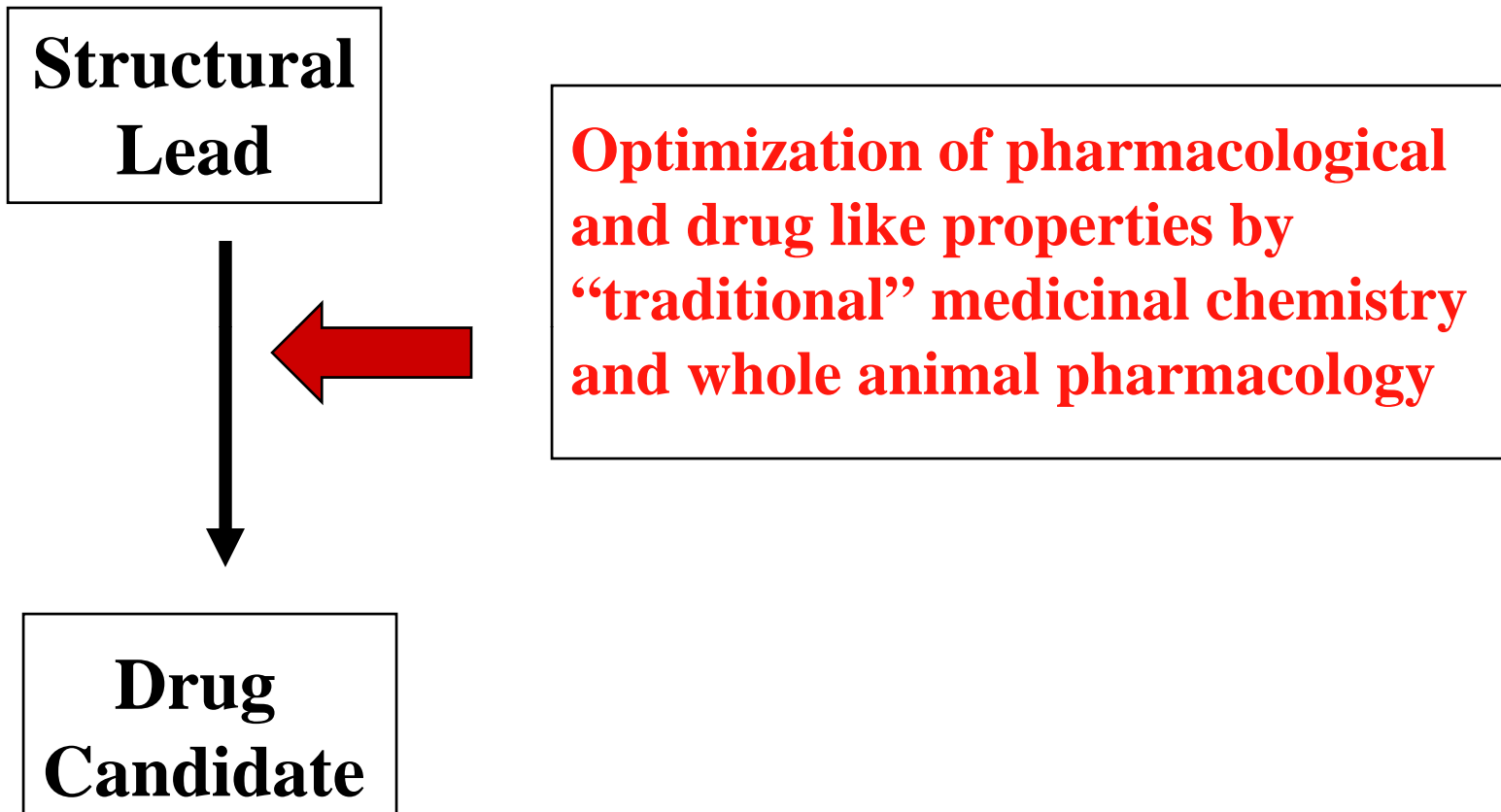


Optimizing the ‘Drug-Like’ Properties of Leads in Drug Discovery

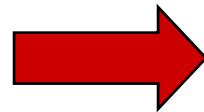
Ronald T. Borchardt
Department of Pharmaceutical Chemistry
The University of Kansas
Lawrence, KS

Drug Discovery Paradigm: 1970s-1980s

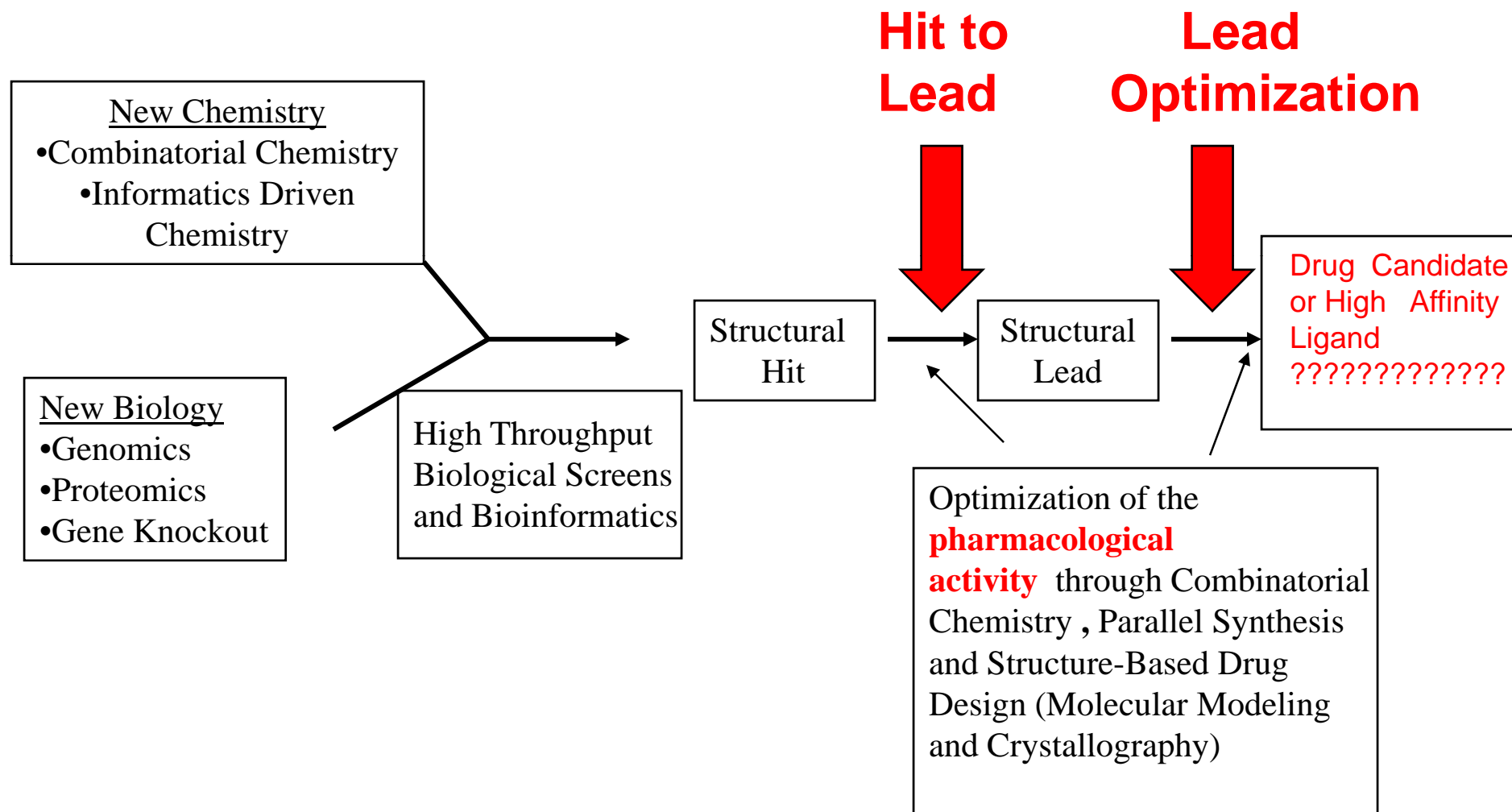


The world of drug discovery changed dramatically
in the late 1980s and early 1990s

