The computational physical chemistry methods as predictors of pharmacokinetics

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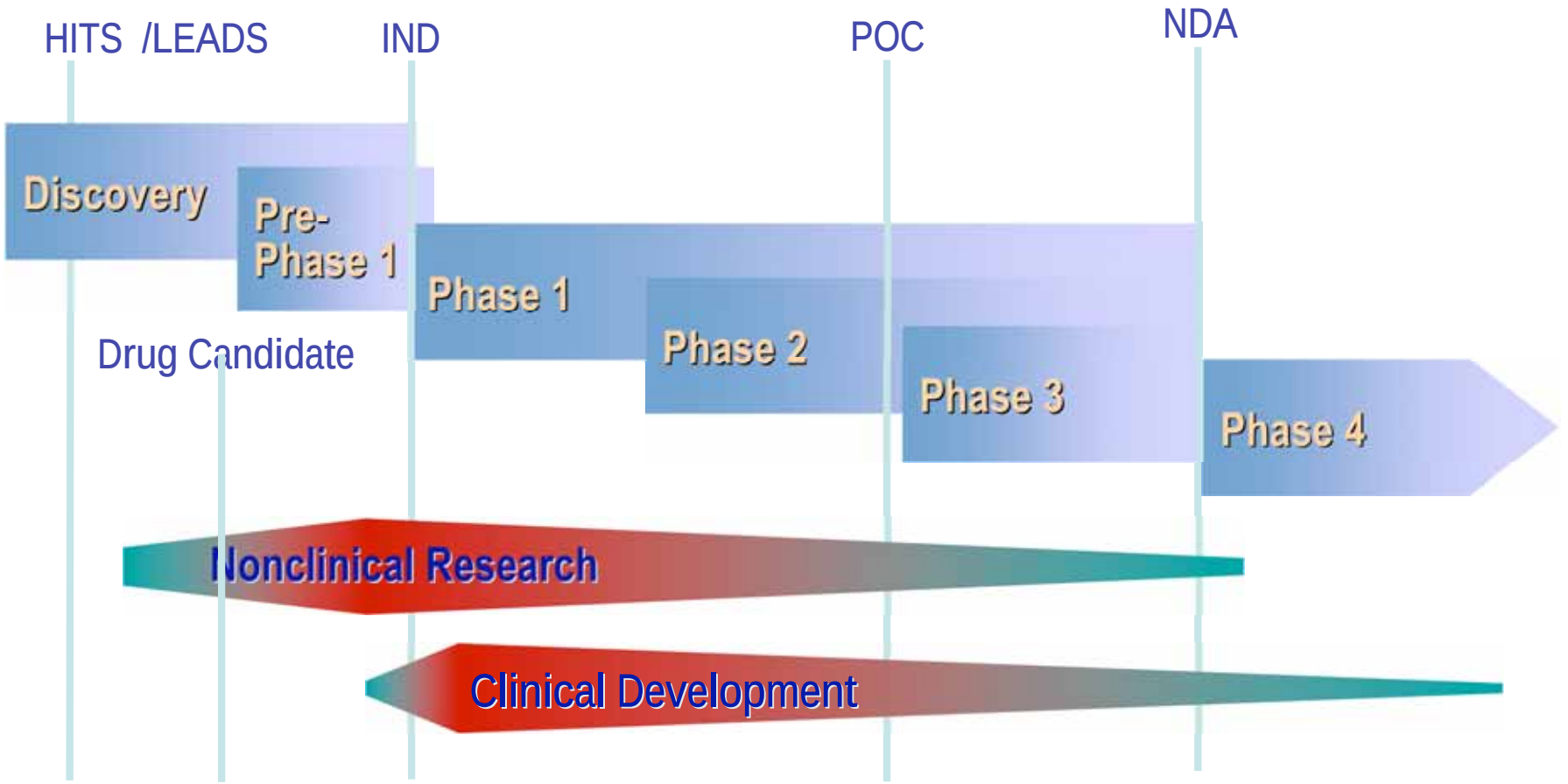
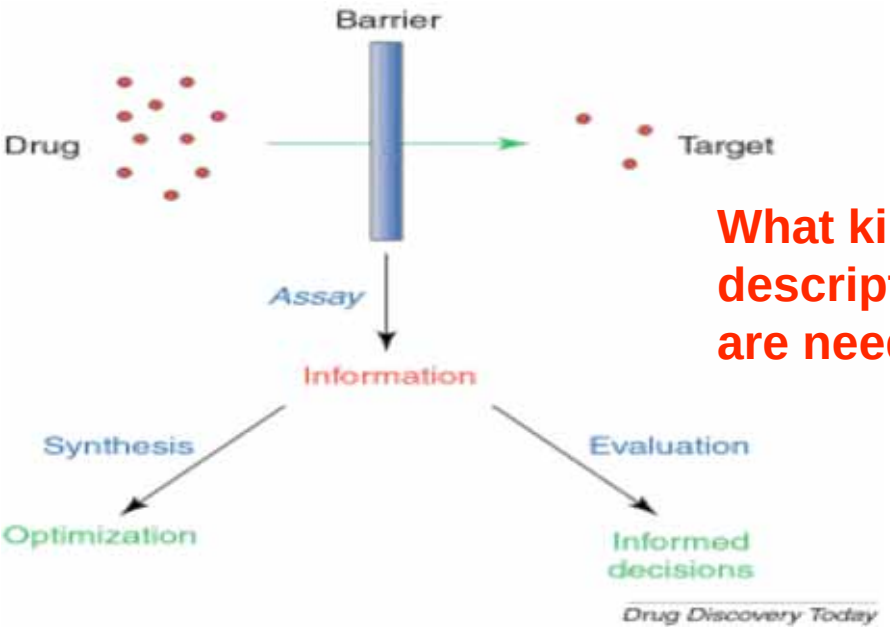
Drug Development Process



