Integrated predictive ADMET/DMPK tools for optimizing exposure and safety in drug discovery and development

Jianling Wang
Executive Director, DMPK
WuXi Apptec
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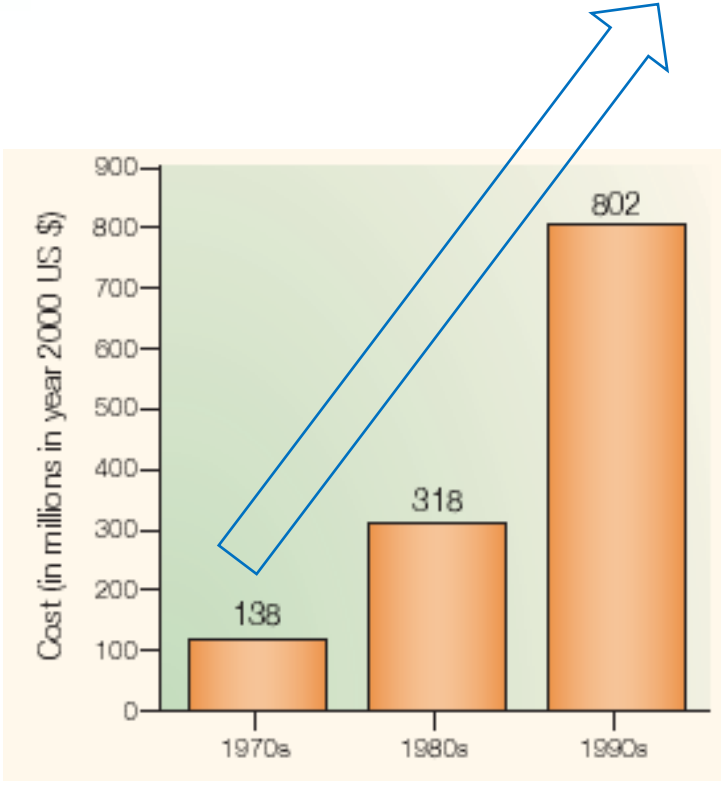
The new trend of drug discovey & development

- **Moving away of “scaling operation” (HTS, combichem, etc.)**
- **Limited new targets – focusing on identification of new ones**
  - Focusing on ID (HCV/HBV), ONC, immunology
  - Rare diseases
  - Collaboration with top universities and clinical hospitals
- **Biologics (emerging and less patent issue)**
- **Large-mid pharmas: acquisition**
- **Many venture capital/virtual companies**
- **Outsourcing (large, mid, small and virtual…..)**
- **Fast growth in China**

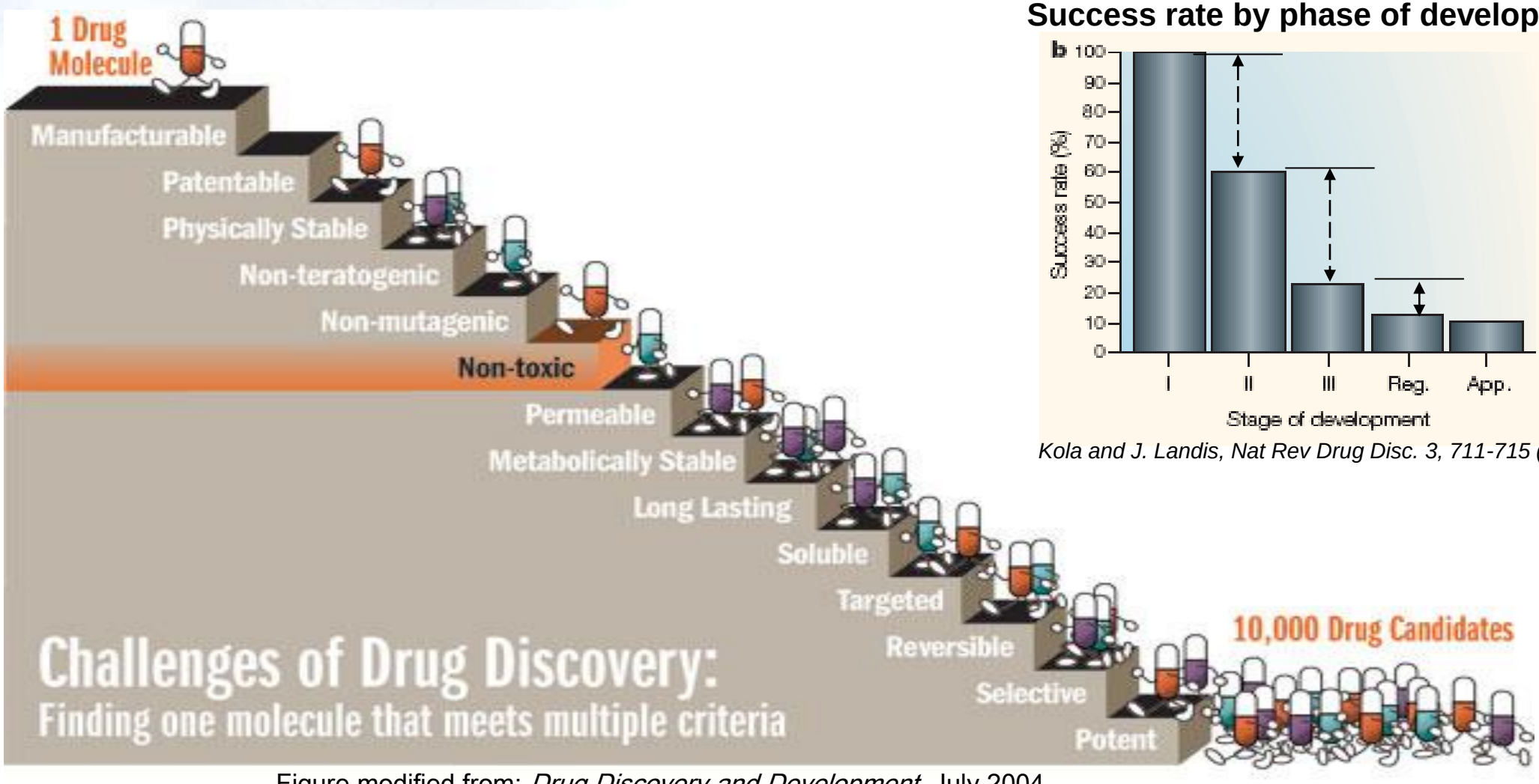
Increased R & D Costs Made Pharmaceuticals a Risky Business



Average costs per new drug
(1980-2004)

(P. Preziosi, *Nat. Rev. Drug Disc.*, 3, 521-526, 2004)

The Challenge: Solving Multiple Issues Simultaneously

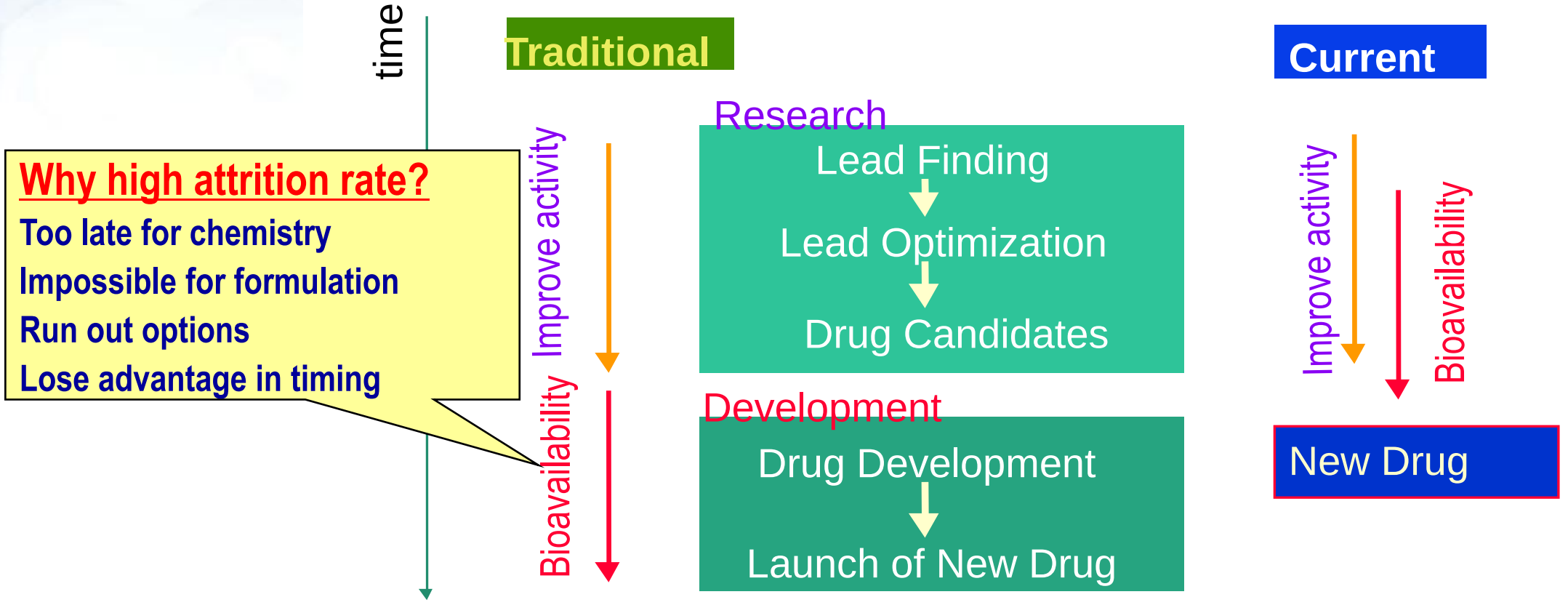


Success rate by phase of development

Kola and J. Landis, Nat Rev Drug Disc. 3, 711-715 (2004)