Testing for “pharmacological” activity
went from being **whole animal-based** to **cell-
and molecular-based testing.**



Drug Discovery Paradigm of the late 1980s and early 1990's

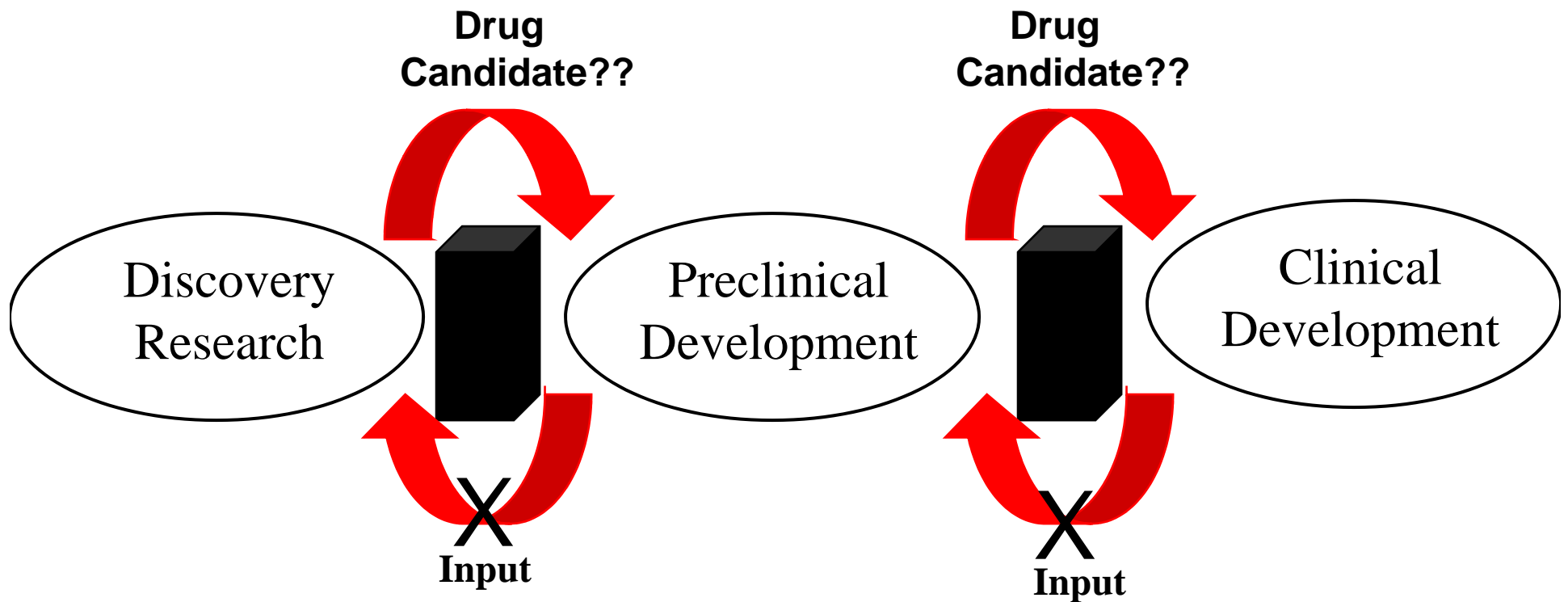


Observation: In the mid-1990s, discovery and development scientists had very different perspectives on the quality of these drug candidates.

Drug Discovery Scientist's Perspective: This new drug design paradigm was generating high quality **drug candidates.**

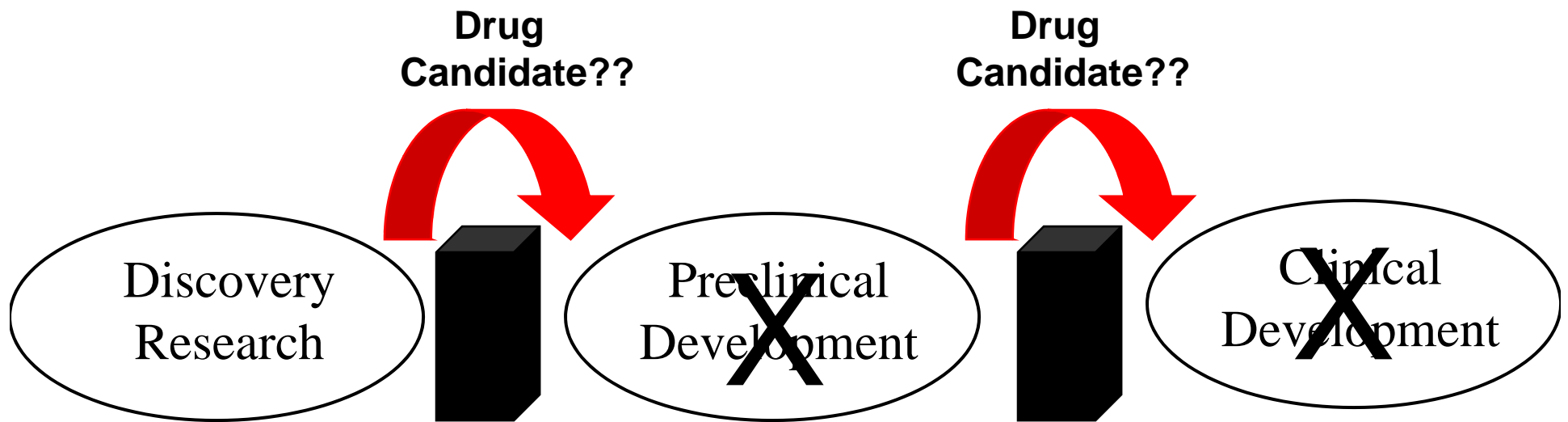
Drug Development Scientist's Perspective: This drug design paradigm was generating **high affinity ligands that were doomed to failure in preclinical and clinical development because they lacked “drug-like” properties.**

Drug Discovery & Development in Big Pharma Companies in the mid-1990s



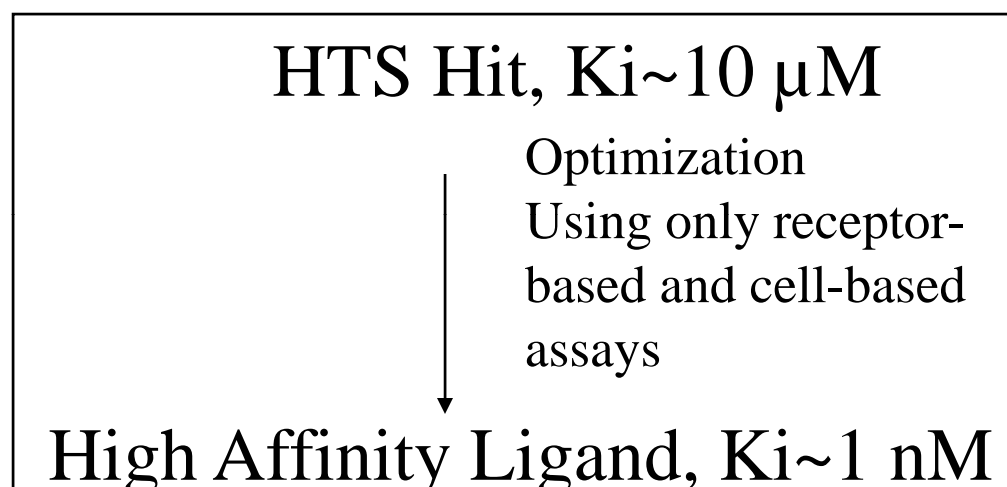
FACT: Because of poor “drug-like” properties, the attrition rate of drug candidates in preclinical and clinical development increased significantly in the 1990s.