Pharmaceutical barrier-assay models provide data for understanding the compound performance in a barrier



What kind of physicochemical descriptors, constants, and properties are needed for permeation?

The use of physicochemical parameters at drug discovery and at drug development processes

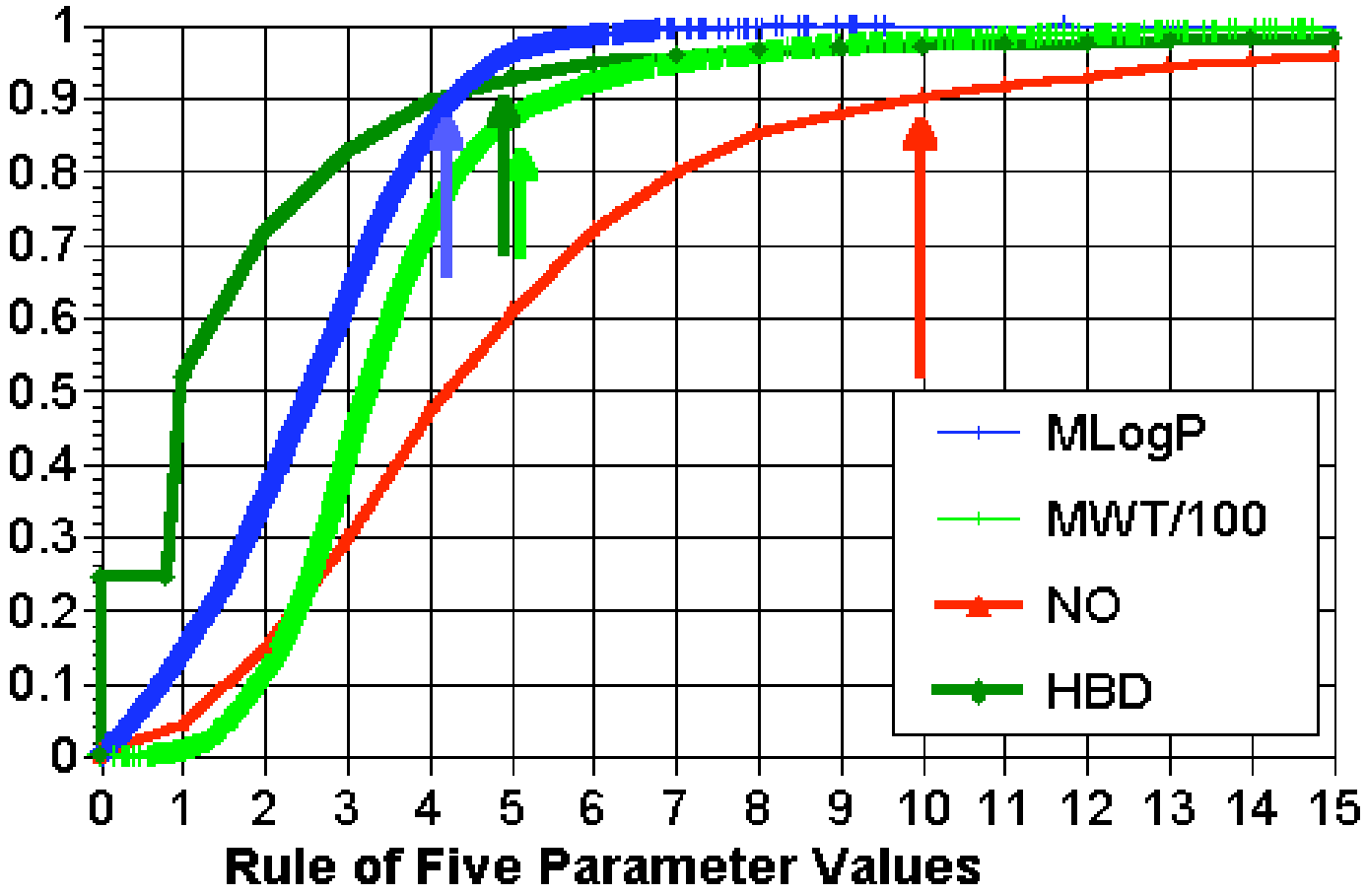
- ***Ranking of real or virtual chemical libraries***: Solubility and permeability calculations are accurate enough to allow or guide the selection
- ***Filtering HTS screening library***: Lipinski's "Rule of five"
- ***The optimization of the lead candidate***: Lipinski's rule, -0.5 < clogP <2.0 and molar refractivity CMR <10, (orally administered drugs)
- ***From the pharmacokinetic point of view***: Poor permeability is worse than poor solubility, no formulation-fix exists
- ***Formulation of the drug***: The knowledge of the BCS of a drug can be utilized to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical, information