Figure modified from: *Drug Discovery and Development,* July 2004

The Revolution of Drug R&D Practice: *Current*

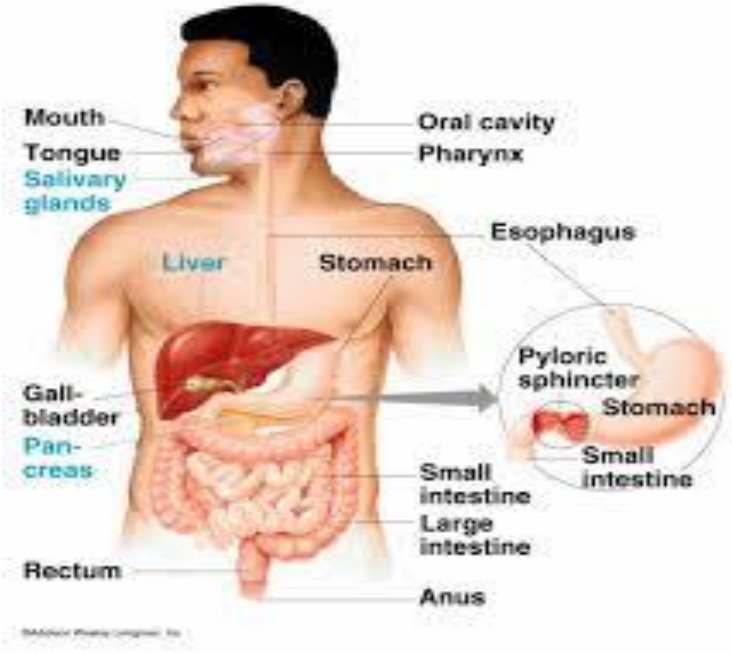


New Strategy: Provide high-quality filters to move from a sequential to a parallel optimization approach of activity vs. properties

Project human ADME/PK properties in drug discovery

In vitro ADME (varying species)
"**Primary**" & "**Mechanistic**" assays

Regular & mechanistic PK

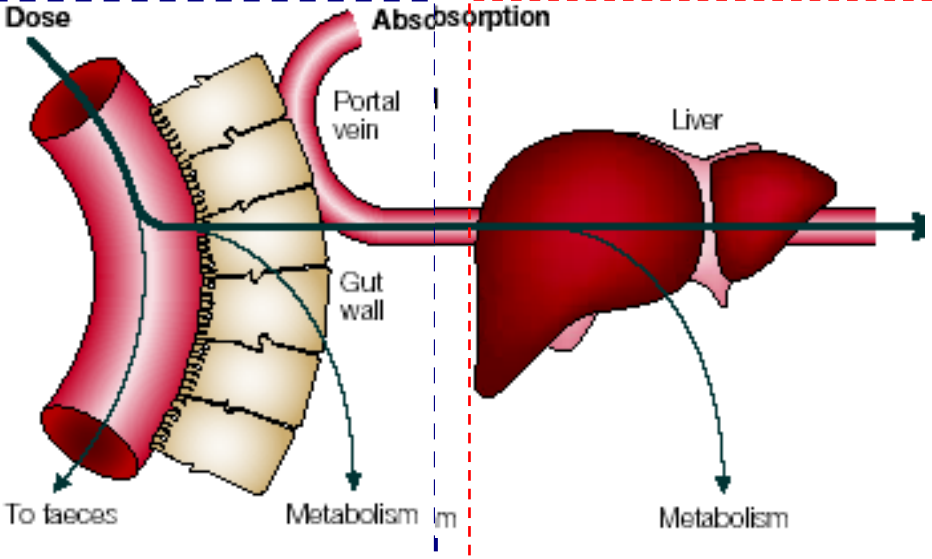


Divergent barriers categorized by physiological functions

(J. Wang et al., *Expert Opinion in Drug Metabolism & Toxicology*, 3(5), 641-665, 2007)

PhysChem & Solubility

-- Eq solubility
-- Ionization
-- Lipophilicity
-- Purity/Stability
-- Kinetic Sol
-- Formulation
-- Sol pH Profile

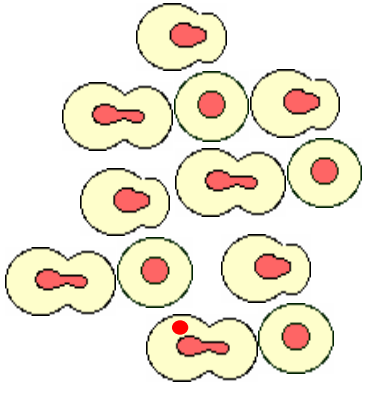


Permeability & Absorption

-- Permeability
-- Transporter/Efflux
-- Gut metabolism
-- Transp Phenotyping
-- Dose Response
-- food effect/fed/fasted
-- SS/GI physiology

Metabolism & Distribution

-- LM/hepatocyte CL
-- Biliary/renal CL
-- Hepatocyte Uptake
-- Blood/Plasma stability
-- Protein Binding
-- Bld/Plas partitioning
-- Met. Phenotyping
-- Met ID/Met Profiling



Safety/DDI Pharm.Promiscuity

--Rev. CYP inhibition
--Time-dependent DDI
--CYP Induction
--Transporter-DDI
--Reactive Metabolites
--Various Toxicity
--Safety Pharmacology

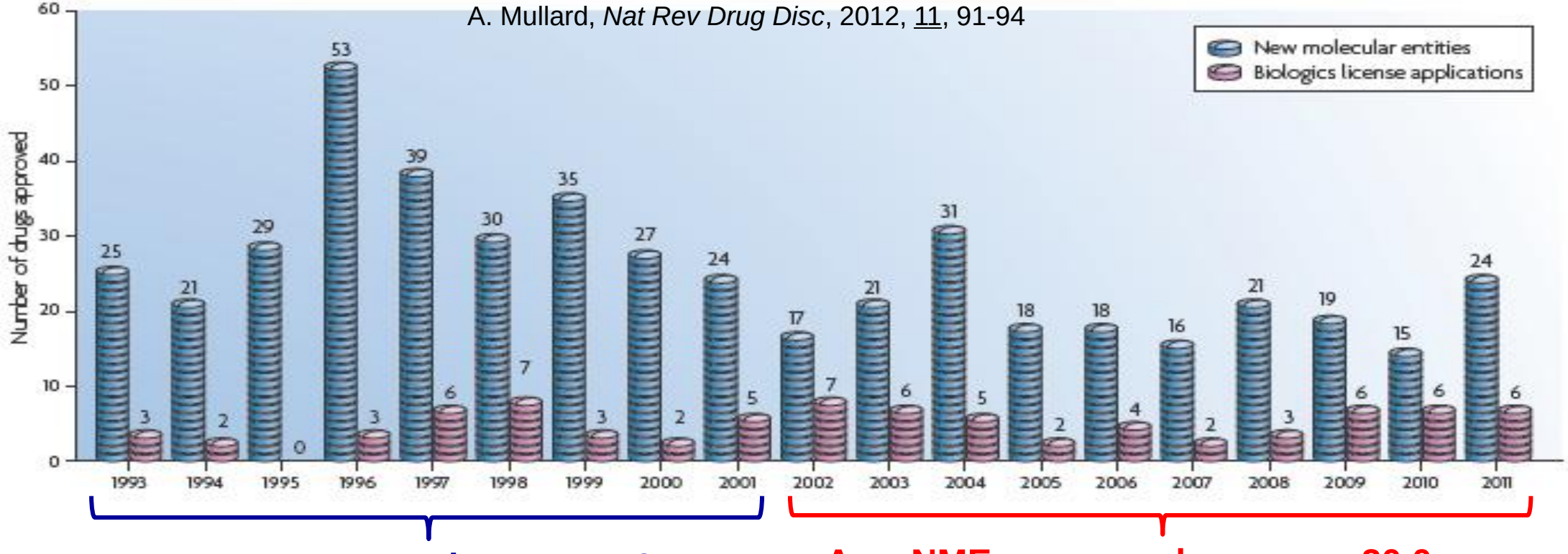
What has been achieved & seems to work well

- Researchers well trained with the fundamental ADMET/PK principles
- A paradigm involving parallel & multi-tiered ADMET/PK tools established
- Technical innovation adopted to meet the required capacity and robustness
- Costs for shifting to higher quality ADMET assays accommodated (e.g. via centralization of operations, reduced sampling rate or via creditable CROs)
- Improved predictivity of in silico ADMET tools developed using ADME/PK data from discovery NCEs.
- Availability of comprehensive in vitro and in vivo mechanistic ADMET tools in generating & testing hypotheses for optimizing NCEs

Did all changes translate to improved industry productivity?

