Swiss Institute of Bioinformatics

A BOILED-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules

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The fate of an oral drug in the body

Oral dosage

Liberation

Active ingredient in **solution**

Absorption

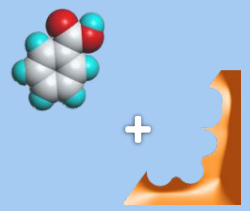
Distribution

Metabolism

Excretion

Pharmacokinetics (ADME)

Interaction with the **therapeutic target** (protein)



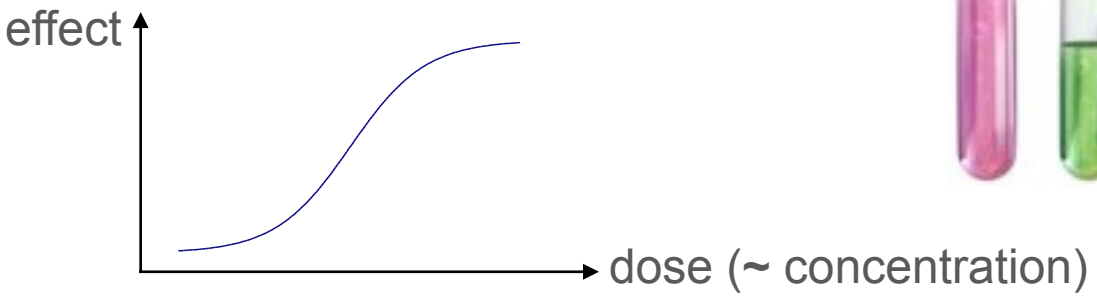
Pharmacodynamics

Therapeutic effect

Clinical impact of ADME

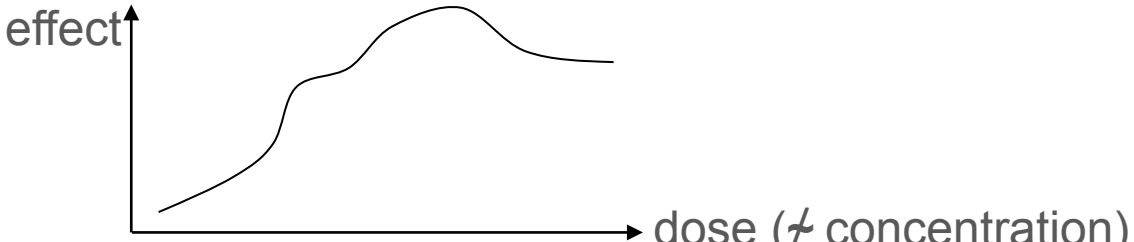
***In vitro*:**

dose → concentration → effect



***In vivo*:**

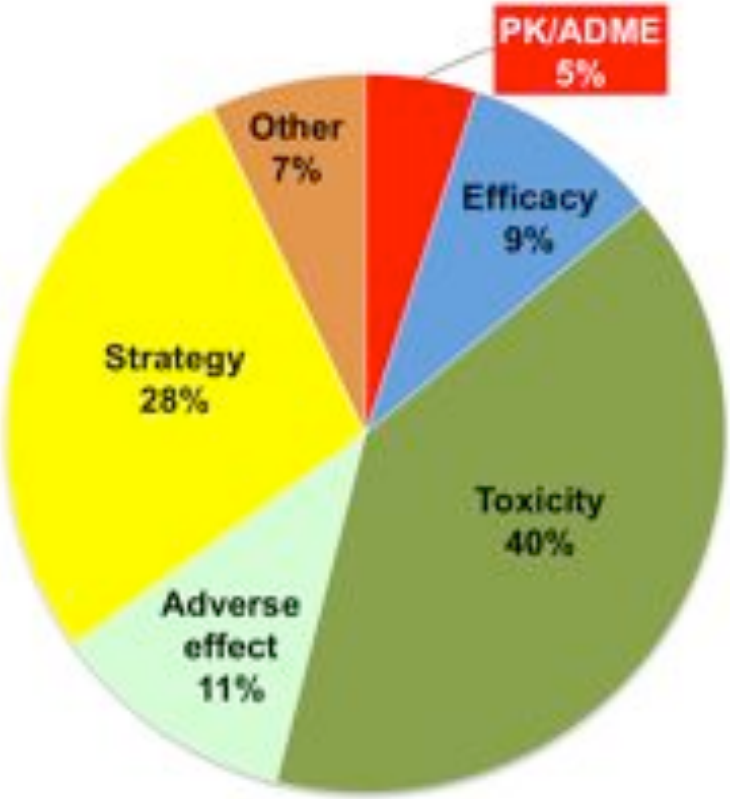
dose → ADME → concentration → effect



Failure for oral drugs in clinical development

1964 - 1985 (phases 2/3)

R.A. Prentis *et al*. *Br. J. Clin. Pharm.* **1988**
T. Kennedy *Drug Discov. Today* **1997**