The Lipinski's "Rule of five"

Poor absorption or ***permeation*** are more likely when there are:

- More than 5 H-bond donors.
- The MWT is over 500.
- The CLog P is over 5.
- The sum of N's and O's is over 10.
- Substrates for transporters and natural products are exceptions.

90% of 7483 INN/USAN drugs are below the Lipinski's rule of 5 parameter limit values



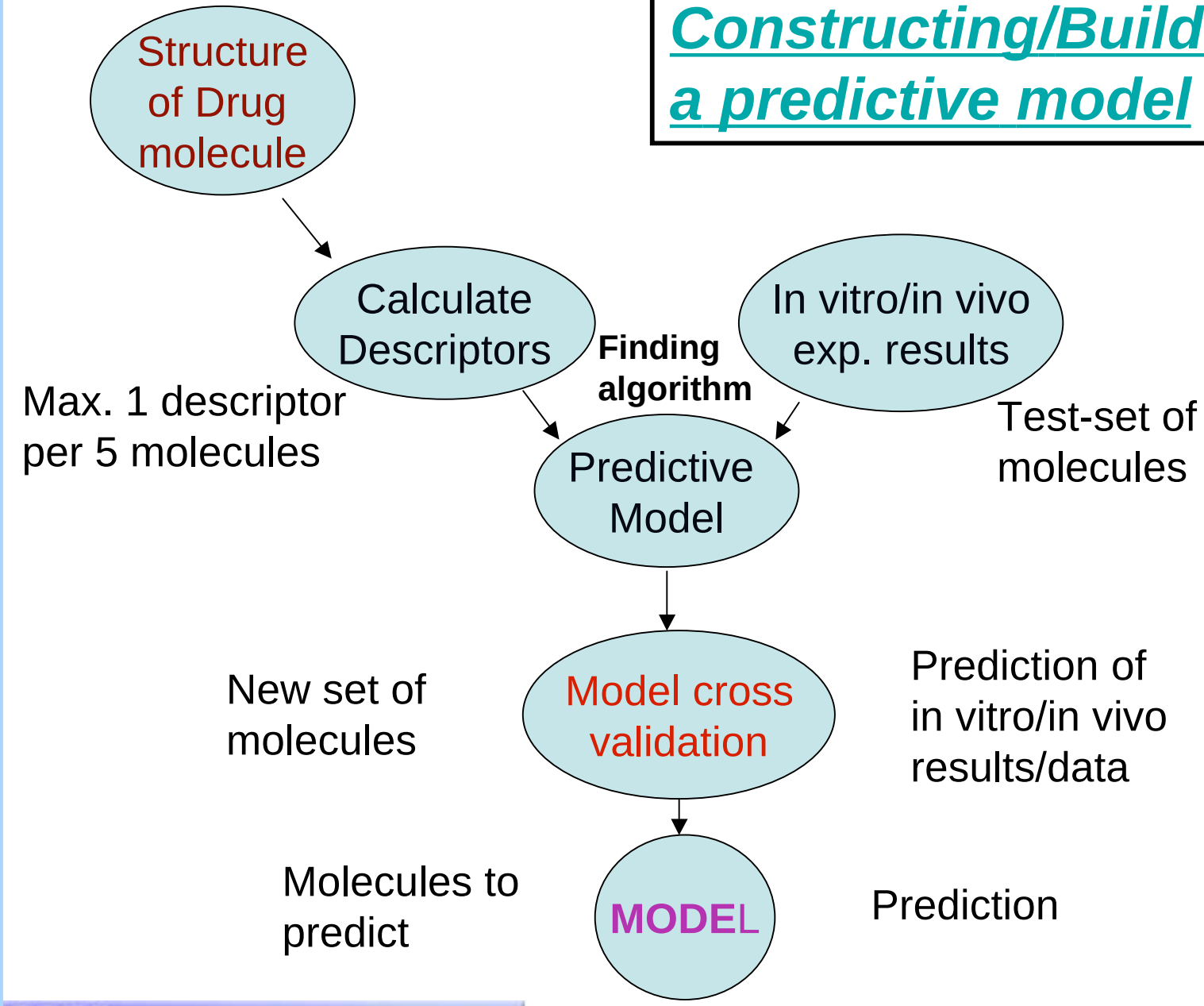
@Lipinski

Why computational modelling?

- The development of predictive computational methods is one of the fast growing disciplines in pharmacokinetics and ADME evaluation
- The computer programs have become easier to use also for non-chemists and modellers