FDA drug approvals since 1993

A. Mullard, *Nat Rev Drug Disc*, 2012, 11, 91-94

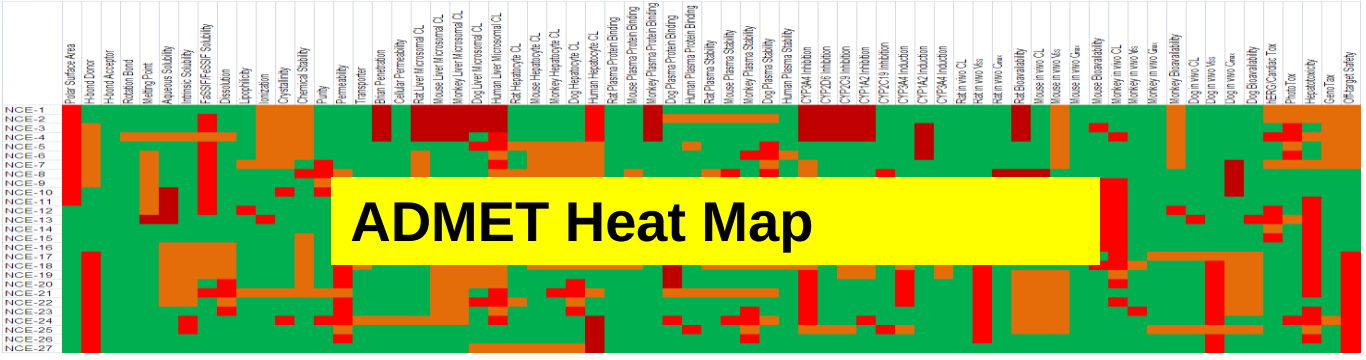


Ave. NMEs approved per year: 31.4

Ave. NMEs approved per year: 20.0

- NMEs approved decreased after 2003 and maintains flat since
- 2011: FDA approved 80% of new applications (Quality vs Quantity)

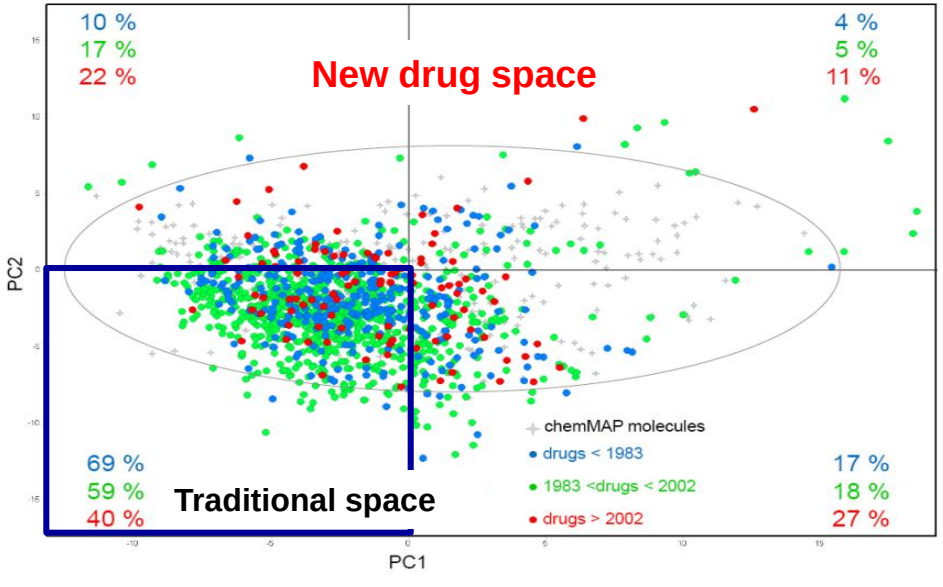
Not work well: new challenges:



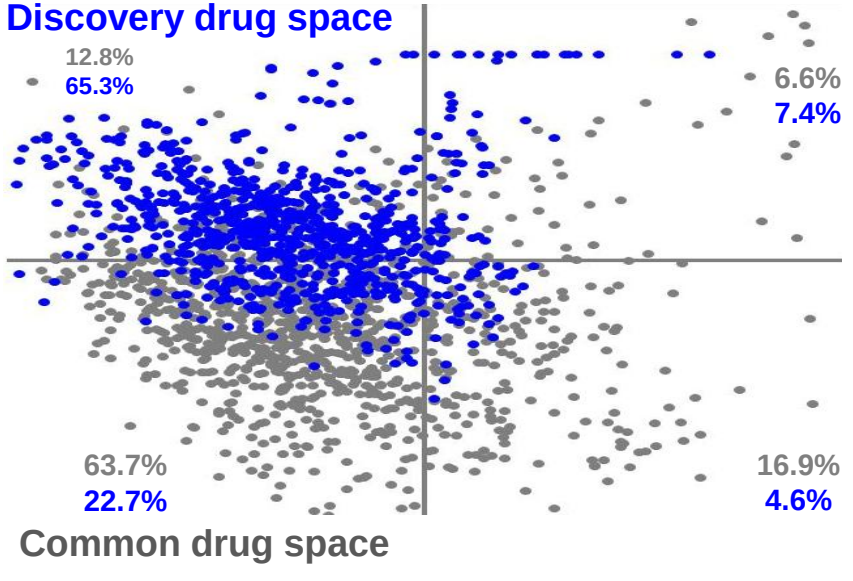
- **Limited R&D budget:** inefficient (in cost & time) usage of resource (low ROI)
- **"Box-checking":**
  - similar weight applied to each property – no function-based priority
  - no interplay considered – physiological interaction of ADMET overlooked
- **Does "More is better" work?**
  - overwhelming ADMET data perceived as "contradictory", w/o full understanding of the mechanisms and their interplay
  - Lose of focus
- **Optimization based on single ADMET property**
- **Looking for a "all-around" perfect molecule**
  - Is there a "perfect" drug in the market?
  - With limited targets and crowded IP space, can industry afford it?

What are the current challenges: new drugs space

- New targets for new and orphan drugs/diseases
- Over-crowded IP spaces: new scaffolds for backups
- NMEs approved >2002 are moving away from the traditional drug space
- Caution when apply “old” rules to NCEs in the new drug space (“no rule”!)

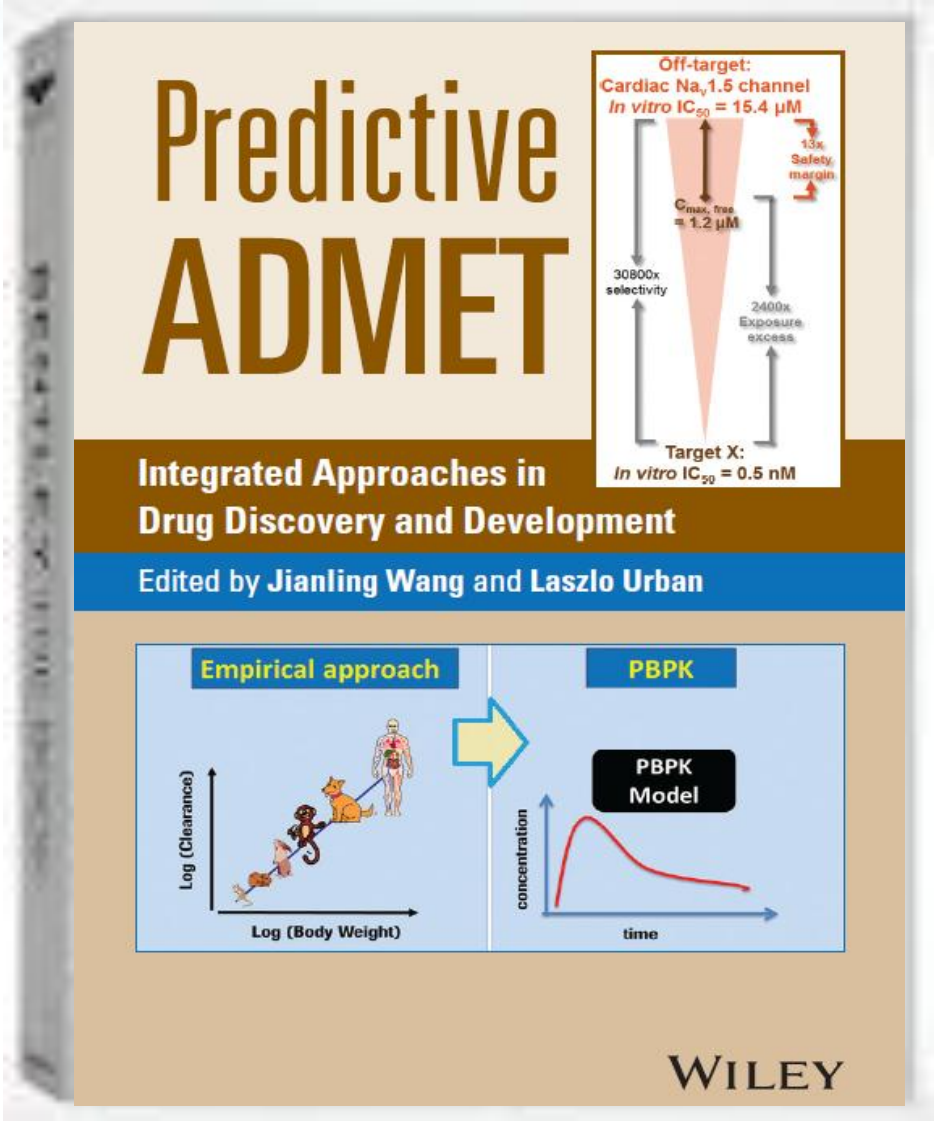


Faller et al., *Drug Discovery Today* (2011), 16, 976-984.