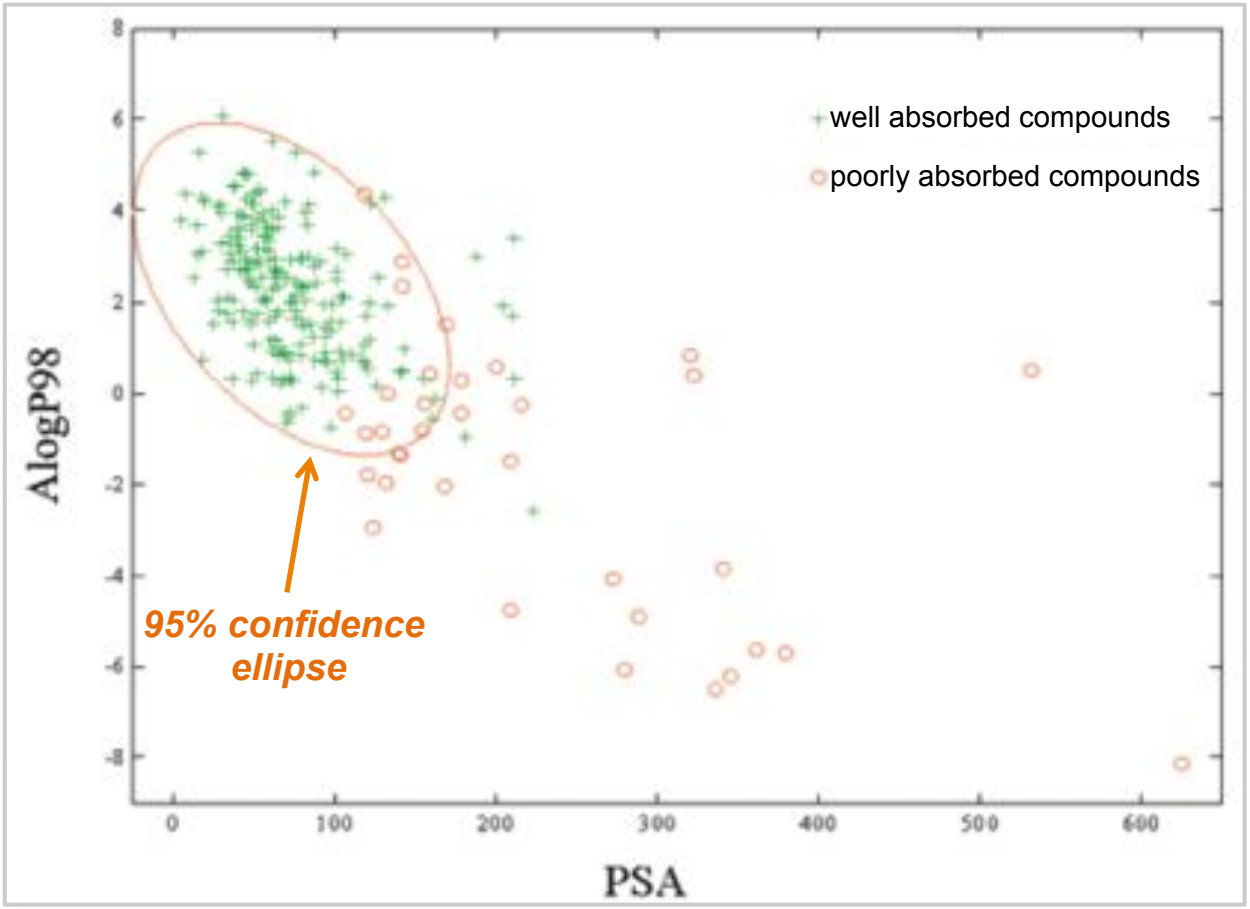


2000 - 2010 (phases 2/3)

M.J. Waring et al. *Nat. Rev. Drug Discov.* **2015**
J. Arrowsmith & P. Miller *Nat. Rev. Drug Discov.* **2013**

- Estimation of ADME at early steps of drug discovery for PK profiles
- Development of computer models to predict ADME from chemical structures

Physicochemical parameters and passive absorption

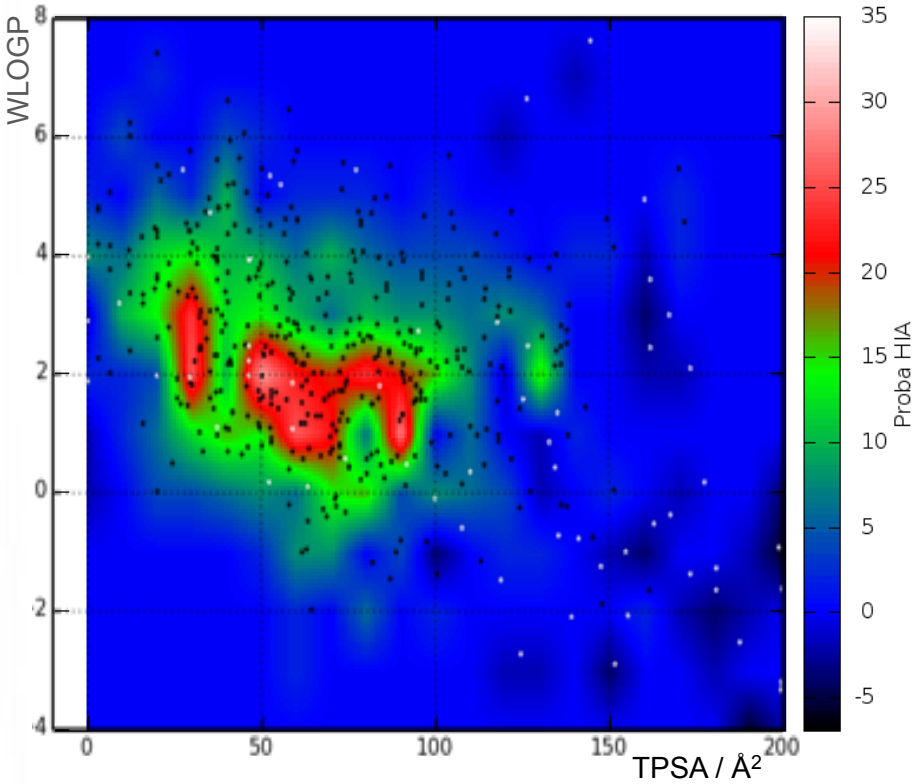


- The **Egan Egg**
- Great **practical utility**
  500+ citations[1,2]
- **Hard to reproduce**
  closed-source descriptors
  partly undisclosed dataset
- **Purely descriptive**
  Delineation of the physicochemical space of well-absorbed drugs.