Drug Discovery & Development in Biotech Companies and Universities in the mid-1990s



Recipe for Failure!!!!

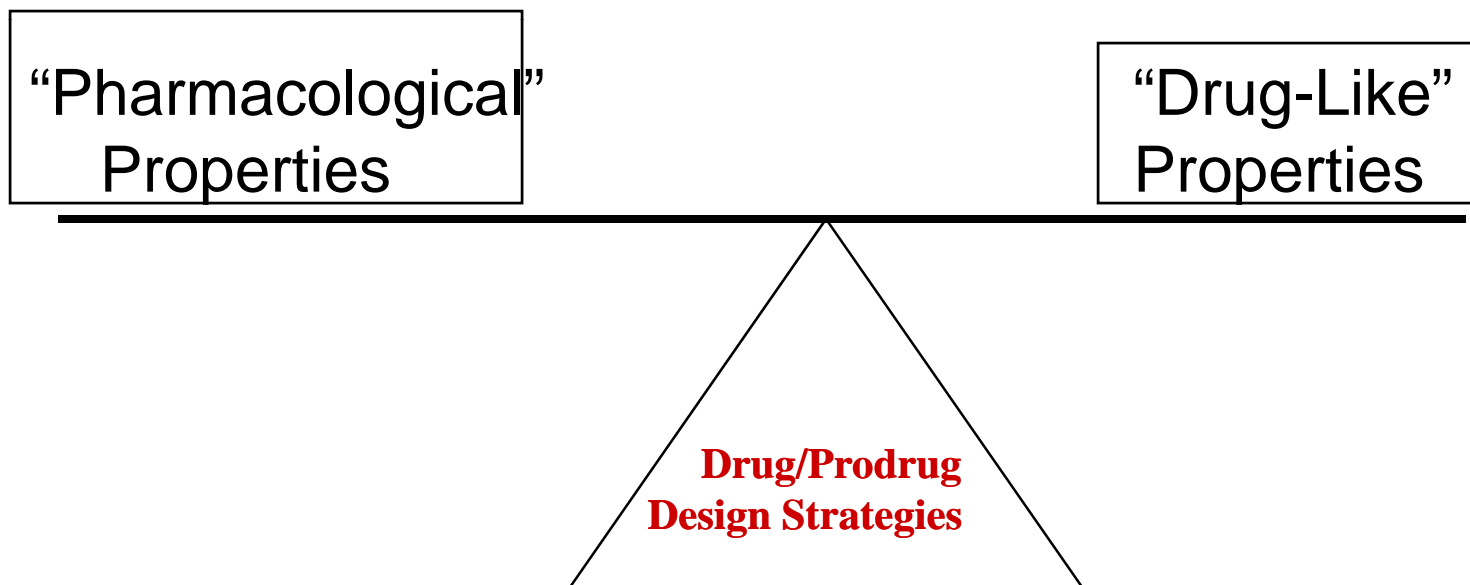
Because of a Lack of Input from Development Scientists, Discovery Scientists Tended to Fall into “The High Affinity Trap”



★ Can “drug-like” characteristics be built back into a high affinity ligand? **NO !**

★ What is the probability of success of a high affinity ligand in preclinical and clinical development? **VERY LOW !**

In the mid to late 1990s, medicinal chemists realized that they needed to fix poor “drug-like” properties of leads using drug design or prodrug design strategies.



“Drug- Like” Properties

ADME/Physicochemical Properties

Physicochemical

- Solubility
- Chemical stability
- Hydrophobicity/hydrogen bonding potential
- Charge
- Size
- Polymorphism

ADME

- Intestinal mucosal cell permeation
- Liver and kidney clearance
- Metabolism
- Transporters
- Protein binding
- Blood-brain barrier permeation
- Target cell permeation

Toxicity Properties

- Inhibition of HERG
- Inhibition of CYP450 isozymes
- PXR transactivation
- Human hepatocyte toxicity
- Mutagenicity
- Covalent protein binding

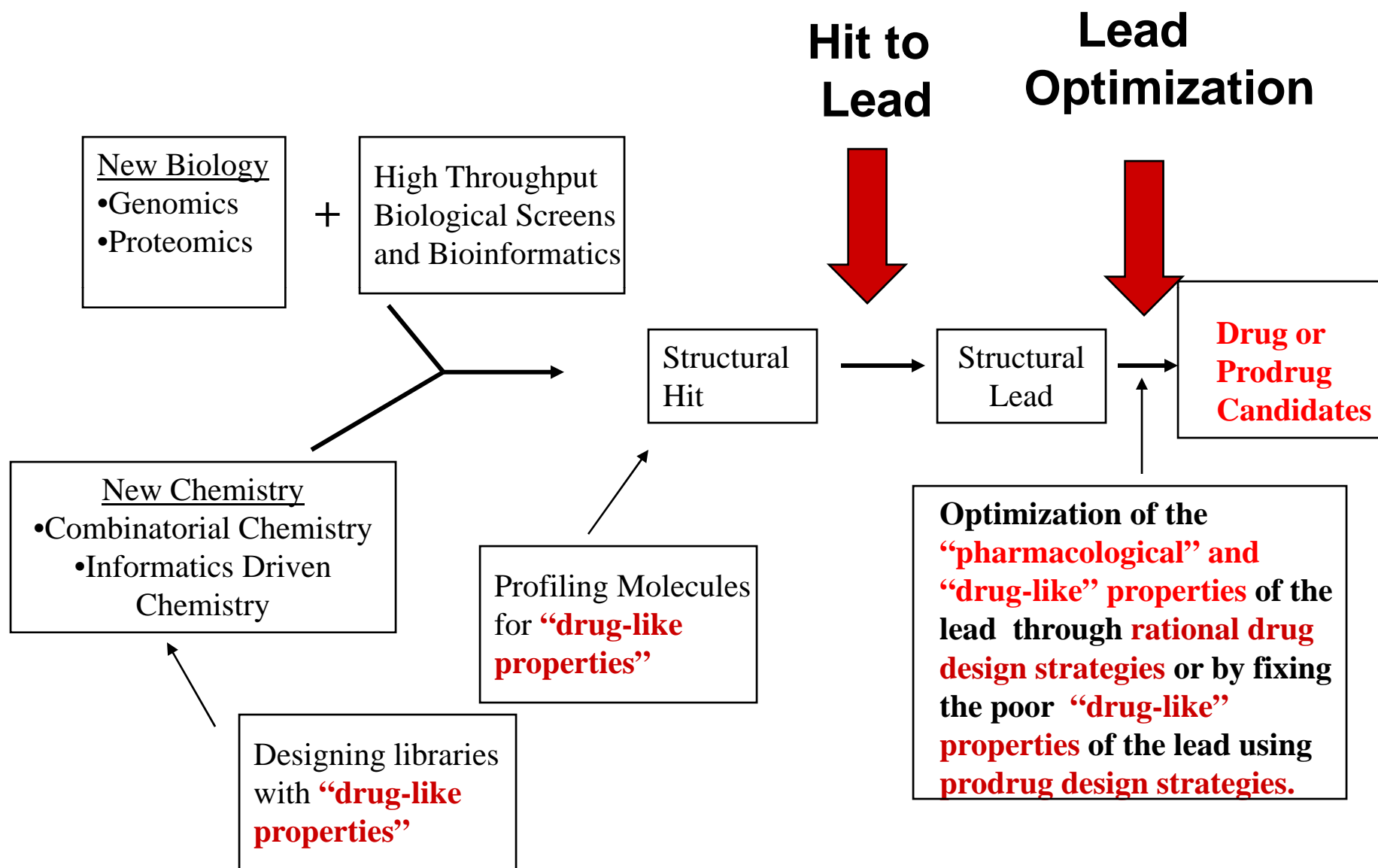
Ref.:

