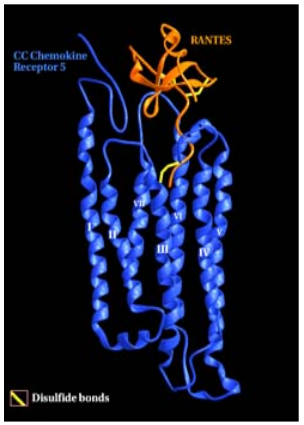
- Chemists give samples in a brown vials
- Compounds are barcoded and stored under GLP conditions (controlled temperature and humidity, in and out documentation,) at 20°C, +4°C, -20°C and/or –80°C (upon stability)
- Chemists have acces to the samples whenever they need them

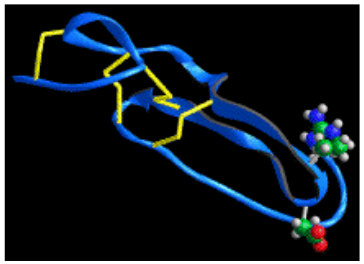
Targets must be evaluated as the product of three factors

Validity of target x **Tractability: ability to manipulate** x **Ability to develop for human use**

Prospecting in the human genome







Protein Therapeutics **Small Molecules**

- Soluble proteins, receptors, antibody targets
- Large binding sites -not suitable for small molecules
- Enzymes, receptors, intracellular targets
- Aiming for oral bio-availability
- Focus chemistry on privileged structures - NCEs

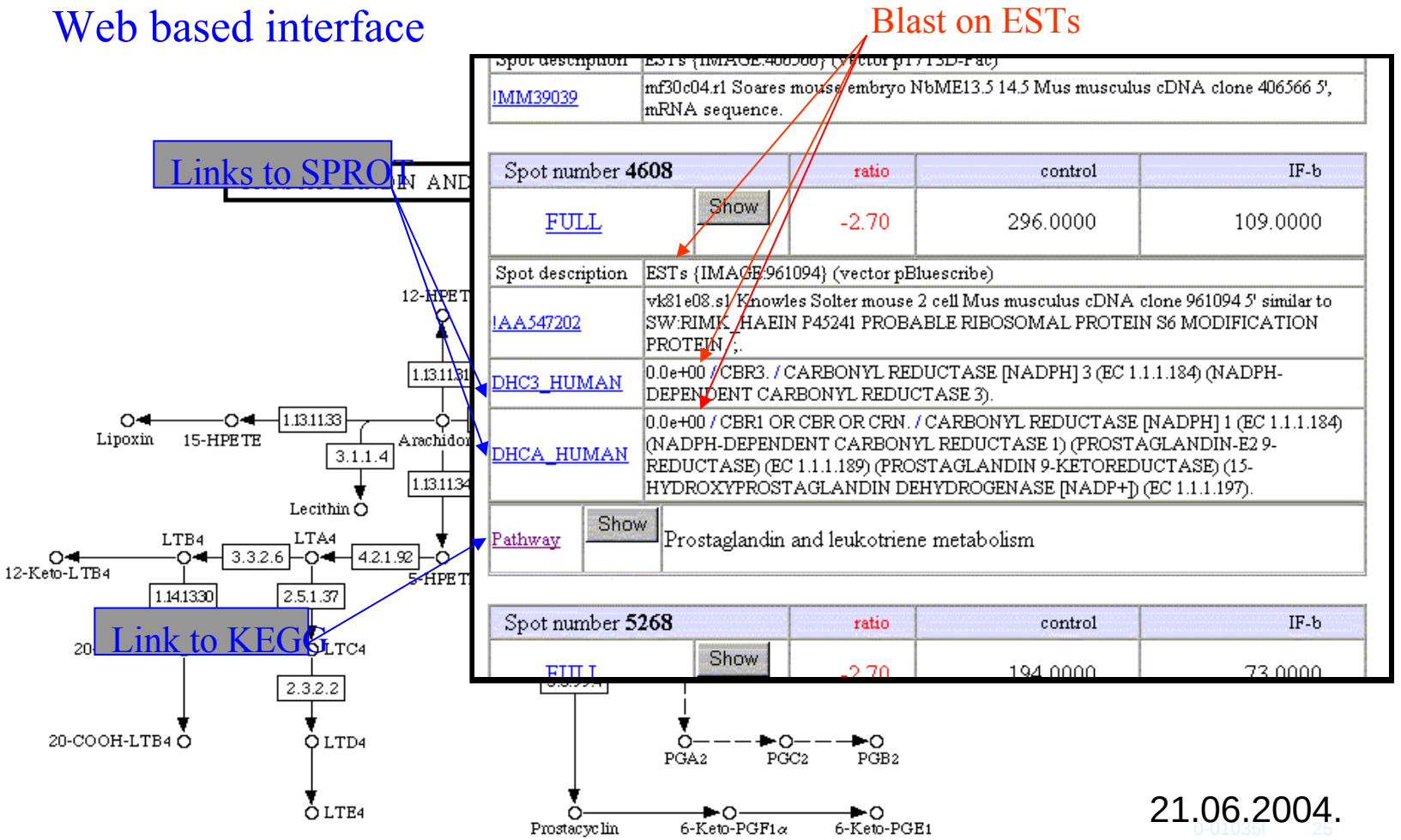
Impact of Genomics and Proteomics Based Drug Discovery