- Chemical space of drug-like compounds is 10^{18} – 10^{64} (depending on applied algorithm) => drug discovery cannot be simplified to a ”synthesize and test” lottery.
- The amount of synthesized drug is low and syntheses are slow
- Inferior ADME properties are still being cited as the most important reason for failure during the clinical phases

  => screening and predicting of ADME properties is important
- ***To reduce and optimize the pre-clinical in vivo animal testing***

Constructing/Building up a predictive model

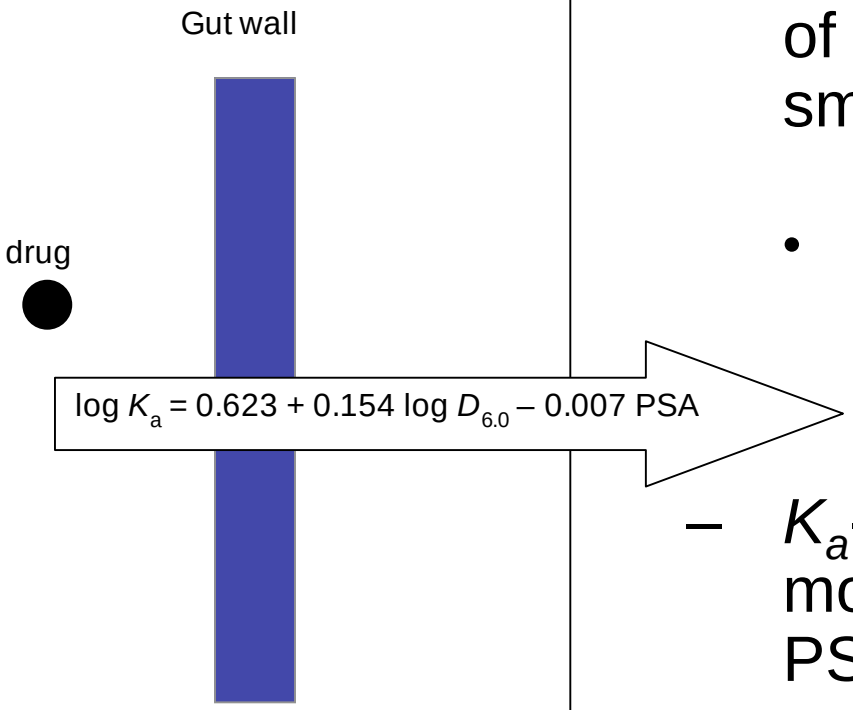


Is it possible to predict in vivo oral absorption based on chemical structure of the molecule?