- R.T. Borchardt, et al, Pharmaceutical Profiling in Drug Discovery for Lead Selection, AAPSPress, Arlington, VA, 2004**
- R. T. Borchardt, et al, Optimizing the “Drug-Like” Properties of Leads in Drug Discovery, AAPSPress, Arlington, VA, 2006**

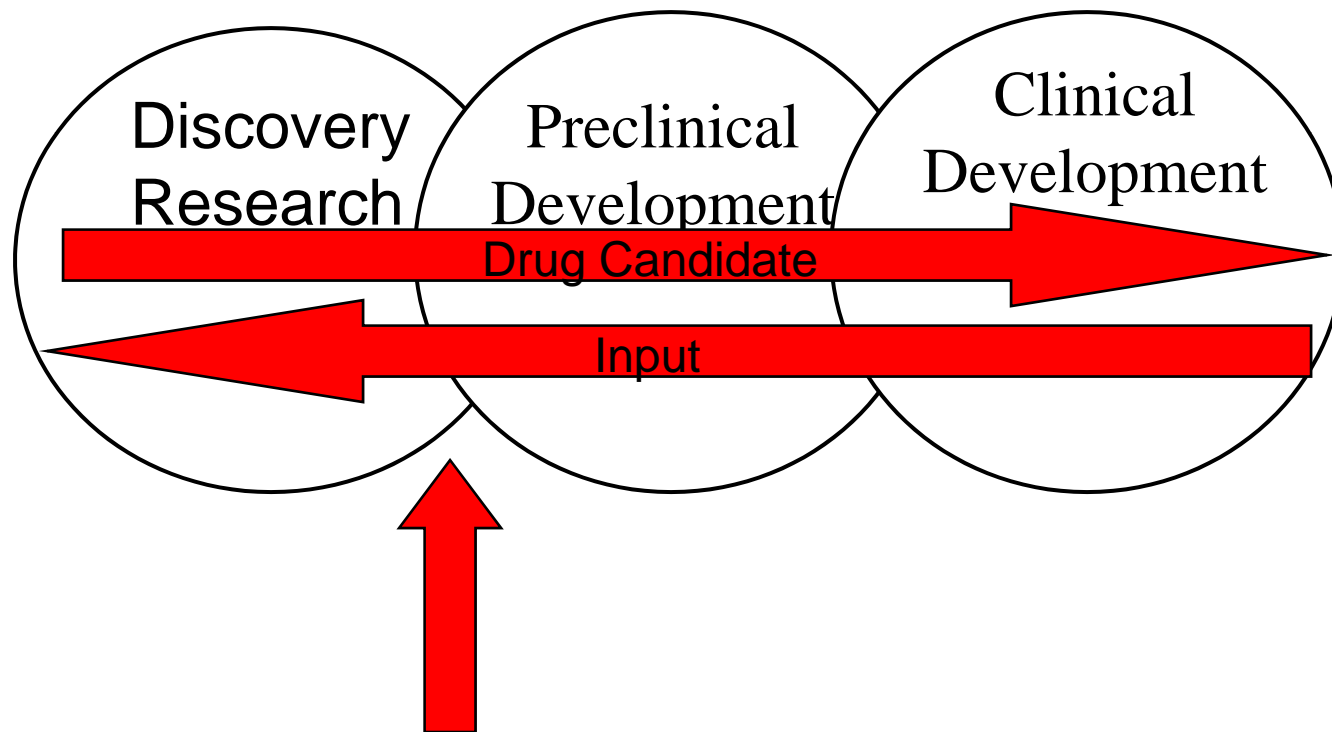
Profiling for “ADME” properties became the initial focus of attention in the mid to late 1990s

- In 1997, Kennedy attributed 39% of the preclinical/clinical failures to ADME/formulation issues.
- Methodologies were readily available to profile compounds for ADME/formulation properties.
- Medicinal chemists could easily relate to ADME/formulation properties since they often could be attributed to specific structural features in a molecule; thus, these properties could be modified through rational drug design.

Drug Discovery Paradigm of the Future

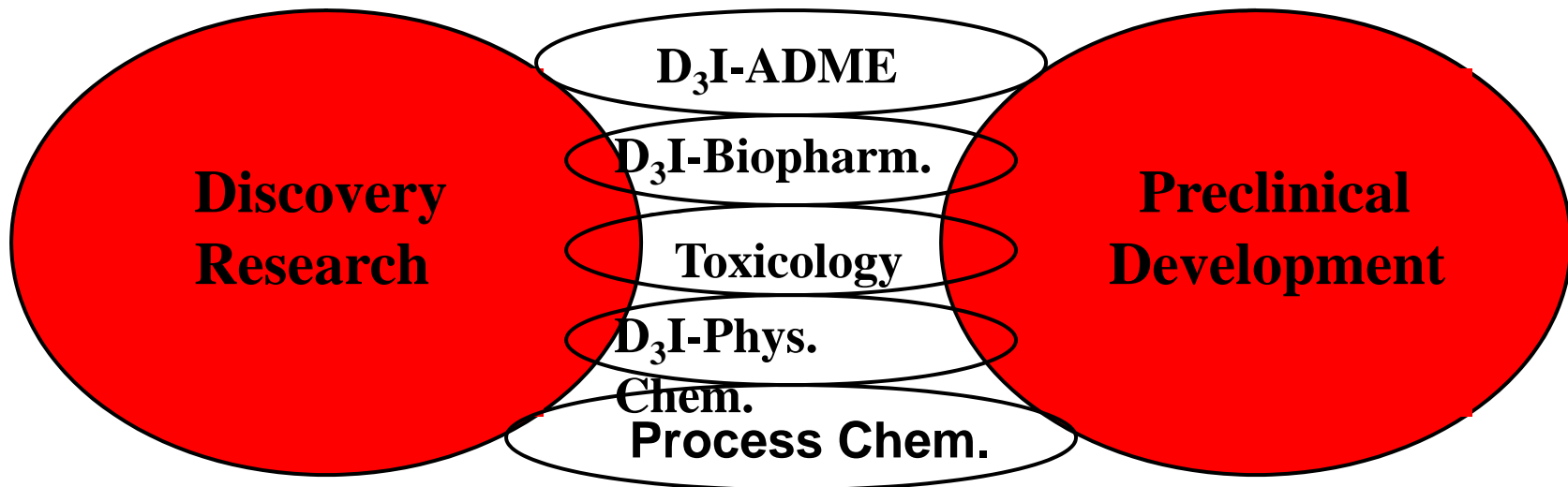


Industry Standard: The Drug Discovery/Development Paradigm is Seamless and Highly Integrated!