- Over the next decade, minimum 5,000 novel targets will be derived from genomic and proteomic based drug discovery
  - selection of "best targets" will be a critical issue

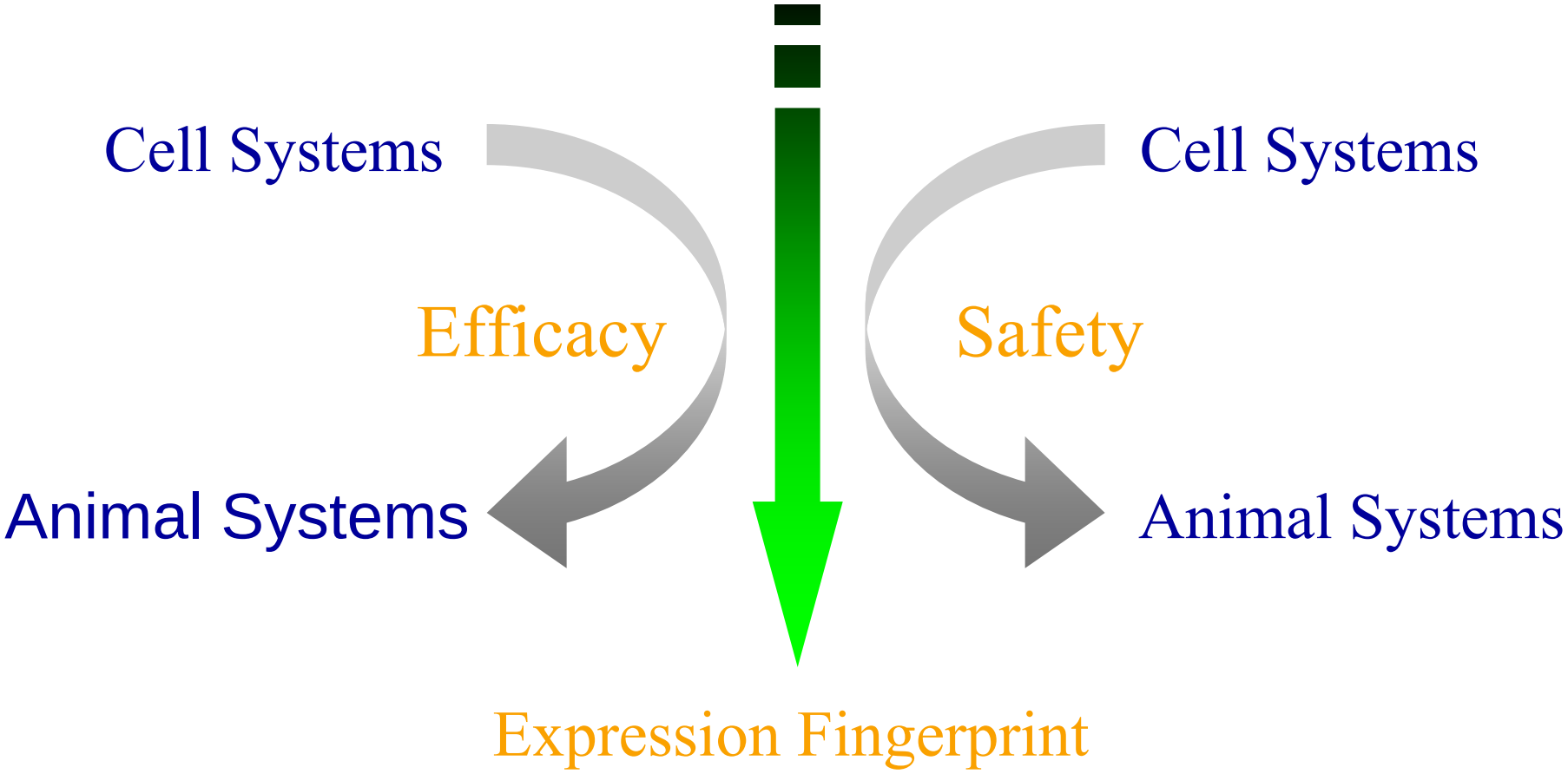
- Most of these will fall into several major classes
  - **Cytokines, Chemokines, and Growth Factors**
    Key Targets for Immunotherapeutic Development
  - **Nuclear Receptors**
    Key Targets for New Pharmaceuticals
  - **Protein Kinases**
    Technologies and Opportunities for Drug Discovery
  - **G protein coupled receptors**
    The Targets of Today's drugs and Tomorrow's Blockbusters
  - **Ion Channels**
    Technology Advances Driving Commercial Opportunities