1. W.J. Egan *et al. J. Med.Chem.* **2000**
2. W.J. Egan *et al. Adv. Drug Deliv. Rev.* **2002**

On the way of laying our own egg

- Dataset : from Shen *et al.*[1]
- Structures : neutralized and translated into SMILES
- Descriptors : WLOGP, in-house implementation Wildman and Crippen[2] Log *P*
  TPSA, topological polar surface area from Ertl *et al.*[3]



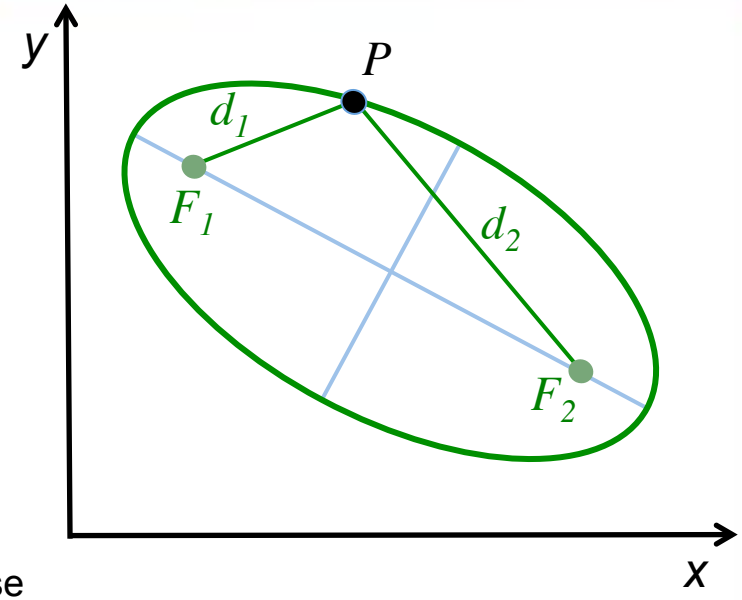
- well absorbed ° pooly absorbed

- Clear signal ✔
- Build the predictive model i.e. finding the classifying ellipse.

1. J. Shen, J. *et al. J. Chem. Inf. Model.* **2010**
2. S.A. Wildman & G.M. Crippen *J. Chem. Inf. Comput. Sci.* **1999**
3. P. Ertl *et al. J. Med. Chem.* **2000**

Methodology for the optimization of the ellipse

- Curation of **training set**[1,2] for **passive** absorption
  - 567 well-absorbed molecules
  - 93 poorly absorbed molecules
- Translated in SMILES, neutralized, aromatized



- **Parameters** geometric definition of the **ellipse**
- **Monte Carlo (MC)** optimization :
  1. generate initial ellipse and **evaluate** for classification
  2. random change ➔ new ellipse to evaluate
  3. use Metropolis criterion to keep or reject the new ellipse
  4. steps 2. and 3. repeated 100'000 times