(Bell & Wang, *Exp. Opin. Drug Metab. Tox.* 8(9), 1131-1155, 2012)

New Data Integration Book: March-2014



Tools:

- **QSAR and PCA-PLS Local ADMET Model**
- **ADMET Diagnosis Models**
- **PATH (Probe ADME and Test Hypotheses):**
- **PK-MATRIX**
- **Chemoinformatic & Chemogenomic ADMET**
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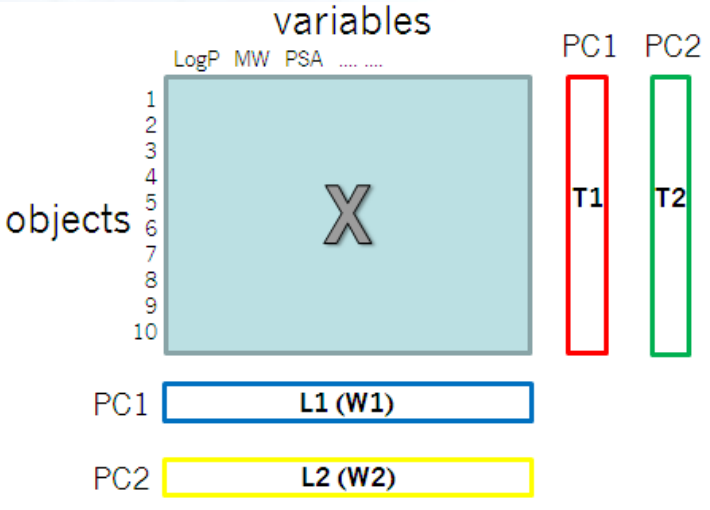
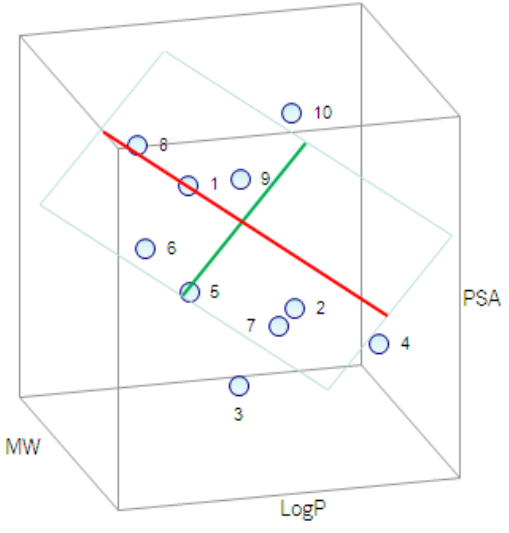
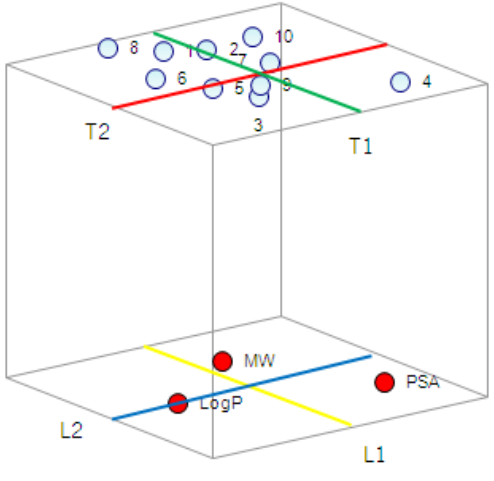
- **PK/PD** (Pharmacokinetic/Pharmacodynamic) **Models**

In Silico Tools: PCA and PLS







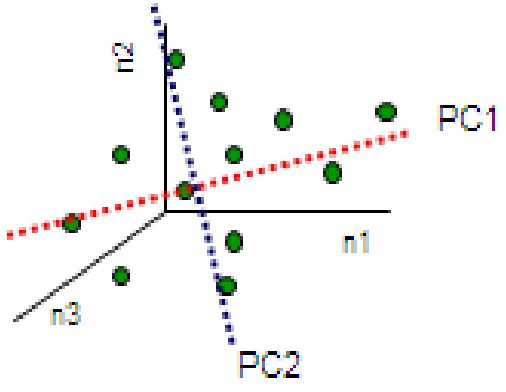
PCA = classification

PLS = regression

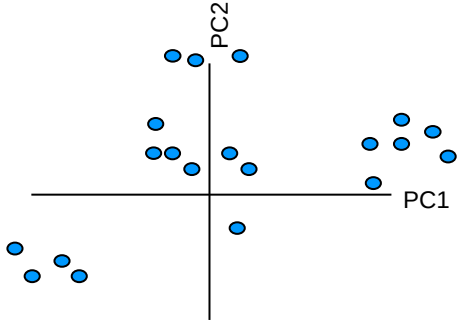
Multidimensional chemical universe maximally explained in 2D or 3D

Principal Component Analysis (PCA): background

- It is *pattern recognition* (not a regression) tool that helps analyze the structure of the data, how variables and objects are related to each other.
- Useful to extract the systematic info in complex tables and to convert it interpretable – ideal for building local models
- PCs are extracted in decreasing order of importance: 2-3 PCs (orthogonal) are able to explain the main X-variance

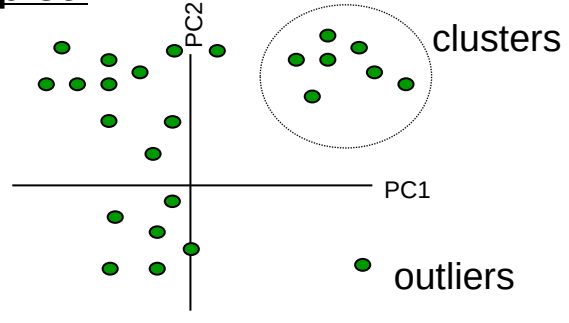


loading plot:



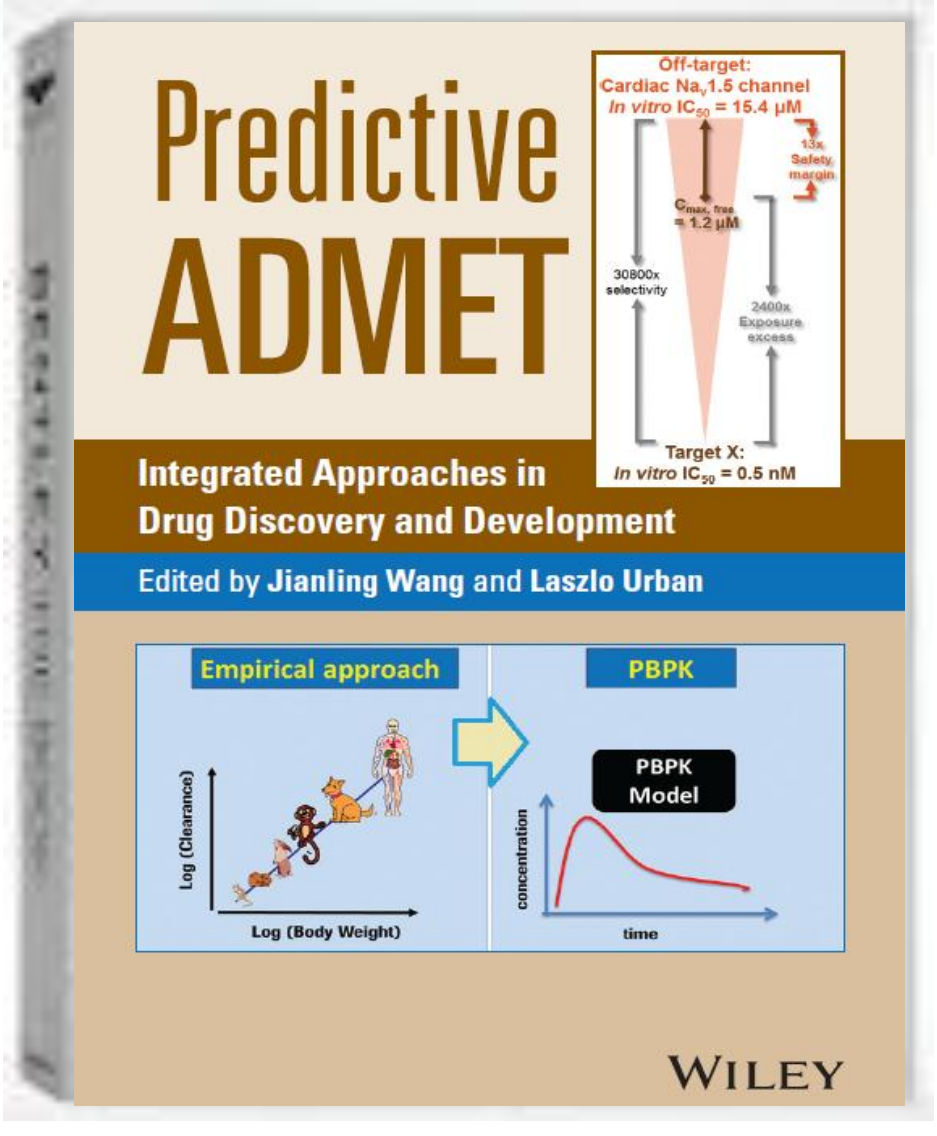
- project original X-variables to a few vectors (PCs)
- highlight or group ***variables*** containing similar or independent information

score plot:



- described in terms of its projection onto the PCs
-understand the distribution & interplay of the ***objects***