**Internal Drug Discovery and Development Interface (D₃I)
Groups and/or Contract Research Organizations (CROs)**

Industry Standard in 2009



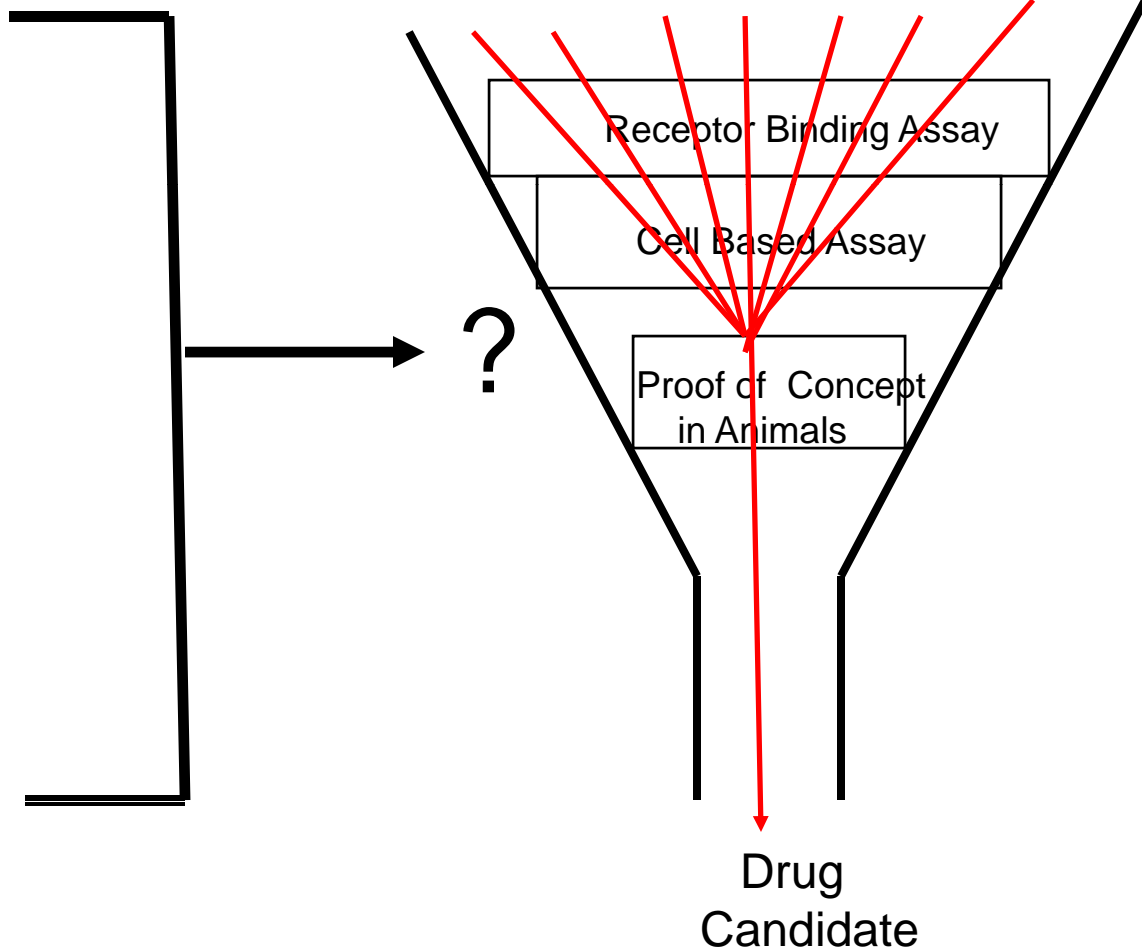
Scientific Challenges for D₃I Groups Resulting from this New Discovery Paradigm

- **How extensively and at what stage of drug discovery should the “drug-like” properties of molecules be characterized?**
- **What “drug-like” property assays should be included in a test funnel?**
- **What is the appropriate balance between in vitro and in vivo experiments?**
- **What is the appropriate balance between “pharmacological” and “drug-like” properties?**
- **New technologies need to be developed to accommodate the increased number of compounds, reduced quantities of compounds, and the tighter timelines in drug discovery.**

Dilemma: What “drug-like” property assays should be included in the “test funnel” and at what stage?

“Drug-Like” Property Assays

- Solubility Assay
- Protein Binding Assay
- Pgp Assay
- Tox. Assays
- Metabolic Stability Assay
- Chemical Stability Assay
- Cell Permeability Assay
- CYP450 Inhibition Assay

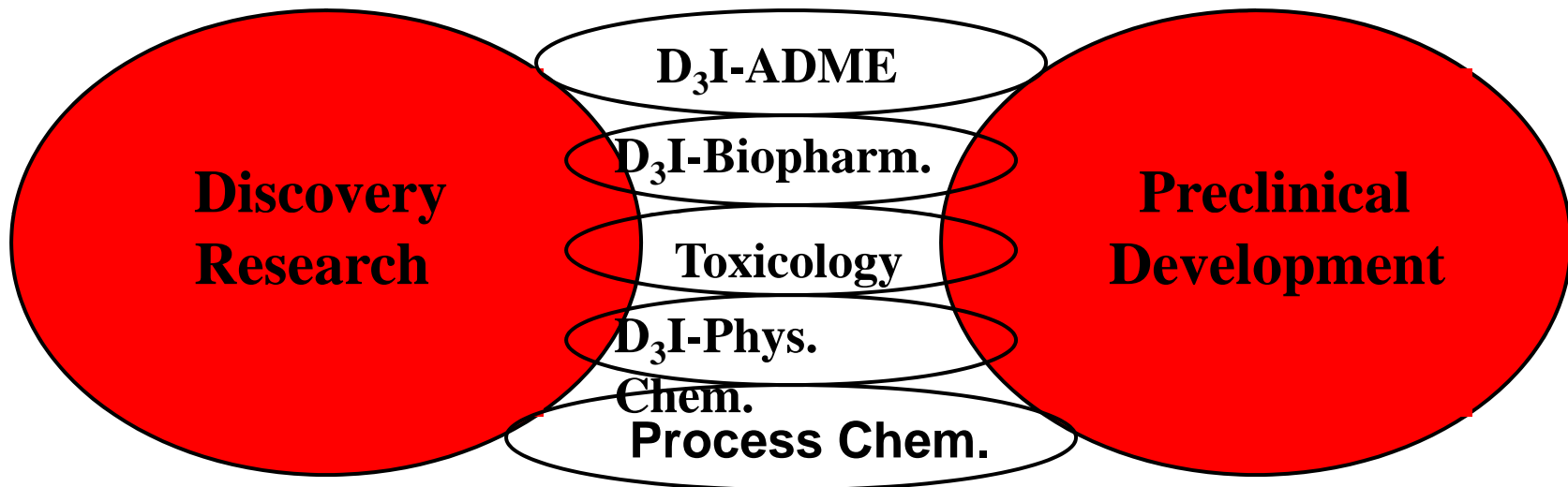


RTB's Opinion: Multidisciplinary teams consisting of discovery and development scientists, including scientists from the various D₃I groups, should be created early in a drug discovery program. These teams should be charged with generating drug candidates that meet the “developability criteria” established by the various groups involved in the preclinical and clinical development of drug candidates.

Factors to Consider in Setting up a Test Funnel for Characterizing the Drug-Like Properties of Structural “Hits” and “Leads” and Candidate Selection.