100'000 parallel runs ➔ 10^{10} ellipses to evaluate for classification

- **Evaluation** : $Score = MCC - 0.05 \times surface$

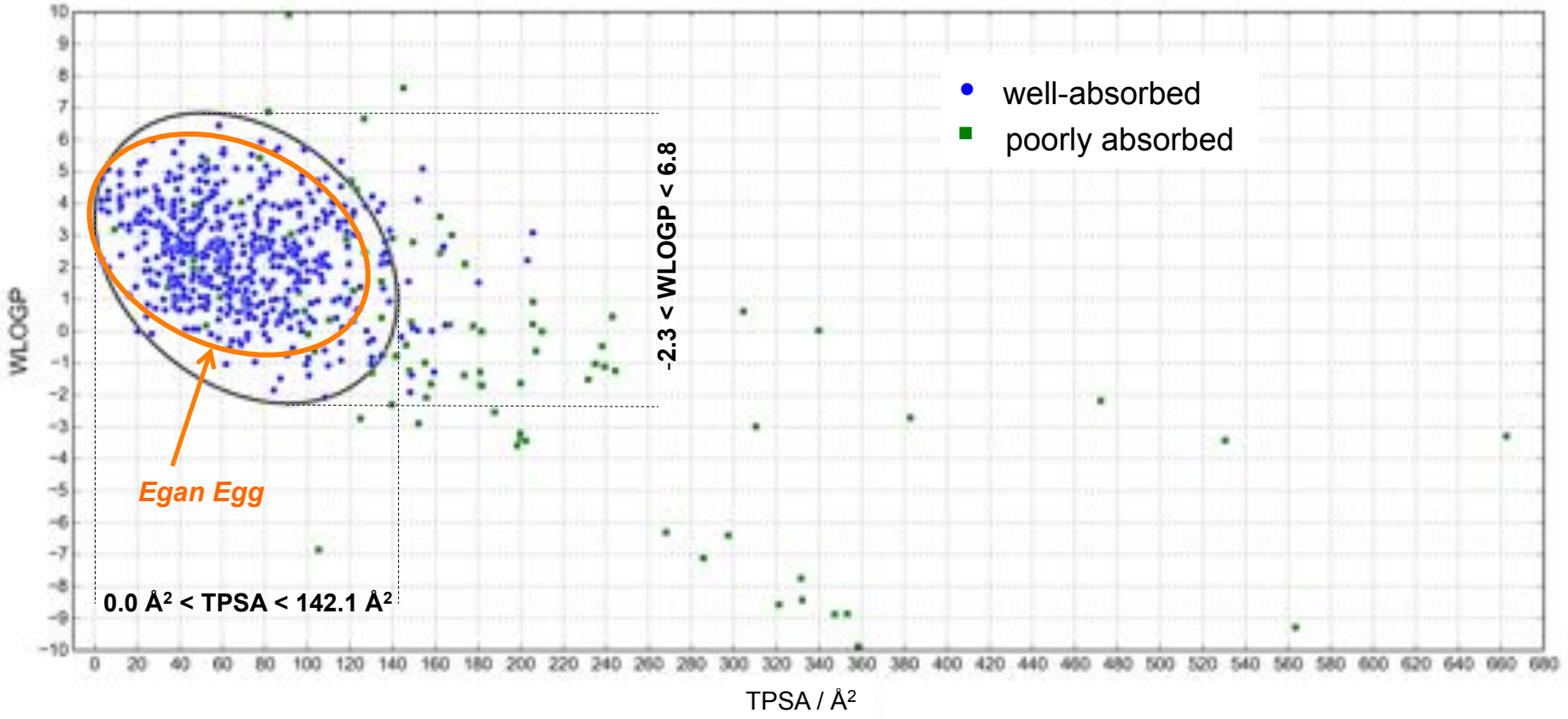
Matthew's Correlation Coefficient

$$MCC = \frac{(TP \times TN) - (FP \times FN)}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

from -1 to +1 (perfect prediction), near 0 for random classification.

1. J. Shen, *et al. J. Chem. Inf. Model.* **2010**
2. D. Newby *et al. Eur. J. Med. Chem.* **2013**

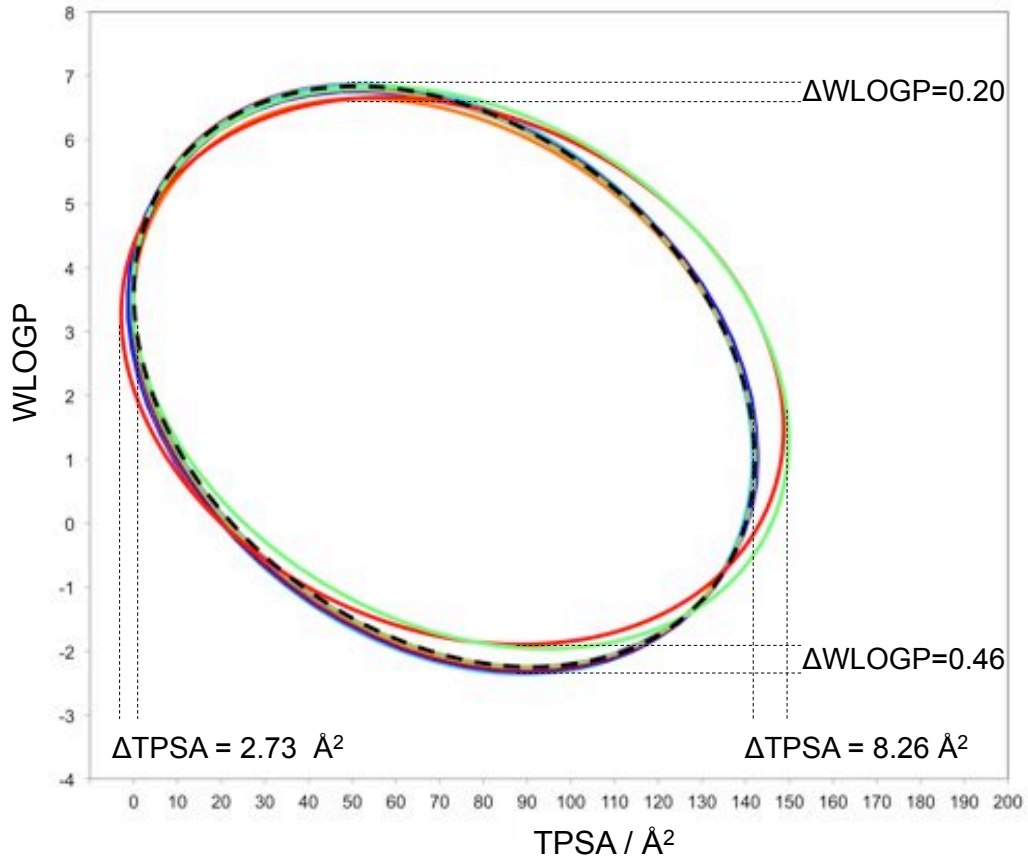
Best classification ellipse for passive absorption



- **MCC = 0.70**
- **Accuracy = 93 %**

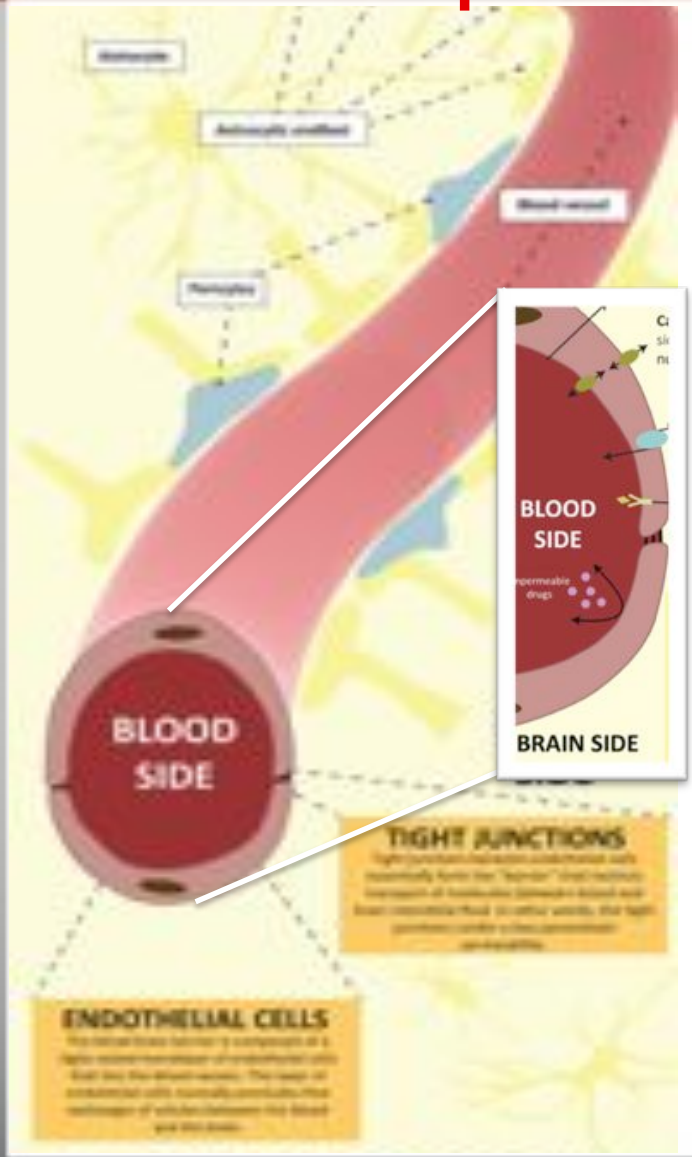
- In accordance with usual guidelines for good absorption
- Consistent with Egan Egg