New Data Integration Book: March-2014



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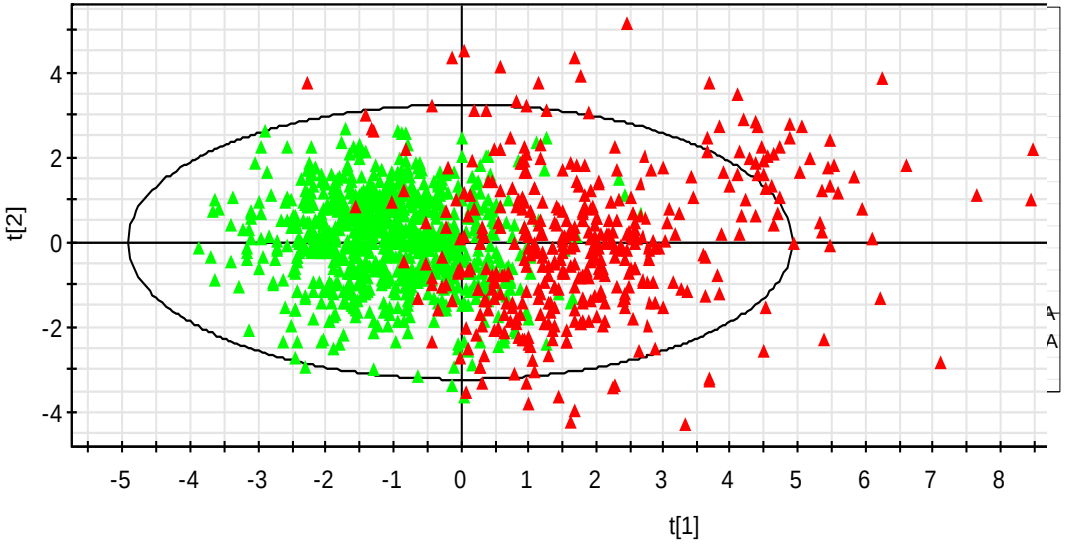
The Primary Goal of the Diagnosis is…

- To dissect a particular parameter/issue (e.g. solubility, permeability, etc.) for a compound or a scaffold by identifying the true root causes, and most influential assay parameters and molecular descriptors
- To purposefully optimize this parameter and, ultimately to avoid candidate failures and project delays.
- To offer a scoring tool of potential (e.g. permeability) risk of virtual molecules, using key molecular descriptors, despite not being a (e.g. permeability) prediction tool (QSAR)

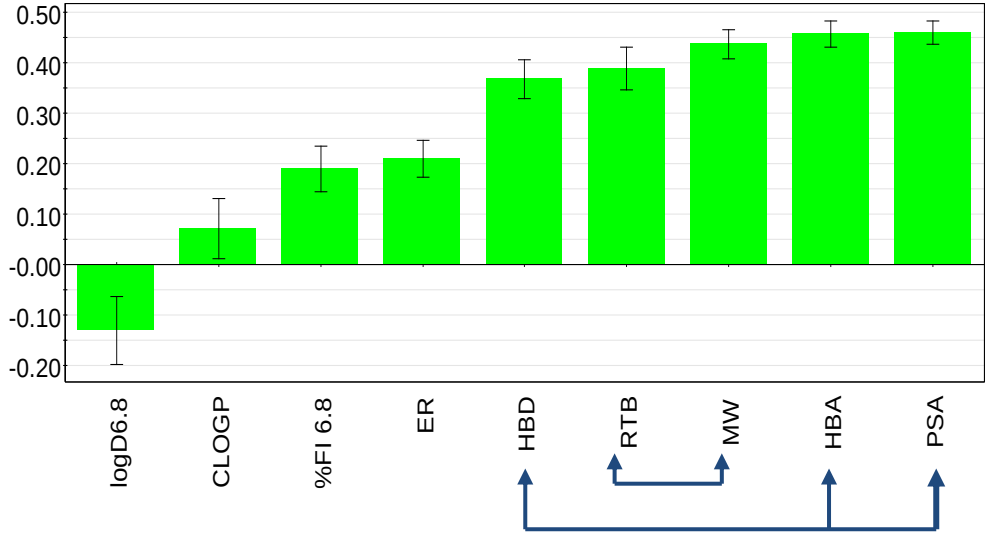
Permeability diagnosis model: Scientific rationale

- Principle component analysis (PCA) on 1259 LL & HH PAMPA/Caco-2 data
- Score plot colored by permeability binning (green: HH and red: LL)
- Loading column plot shows importance of descriptors [clogP, PSA, HBA/HBD, MW, RTB, ER, %FI and logD6.8 (Moka)] and their impact on decreased Calc Fa%

Score Plot (2nd component fitted)



Loading Column Plot
(Impact on decreased Calc Fa%)



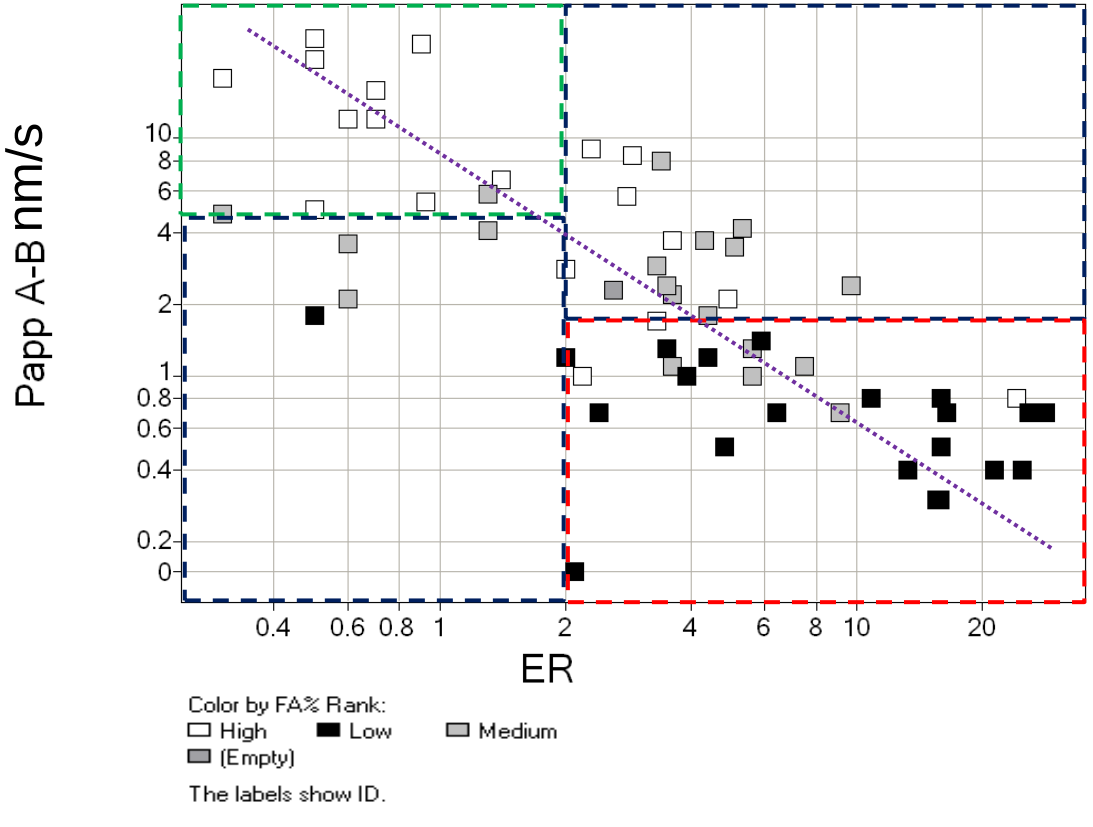
Wang & Skolnik. *Current Topic Medicinal Chemistry* (2013) **13**(11), 1308-1316..

Efflux greatly affects NCEs with poor passive permeability

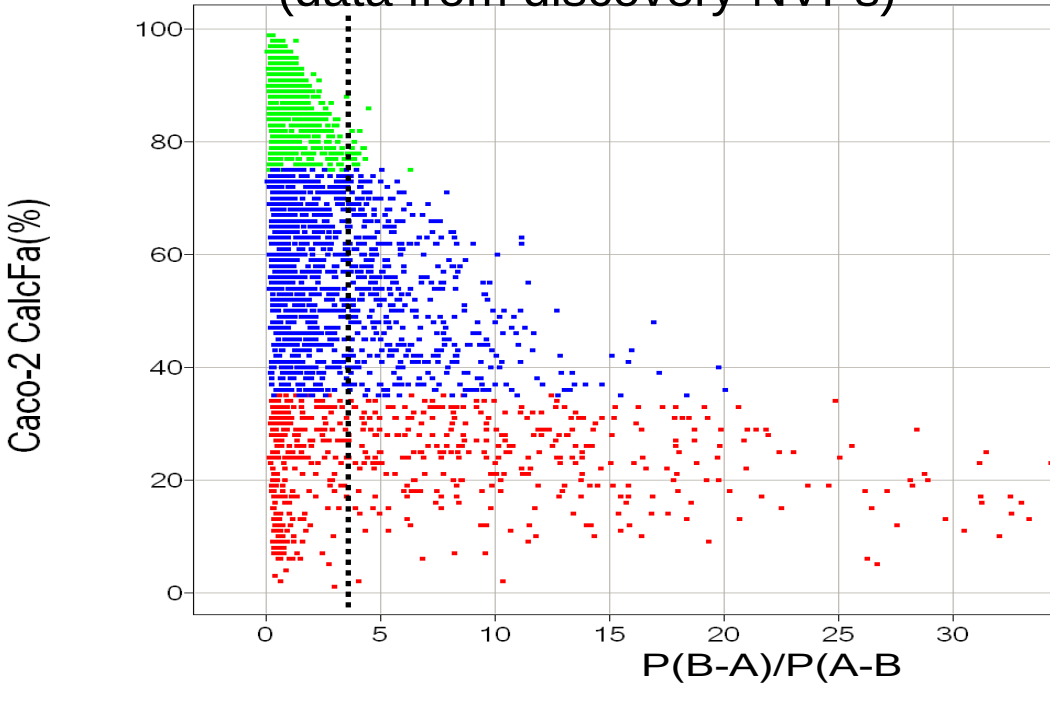
- Caco-2 permeability inversely correlates to ER
- For GI absorption, the impact of transporters in vivo may be limited