Massive literature search was performed.

Criteria:

- human i.v. and p.o. data available
- poor solubility compounds excluded
  (dissolution is not the rate limiting step of absorption)
- FA value exists



- The absorption rate constants (K_a) of 22 passively absorbing drugs in small intestine were determined
  - deconvolution based on i.v. ja p.o. data from literature
- K_a-values were correlated with the molecular descriptors (MW, log P, PSA…) of the drugs
  - multivariant analysis
  - an predictive equation was obtained for K_a that can be then correlated with FA

Multivariant-analysis

Training set

- *the* K_a-values of 22 passively absorbing drugs were correlated with the computationally obtained molecular structure based physicochemical molecular decriptors

- log D (pH 5,5; 6,0; 6,5; 7,4)
  - ACDlabs-software
- PSA
  - SAVOL-software
- log P
  - ACDlabs- and ClogP for Windows – softwares
- HBD
  - the sum of OH- and NH-groups
- HBA
  - The sum of O- and N-atoms
- MW

Obtained QSPR-models and their statistics

$\log K_a = 0{,}623 + 0{,}154 \log D_{6,0} - 0{,}007$ PSA

($Q^2 = 0{,}75$; $R^2 = 0{,}76$; RMSE = 0,25)

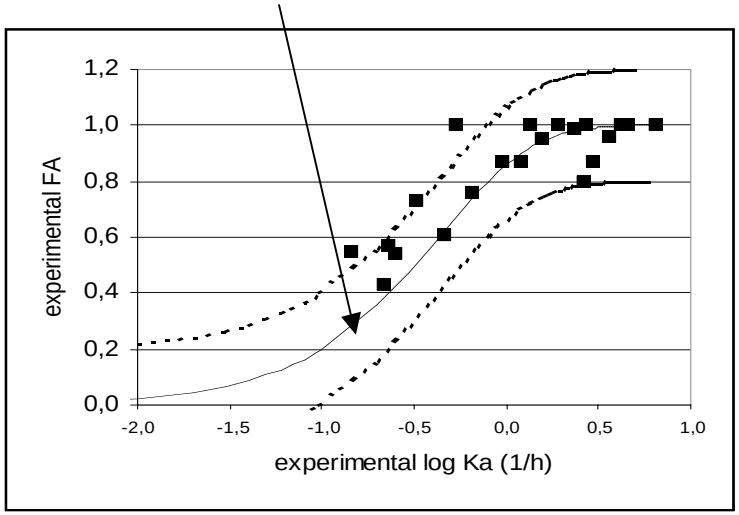
$\log K_a = 0{,}424 + 0{,}143 \log D_{6,0} - 0{,}129$ HBD

($Q^2 = 0{,}74$; $R^2 = 0{,}75$; RMSE = 0,26)

$\log K_a = 0{,}636 + 0{,}098 \log D_{6,0} - 0.004$ PSA $- 0{,}088$ HBD

($Q^2 = 0{,}69$; $R^2 = 0{,}71$; RMSE = 0,28)

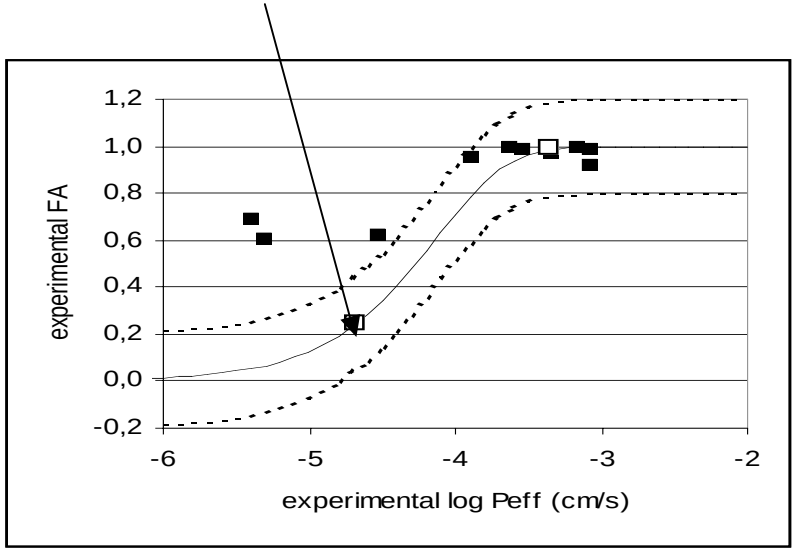
ideal ratio of K_a ja FA



FA-values obtained from literature

(FA = fraction of drug absorbed from the dose)