10-fold crossvalidation



- MCC_{CV} = 0.65 / $Accuracy_{CV}$ = 92%
- Internal robustness ✔

Another important physiological barrier : BBB

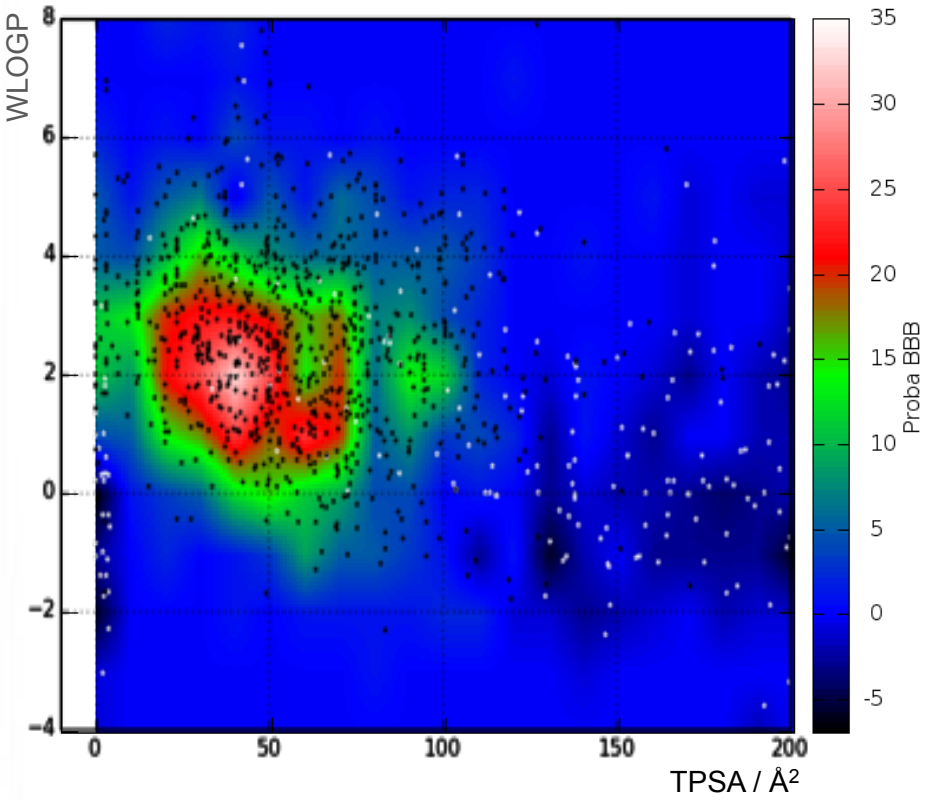


- **Blood-Brain Barrier** (BBB) is an effective **shield** protecting the brain :
  - **physical** barrier
    e.g. tight junctions preventing paracellular penetration
  - **biochemical** barrier
    enzymatic activities and active efflux
    e.g. P-glycoprotein 1 (P-gp) pumping out
- **Passive diffusion** through BBB is the **major route** for drugs to access the brain from the bloodstream.[1]
- Fundamental for the **distribution** of central-acting drugs
  or reversely for limited **unwanted effects** of peripheral drugs (or any molecule)

1. L. Di *et al. Drug Discov. Today* **2012**

Heatmap for passive diffusion through BBB

- 156 permeant molecules (log *BB* > *0*, •) and
- 104 non-permeant molecules (log *BB* < *0*, °) taken from Brito-Sanchez *et al.*[1]