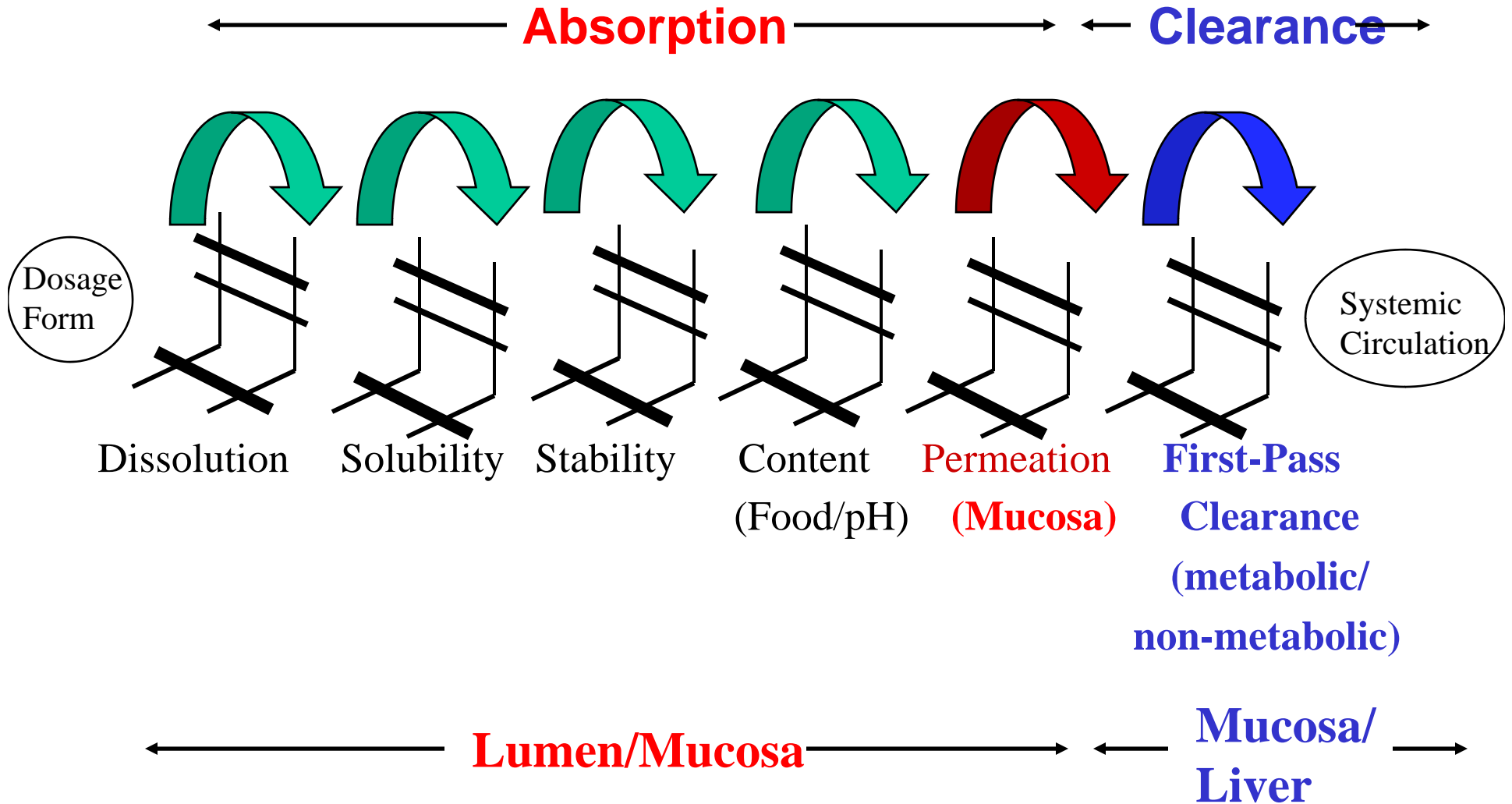
- Anticipated route of administration (e.g. oral vs i.v.).
- Location of the therapeutic target (e.g. brain vs heart).
- Therapeutic indication (e.g. cancer vs blood pressure).
- Desired dosing regiment (e.g. b.i.d.).
- The known undesirable “drug-like” properties (e.g. Pgp, HERG, 2D6, 3A4) of the structural “hits” and “leads”.
- Need flexibility to modify the “test funnel” as necessary.

How can D3I Groups and/CROs contribute to Drug Discovery in Big Pharma and Biotech Companies?

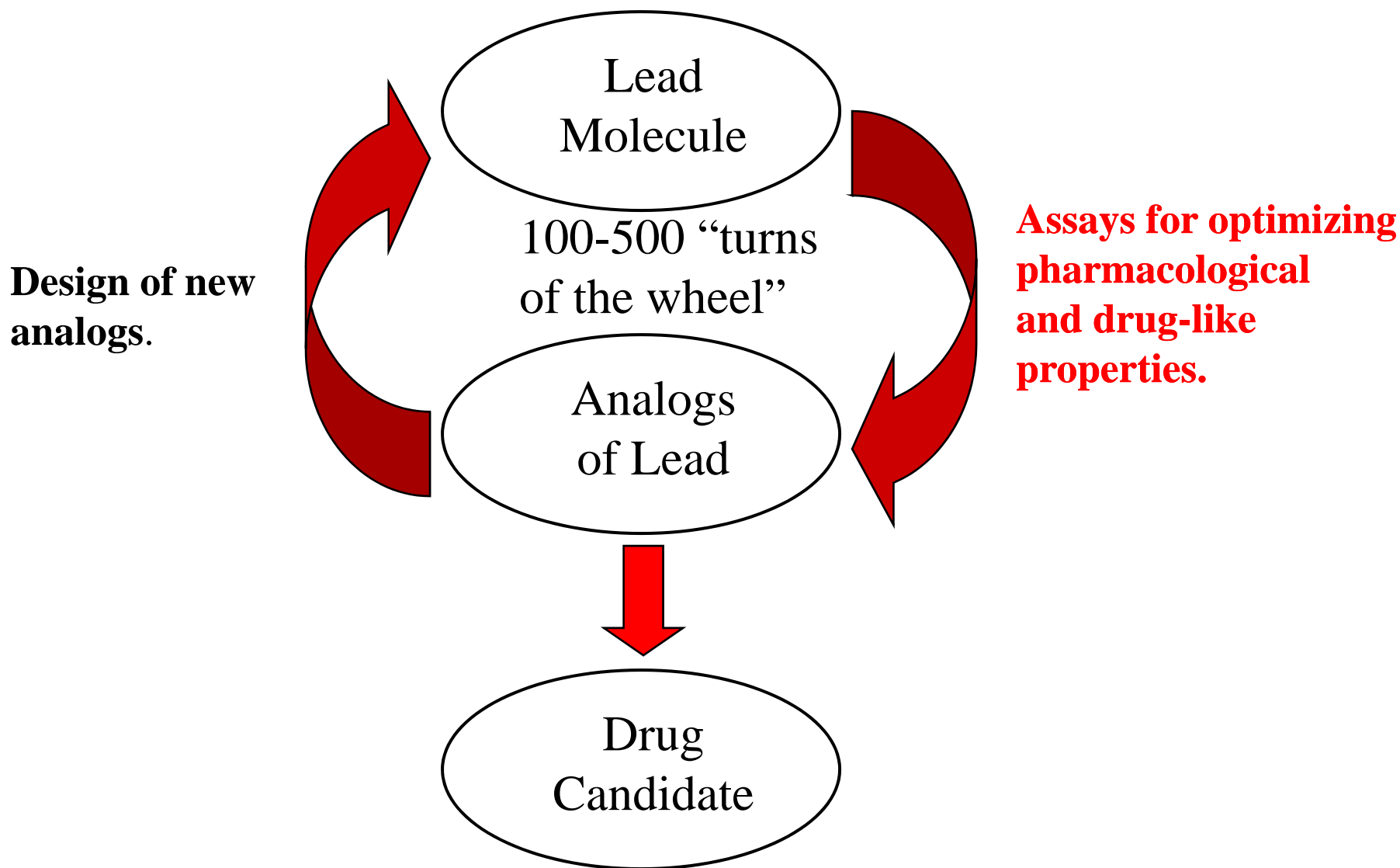


Profile hits and leads for “drug-like properties”.