ideal ratio of P_{eff}:n ja FA



FA-values obtained from literature

P_{eff} = effective permeability at small intestine

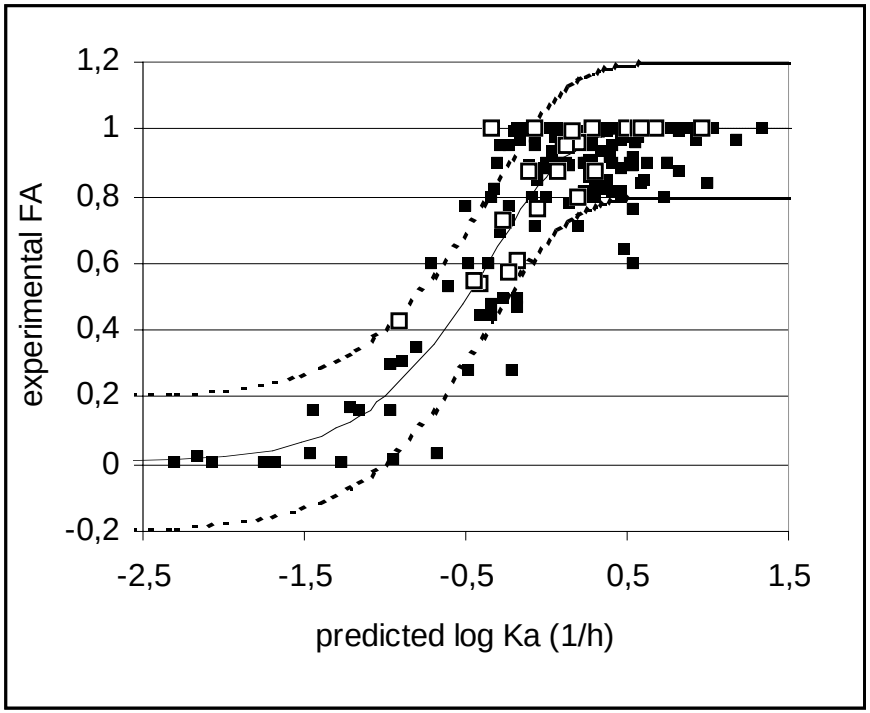
- obtained by isolating a 10 cm segment of jejunum for drug absorption
- difficult and time consuming
- P_{eff} has been measured for about 30 drugs

Testing of the model

Test set of 169 drugs

Criteria:

- permeability is the rate limiting step
- mainly absorbed by passive diffusion
- FA-values from literature