- Clear signal ✔
- narrower space ✔

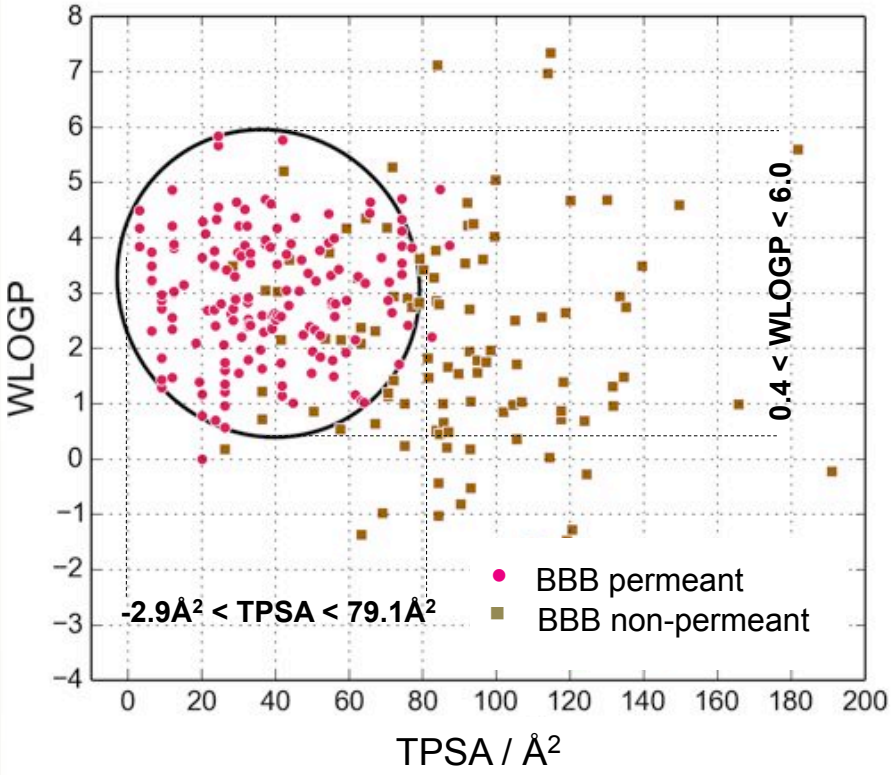
- Optimization of a different ellipse

  same method
  same descriptors

1. Y. Brito-Sánchez *et al. Mol. Inf.* **2015**

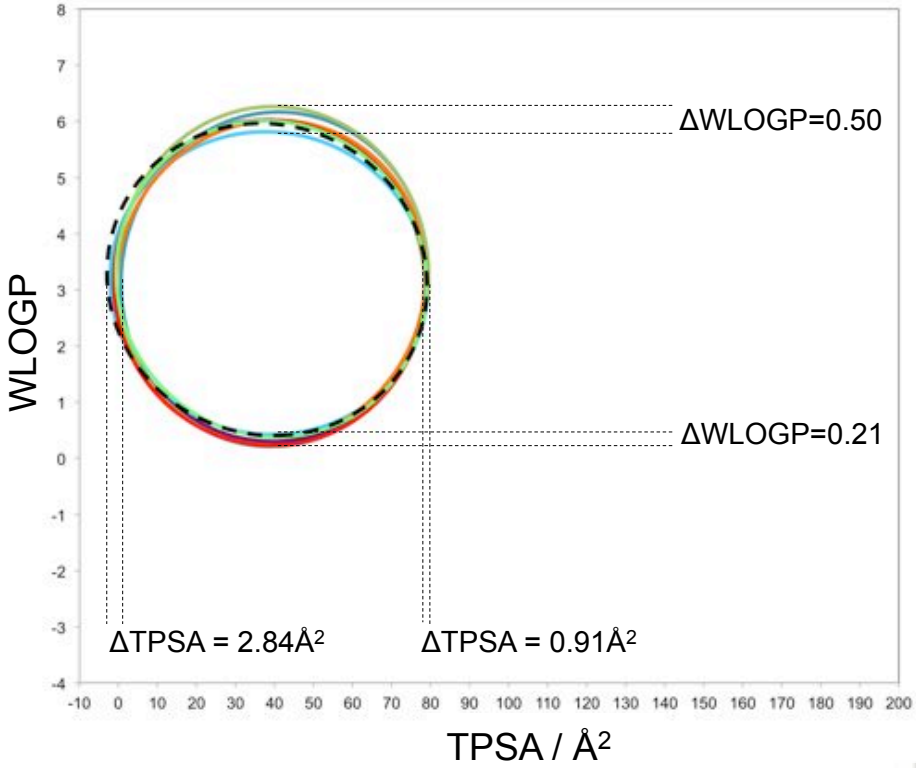
Best classification ellipse for passive BBB permeation

Final model



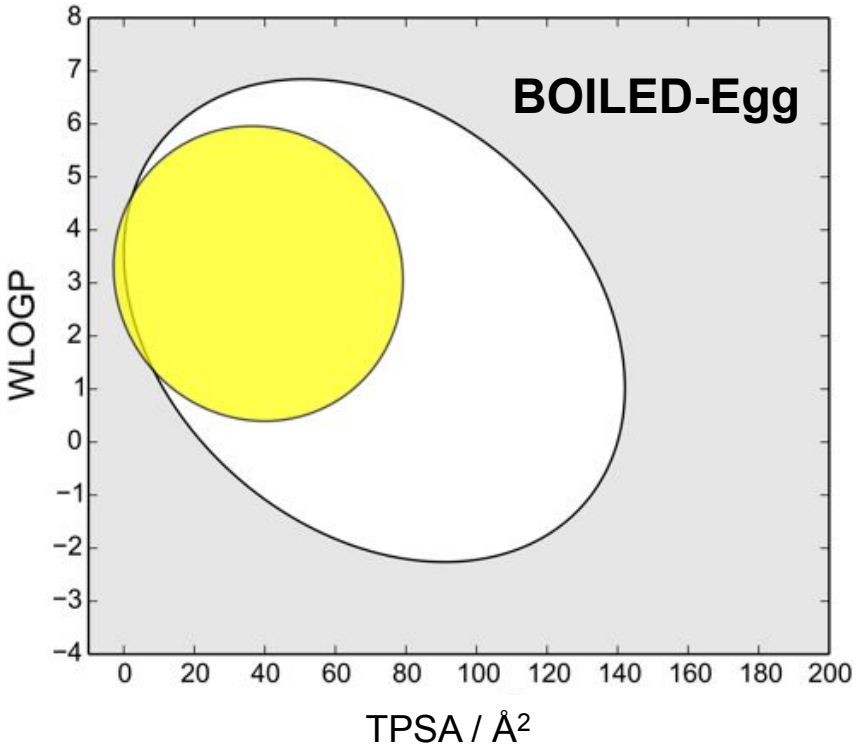
- **MCC = 0.79**
- **Accuracy = 90 %**
- Consistent with common guidelines for brain penetration