Bioinformatics helps us to integrate and automate our data analysis

- Key step: Getting the data into the hands of the biologists



Efficacy and Safety Are Flip Sides of the Same Coin

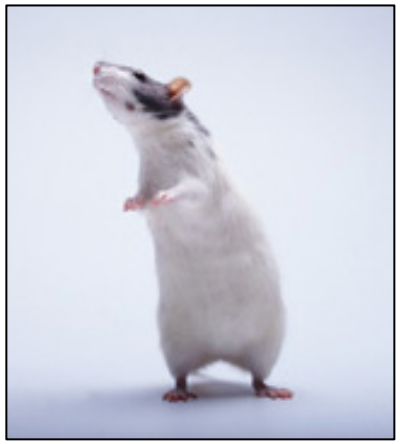


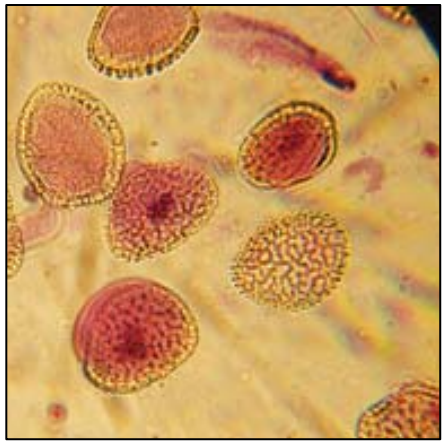
2015: Dream or Reality?