Lin, Skolnik & Wang et al., DMD **2011** 29(2), 265-274

(data from marketed drugs)



(data from discovery NVPs)

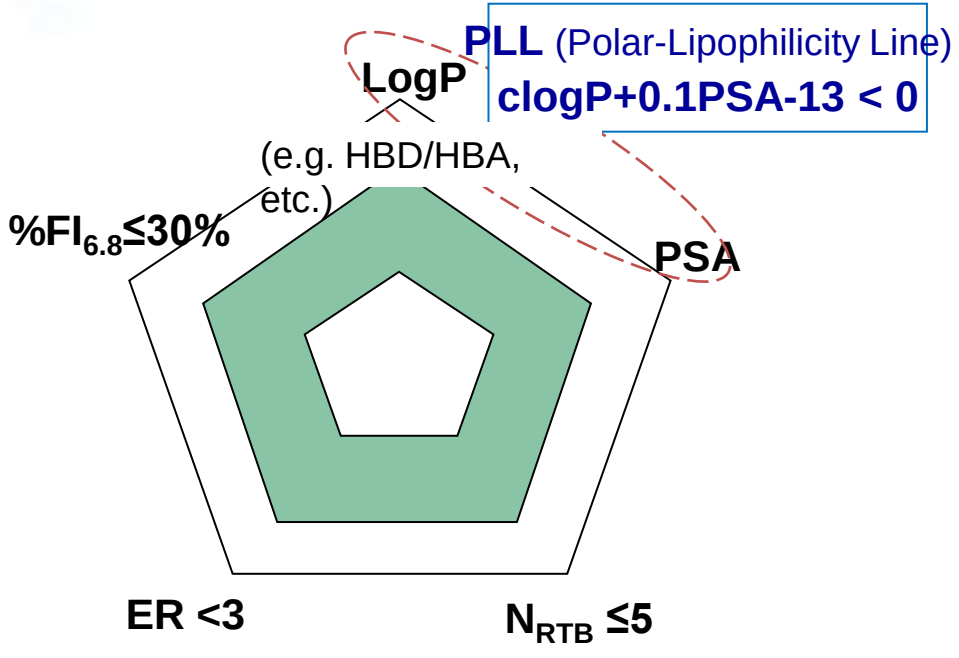


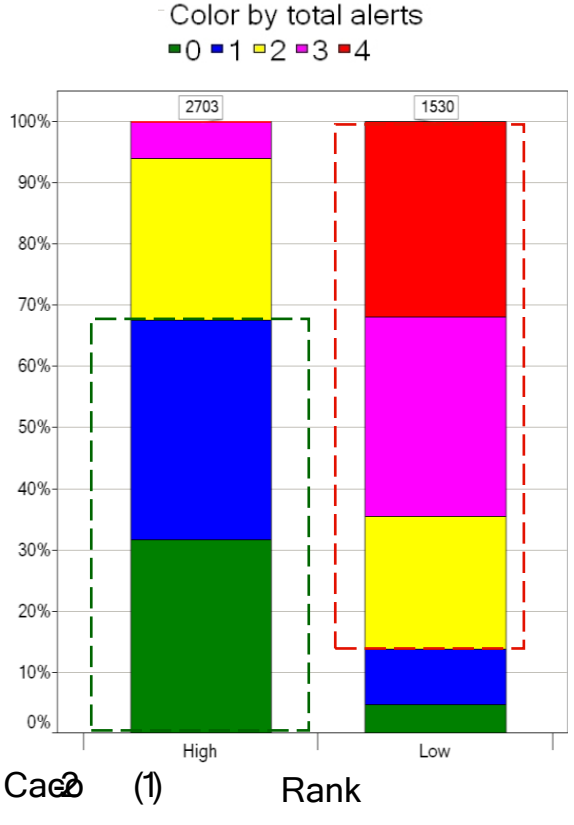
Wang & Skolnik. *Current Topic Medicinal Chemistry* (2013) **13**(11).

Permeability Diagnosis Model: performance of the model

Wang & Skolnik. *Current Topic Medicinal Chemistry* (2013) **13**(11).

- **4-5 critical parameters identified:**

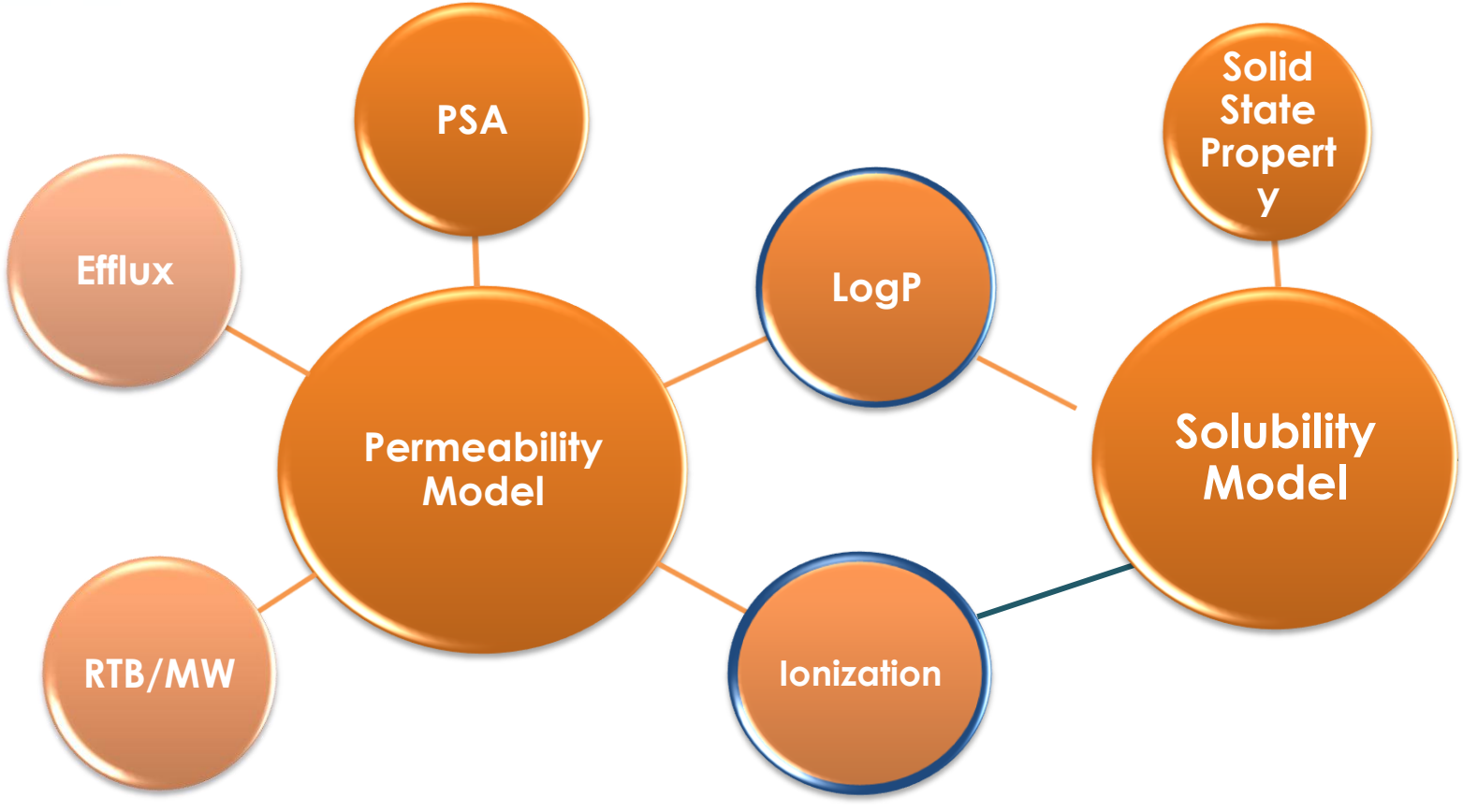




- **Reliability of permeability diagnosis:**
  - 85% **Low** permeable NCEs with 2-4 violations/flags (Diagnosis-L)
  - ~70% **High** permeable NCEs with 0-1 violation/flag (Diagnosis-H)