Key “Drug-Like” Properties Impacting Developability of an Orally Administered Drug Candidate



The Iterative Process is Crucial to Small Molecule Drug Discovery: Lead Optimization



Lead Optimization: Profiling “ADME” Properties

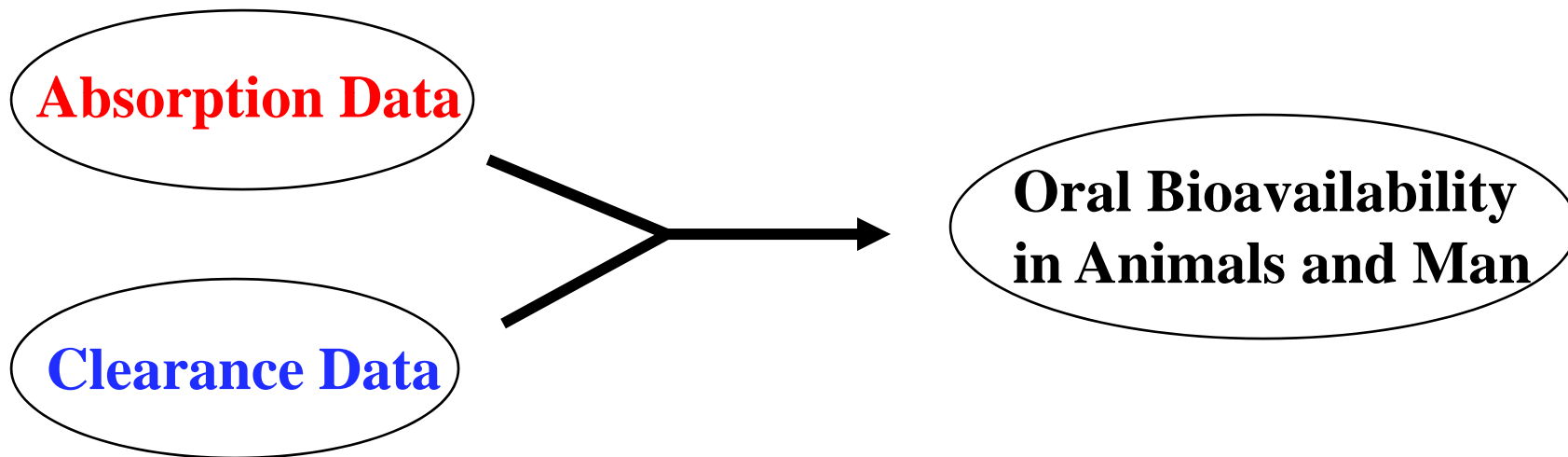
Experimental

- **Vehicle selection for PK, Safety and Efficacy Studies**
- **Equilibrium Solubility (pH 1, pH 6.5)**
- **Mechanistic Cell Permeation Studies**
- **Stability in Microsomes/Hepatocytes (species comparisons)**
- **Profiling for specific cytochrome P-450s**
- **Metabolite Identification**
- **Mechanistic Biopharmaceutical Studies**
- **Full PK Characterization**

Red- Absorption/Blue-Clearance/Black-Absorption & Clearance

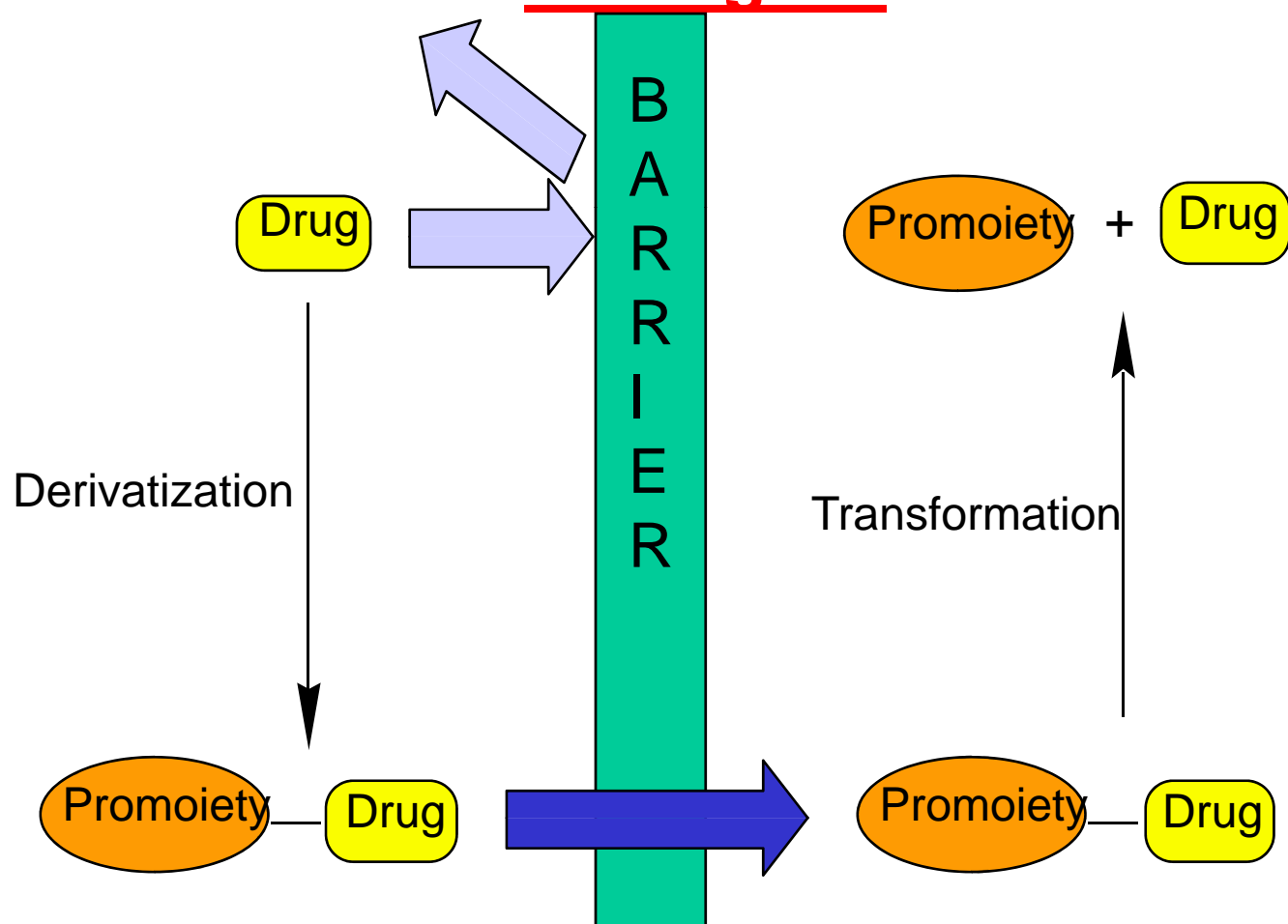
Lead Optimization: Profiling “ADME” Properties