10-fold crossvalidation

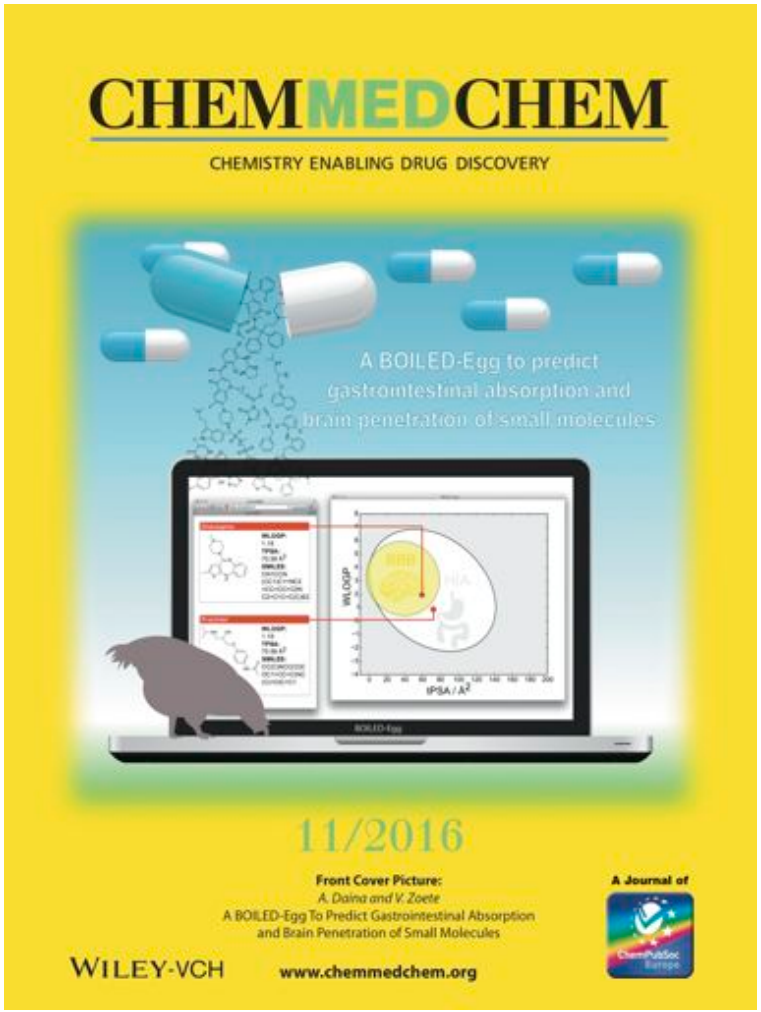


- MCC_{CV} = 0.75 / ACC_{CV} = 88%
- Internal robustness ✔

BOILED-Egg: merging both models



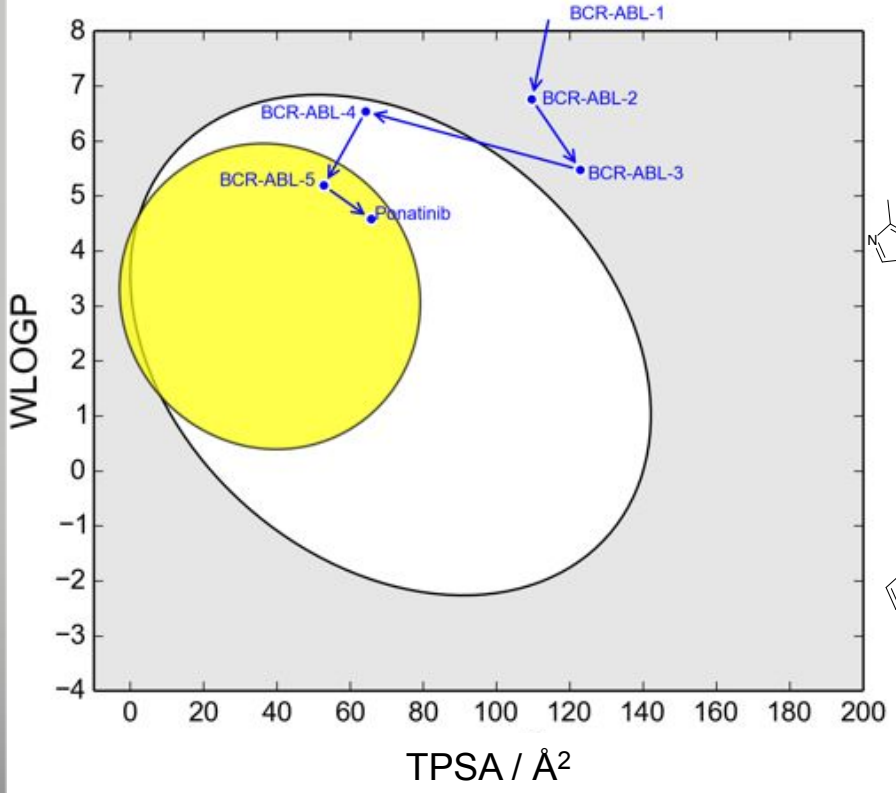
- Same referential
- Brain Or IntestinaL EstimateD permeation
- Yolk and white not mutually exclusive

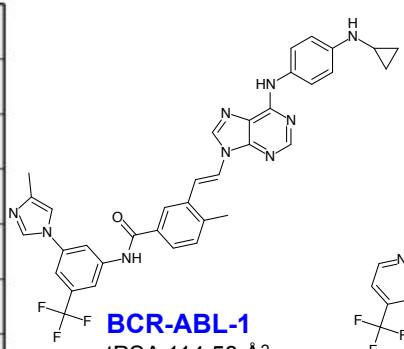


1. A. Daina & V. Zoete, *ChemMedChem* **2016**

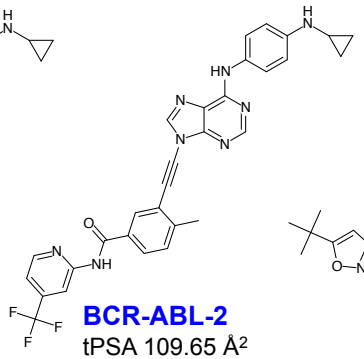
BOILED-Egg to track drug optimization path

- Exercise: Lead optimization of BCR-ABL tyrosine kinase inhibitors to anti-cancer Ponatinib[1].
- Successive PD and PK optimization steps.