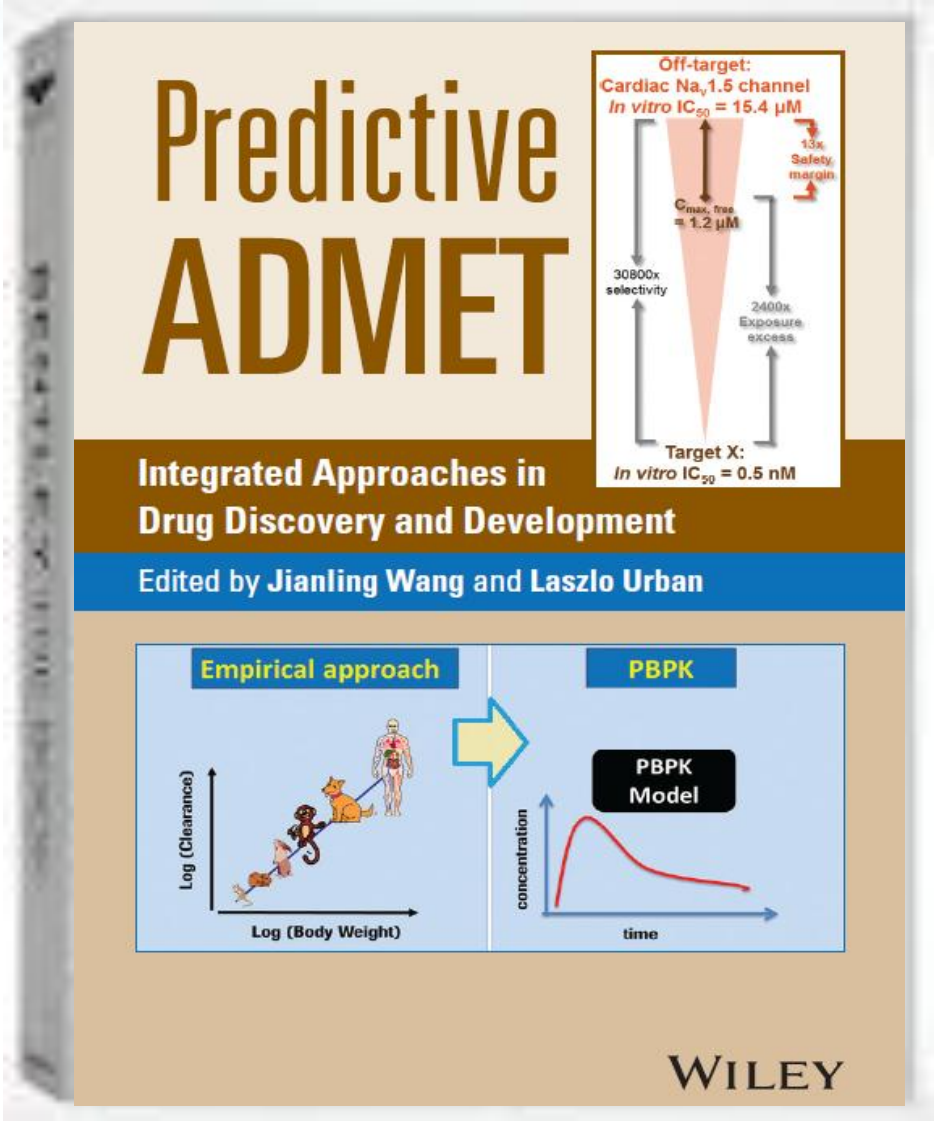
Diagnosis Models: considering property interplay

Critical for multi-parameter optimization



(Others: hERG, DDI, transporters, toxicity and primary activity)

New Data Integration Book: March-2014



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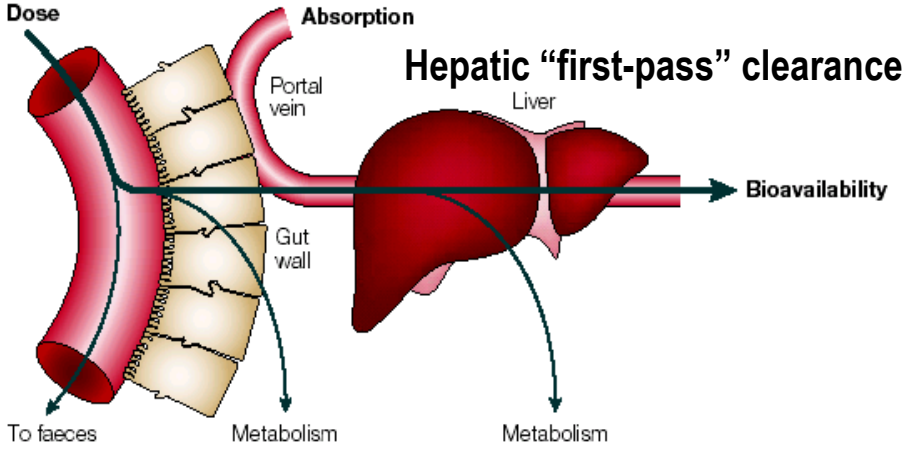
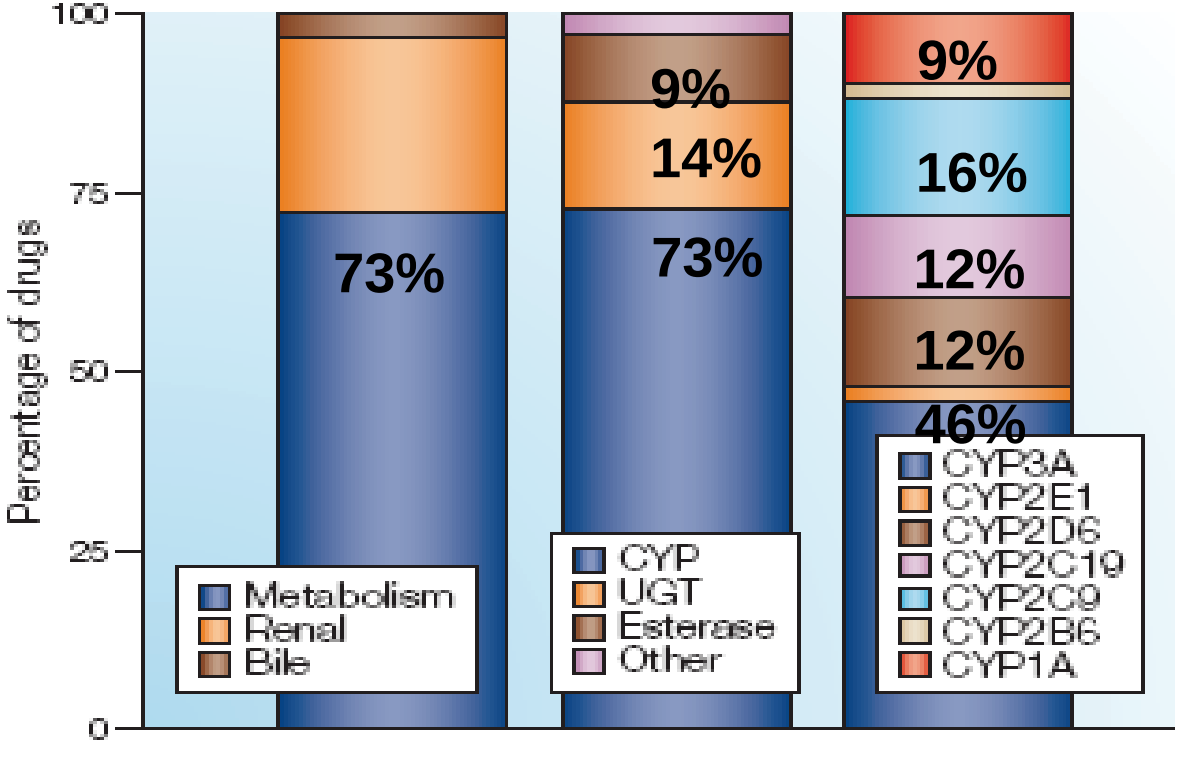
Metabolism:

Routes of elimination of the top 200 most prescribed drugs in 2002

(L. C. Wienkers & T. G. Heath, *Nature Reviews Drug Discovery*, **4**, 825-833, 2005)



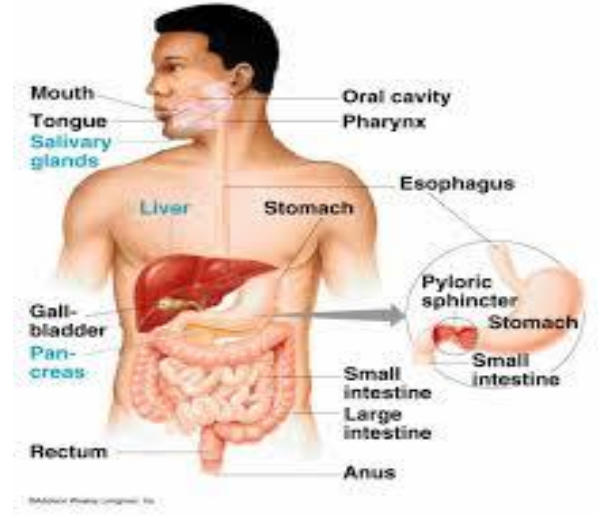
Fa % ≠ Bioavailability



- **~73% of marketed drugs primarily metabolized by CYP450s** (phase I)
- **~96% of marketed drugs metabolized by CYP450s, UGTs or Esterases** (Phases I & II)
- **~95% of CYP-related metabolism carried out by 3A4, 2C19, 2D6, 2C19 & 1A**