- Innovation moving from *in vivo* to *in vitro* to *in silico*

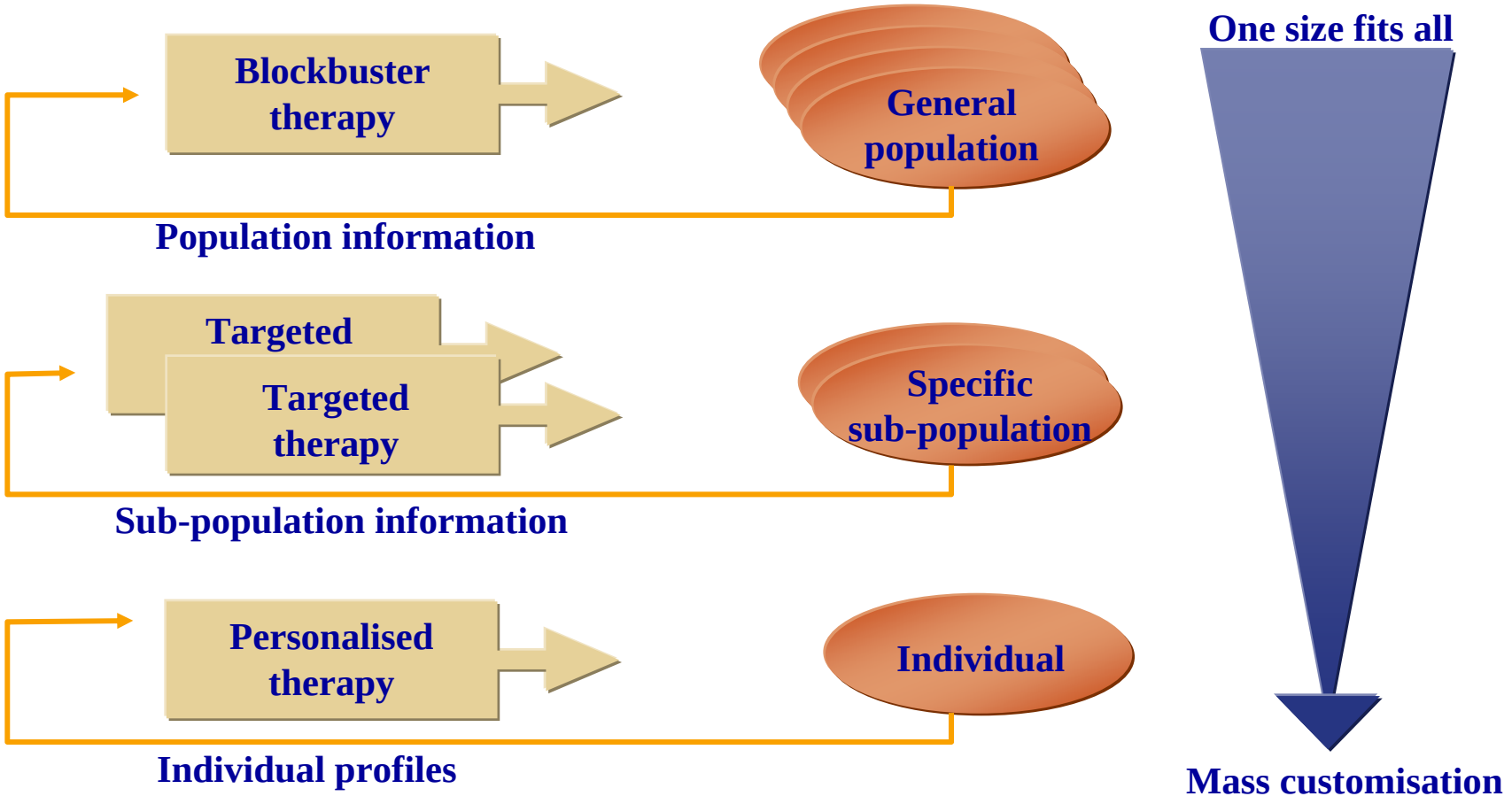
or

- Better integration of *in vitro*, *in vivo* and in *silico*



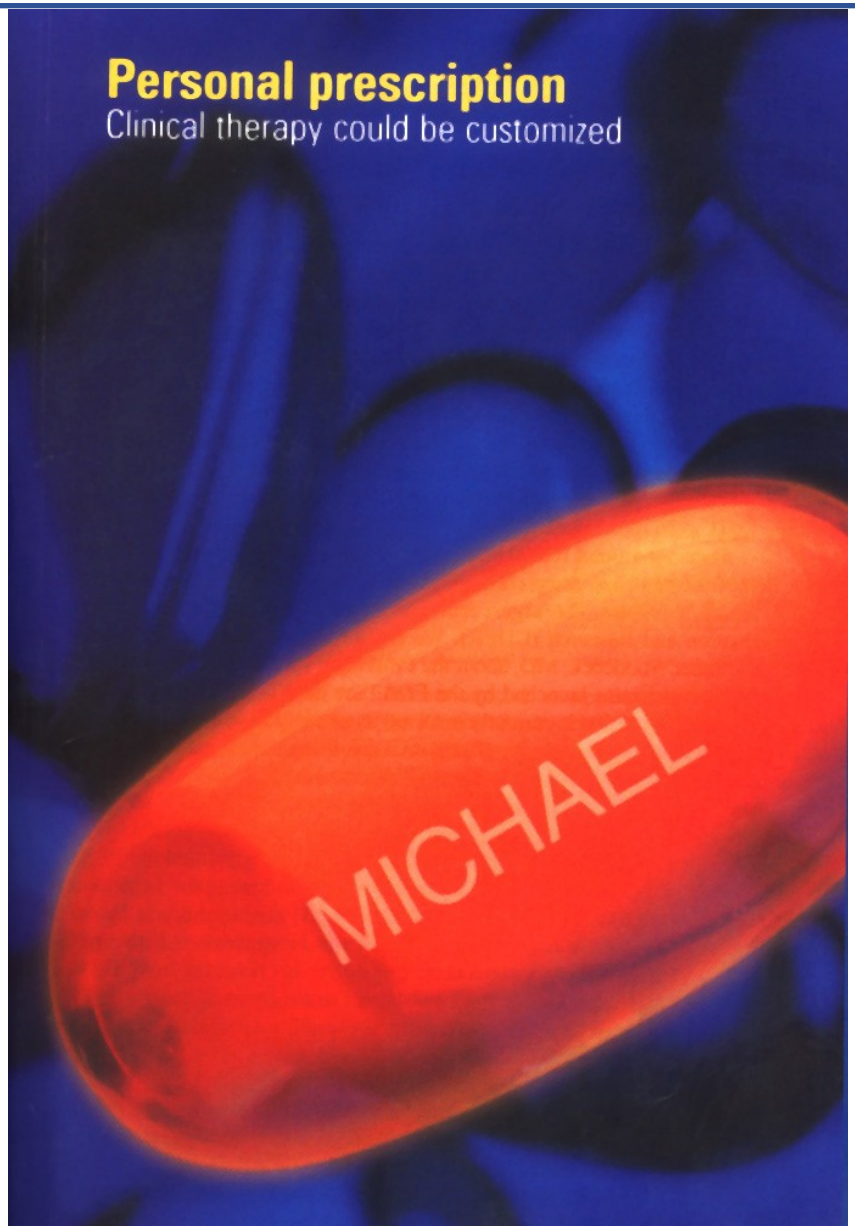


Towards the new model for R&D



Vision

Science fiction or reality?



Acknowledgements

Special thanks to:

Roberto Antolović

Damir Nadramija

Many thanks to: Vesna Mesar

Dražen Radošević

Ivan Bašic

Dražen Borčić