In Silico Predictions

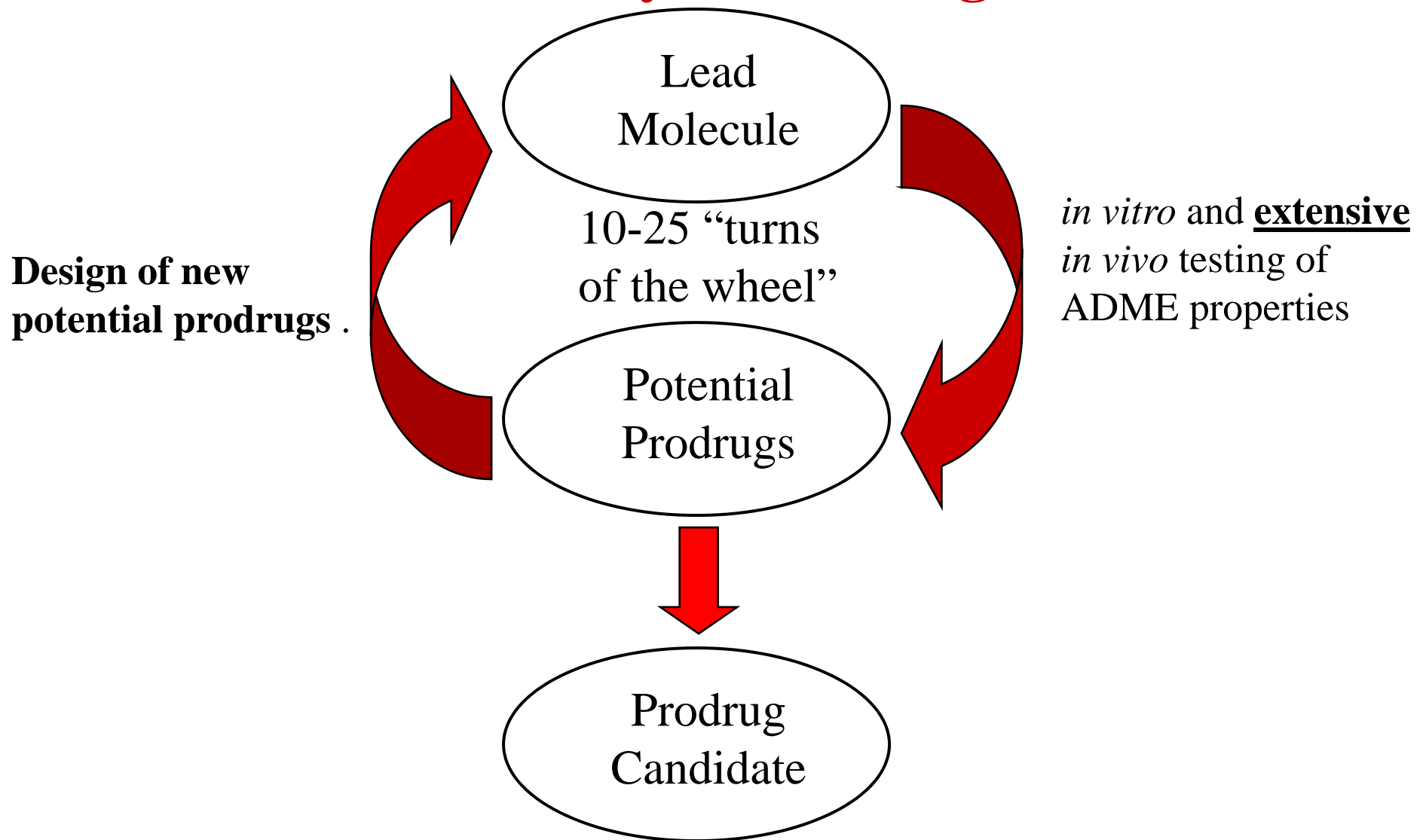


Red- Absorption/Blue-Clearance/ Black-Absorption & Clearance

In the mid to late 1990s, medicinal chemists realized that they could also fix poor “drug-like” properties of leads using prodrug design strategies.



The Iterative Process is Crucial to the Discovery of Prodrugs!!!!!!



Barriers

- Solubility**

- Stability**

- Permeability**

- Presystemic Metabolism**

Reference: Prodrugs: Challenges and Rewards (V. Stella, R. T. Borchardt, M. Hageman, R. Oliyai, J. Tilley and H. Maag, Eds Springer, New York, NY, 2007).

Other Contributions of a D₃I-ADMET Group to Drug Discovery

- Help the drug discovery team understand the interplay of ADME properties (e.g., permeation) and physicochemical properties (e.g., solubility, physical form).
- Help the drug discovery team understand the therapeutic relevance of ADMET properties; thus, providing them with the information they need to “de-risk a compound”.
- Help the drug discovery teams understand the molecule’s metabolism at a organ/cellular/molecular level; thus, providing medicinal chemists the information they need to do rational drug design.

Oher Contributions of D₃I-Biopharm. And D₃I-Phys. Chem. Groups to Drug Discovery

- Develop vehicles for animal experiments that will permit complete and accurate characterization of a compound's PK, safety and efficacy properties.
- Help the drug discovery team understand the interplay of ADME properties (e.g., permeation) and physicochemical properties (e.g., solubility, physical form).
- Based on ADME and physicochemical properties of a molecule, help the drug discovery team predict how formulations will affect the molecule's exposure in animals and man.

Pharmacological and Drug-Like Criteria for Clinical Candidate Selection

- **Excellent potency in receptor-based and cell-based assays.**
- **Excellent potency in appropriate animal model (i.e., a successful “proof of concept” experiment).**
- **Acceptable exposure in rodent and non-rodent models after oral dosing allowing for chronic toxicology studies.**
- **Wide “therapeutic window”.**
- **Bioavailabilities of >20% in relevant animal species.**

Red = pharmacological; Black = drug-like

Pharmacological and Drug-Like Criteria for Clinical Candidate Selection

- **Half-lives after oral dosing in relevant species that would be consistent with anticipated dosing regiment.**
- **No significant accumulation after chronic oral dosing.**
- **Devoid of significant inhibitory or inducer effects on key isozymes of cytochrome P-450 (3A4, 2D6, 2C9, 2C19).**
- **Preferably not having a single isozyme of cytochrome P-450 (e.g. 3A4, 2D6) involved in the clearance of the molecule.**
- **Devoid of QT interval prolongation effects.**

Red = pharmacological; Black = drug-like

Pharmacological and Drug-Like Criteria for Clinical Candidate Selection

- **Devoid of significant substrate or inhibitor activity for efflux transporters (e.g. p-glycoprotein).**
- **Achieve acceptable brain levels after oral dosing (brain/plasma levels = approx. 1)**
- **Physicochemical properties (e.g. acceptable solubility, stable polymorph, chemical stability) consistent with the development of a clinically useful oral dosage form.**
- **Synthetic process for the API consistent with the development of a commercially viable product.**

Red = pharmacological; Black = drug-like

Conclusions

- **Molecules having poor drug-like properties are now viewed as too risky for advancement into preclinical development.**
- **Drug candidates are being designed with optimal drug-like properties in mind.**
- **With the help of scientists in internal D₃I groups or external CROs, medicinal chemists can now rationally optimize the drug-like properties of leads.**