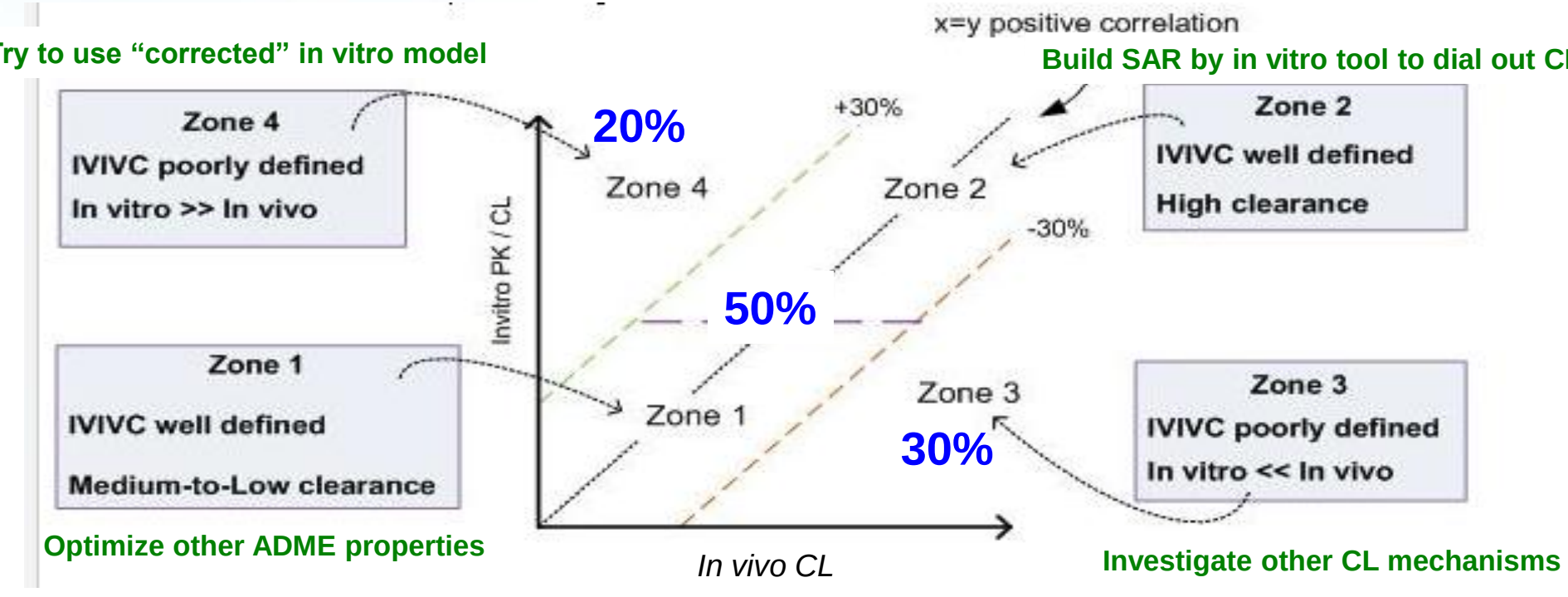
ADME/PK: bridge the in vitro – in vivo data

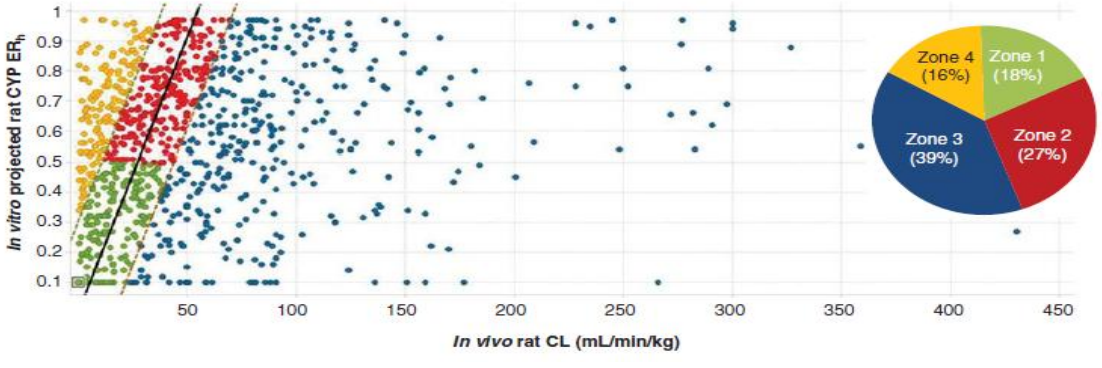
In vitro metabolic systems:
- Microsomes +/- UGT
- S9
- hepatocyte
- in vitro b-clear system



PATH-CL: Define project-specific optimization strategy

(Bell & Wang, *Expert Opinion in Drug Metabolism & Toxicology*, 8(9), 1131-1155, 2012)



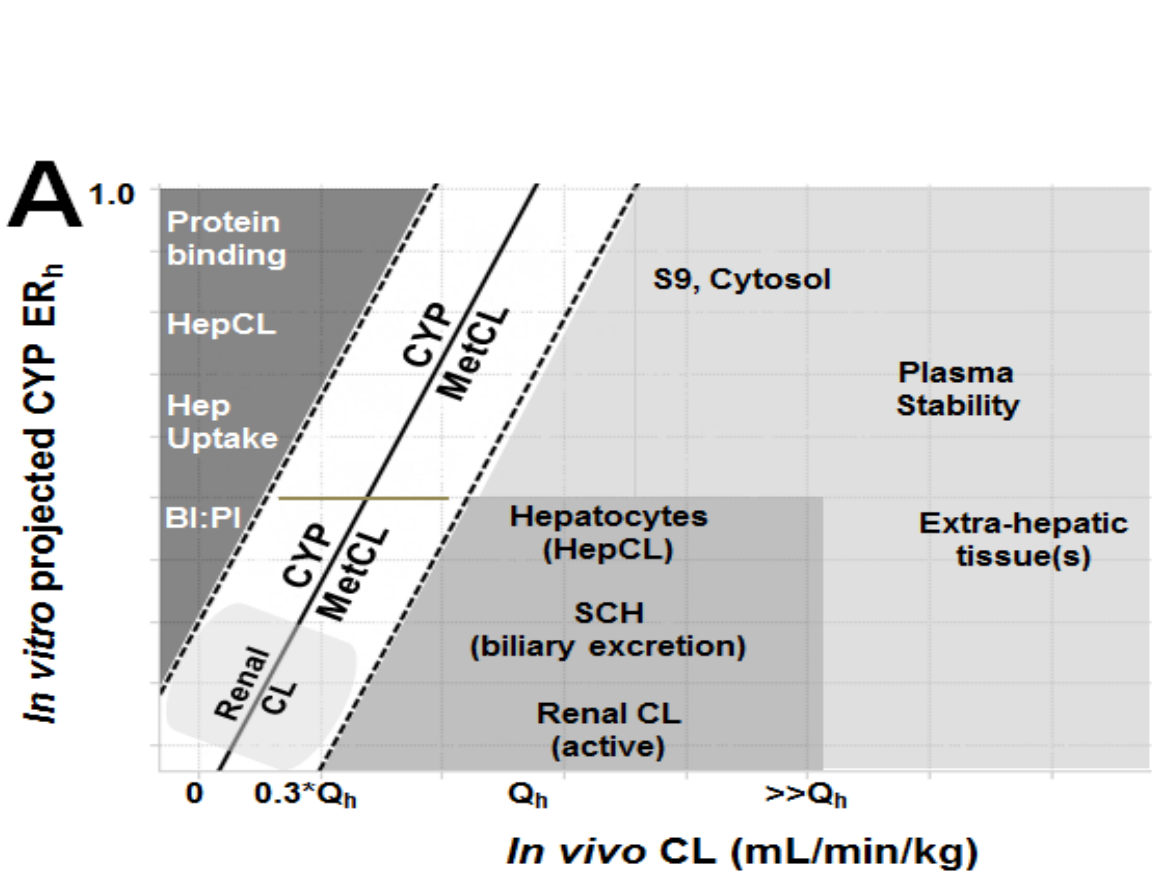


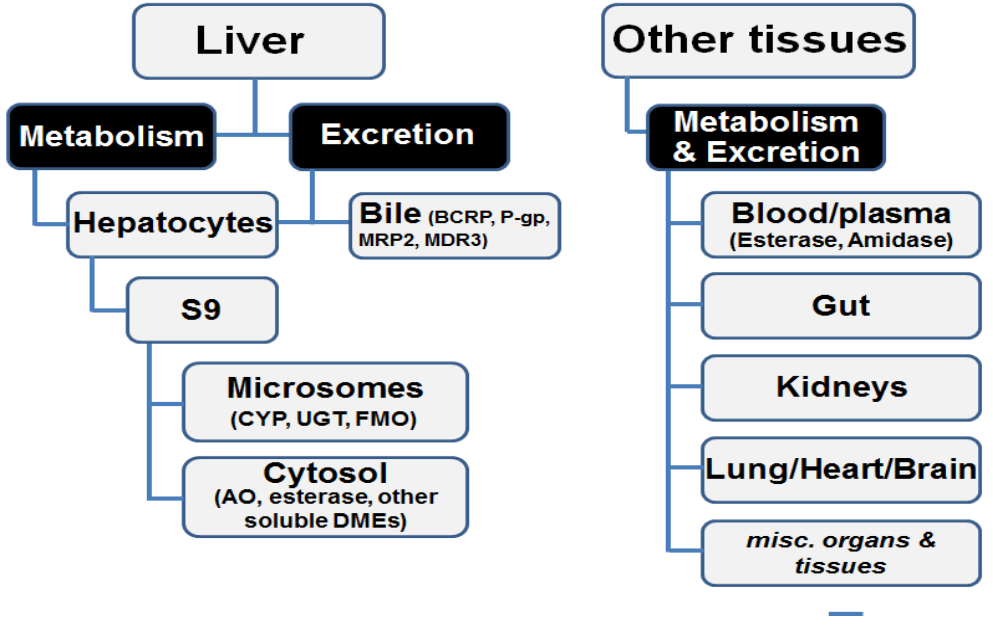
PATH-CL: Probe ADMET & Test Hypotheses

(Bell & Wang, *Expert Opinion in Drug Metabolism & Toxicology*, 8(9), 1131-1155, 2012)

- Hypothesize mechanisms responsible for IVIV gap & propose experiments

$$Cl_{total} = Cl_{hepatic} + Cl_{non\text{-}hepatic}$$





Bell, Skolnik & Bednarczyk in *"Predictive ADMET: Integrated approaches in Drug Discovery and Development"* (Wang & Urban, Eds.), John Wiley & Sons, in press.

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Adam Amaral
Bailin Zhang
Tim He

Collaboration:

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Dave Barnes
Ty Gould
Stefan Peukert
Sunkyu Sum
Jeremy Beck
Clayton Springer
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Amin Kamel
Laszlo Urban