$\log K_a = 0.623 + 0.154 \log D_{6.0} - 0.007\ \mathrm{PSA}$

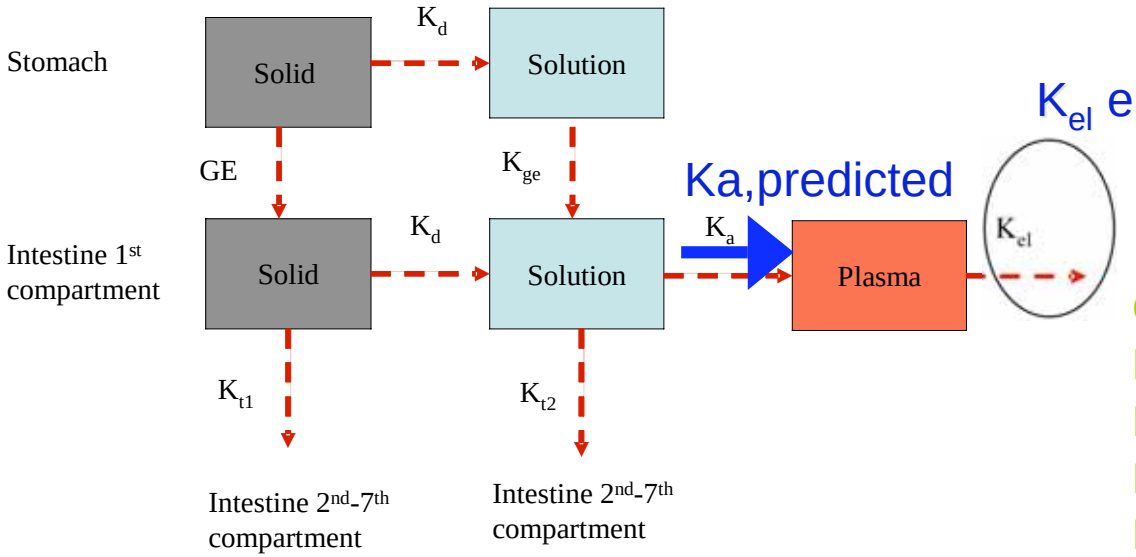
J Med Chem 2006;49(12):3674-81

Conclusions

- *The value of* K_a can be predicted virtually
- Models are simple
- Models can be used for the molecules if
  - permeability is the rate limiting step of absorption, not dissolution
  - drug absorption mainly via passive mechanism

The predicted K_a-values can be combined into Compartment Absorption and Transit (CAT) model

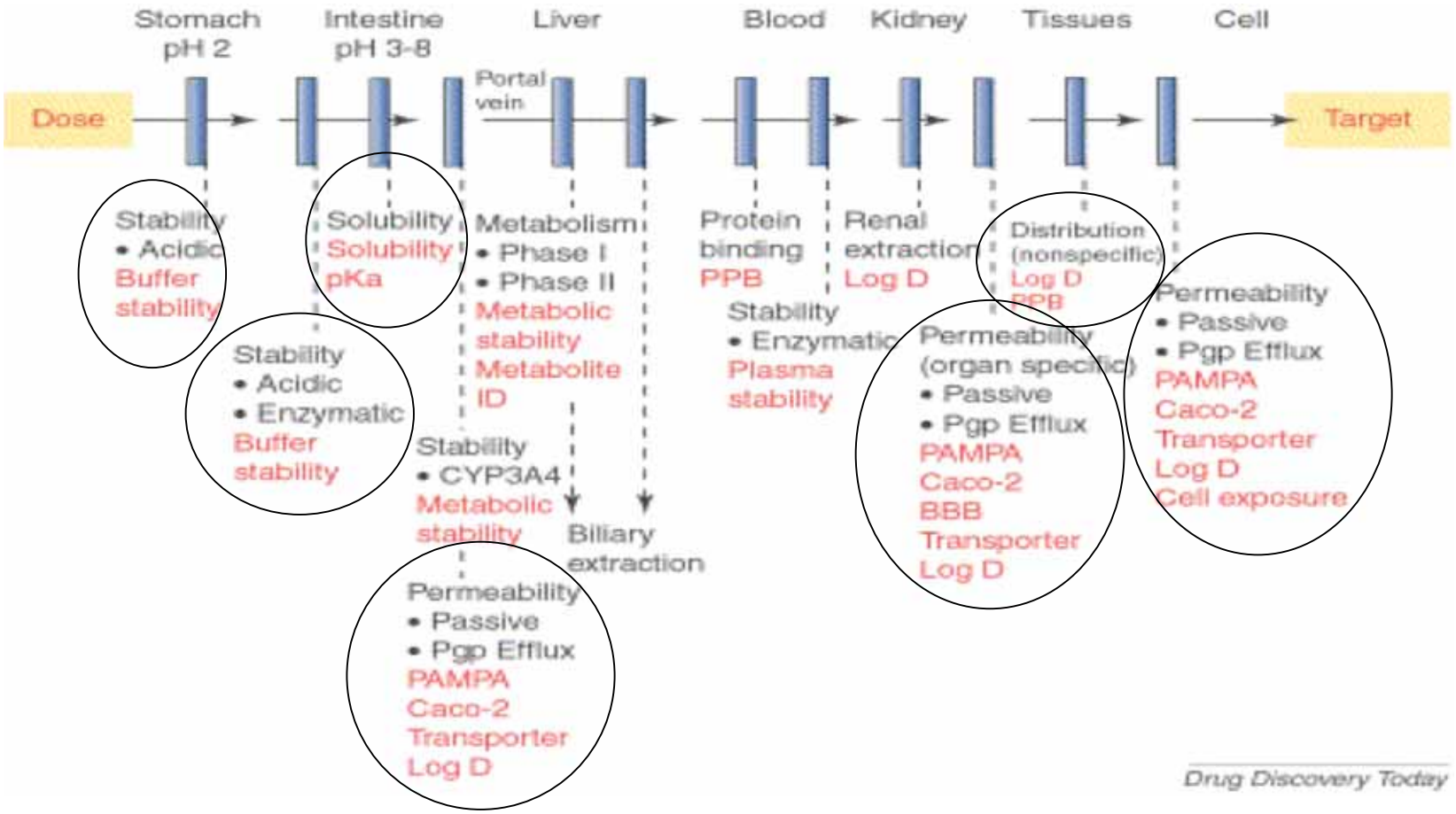
--> is it possible to predict concentration profile in plasma based on computation ?



GE gastric emptying
K_{ge} GE rate constant
K_d dissolution rate constant
K_t transit rate constant
K_a absorption rate constant

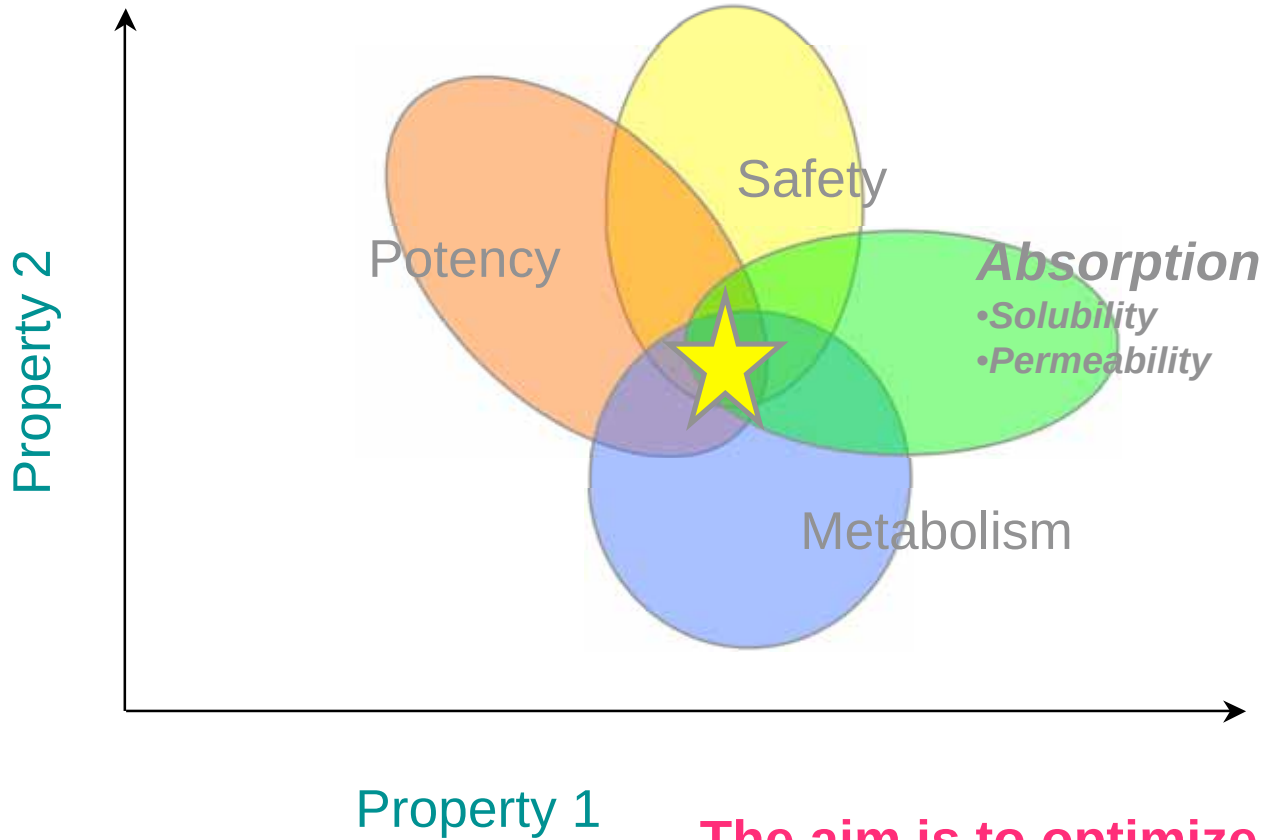
***In silico* or *in vitro* prediction of absorption and elimination rates and volume of distribution are required for successful prediction**

There are several kinetic barriers and factors.
Some can be predicted based on physicochemical properties.
Some of them are active processes (transport, metabolism)



Drug Discovery Today

The properties of the compound have to overlap



The aim is to optimize the parameters based on in silica calculations/simulations and in vitro experiments

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