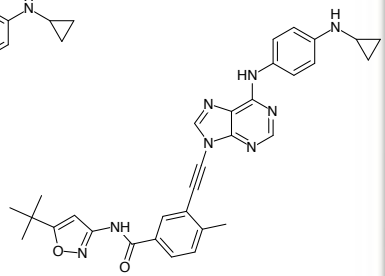




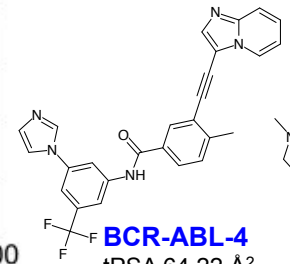
BCR-ABL-1
tPSA 114.58 Å²
WLOGP 8.34



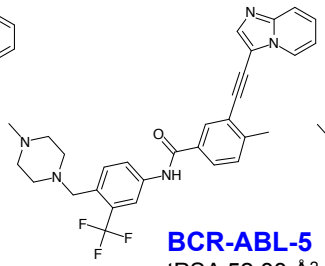
BCR-ABL-2
tPSA 109.65 Å²
WLOGP 6.76



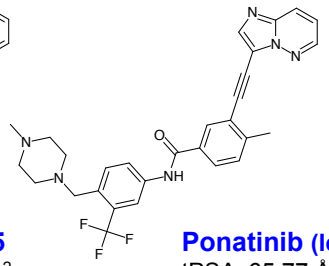
BCR-ABL-3
tPSA 122.79 Å²
WLOGP 5.48



BCR-ABL-4
tPSA 64.22 Å²
WLOGP 6.54



BCR-ABL-5
tPSA 52.88 Å²
WLOGP 5.19

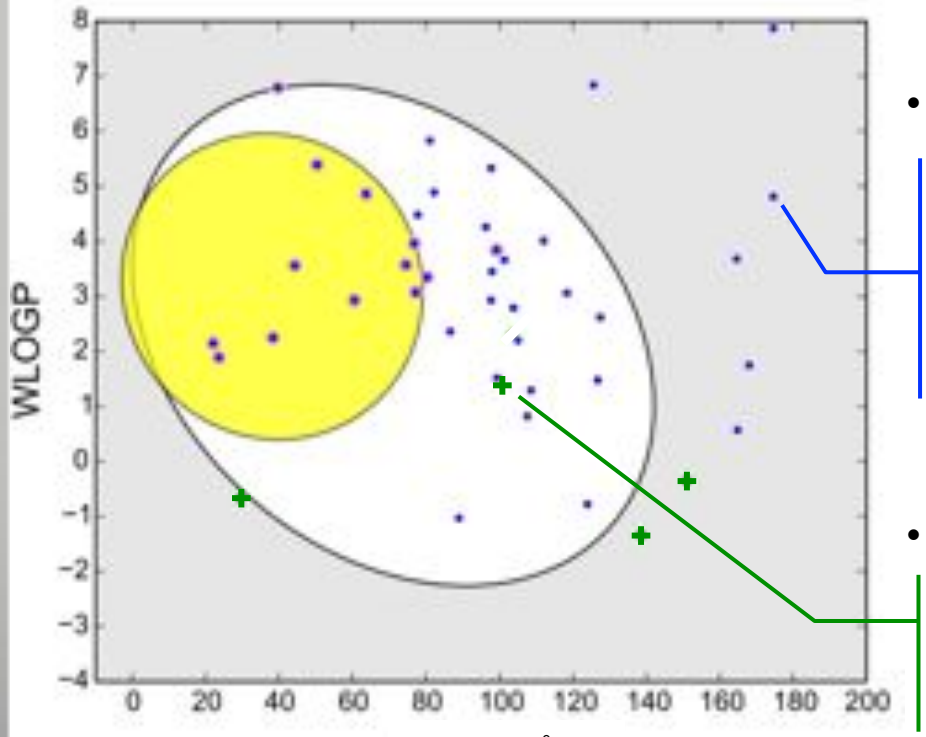


Ponatinib (Iclusig®)
tPSA 65.77 Å²
WLOGP 4.58

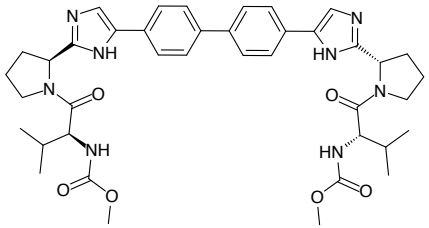
1. W.S. Huang *et al*. *J. Med. Chem.* **2010**

BOILED-Egg to map new FDA drugs

- Exercise: map 46 NCEs accepted by the FDA in 2014 and 2015
- Colored according to usage label
- 83% consistency for route of administration and in/out « white »

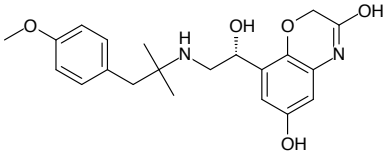


- 6 false negatives (FN)



Daclatasvir
Good absorption
Active transport[1] OCT1

- 1 false positives (FP)



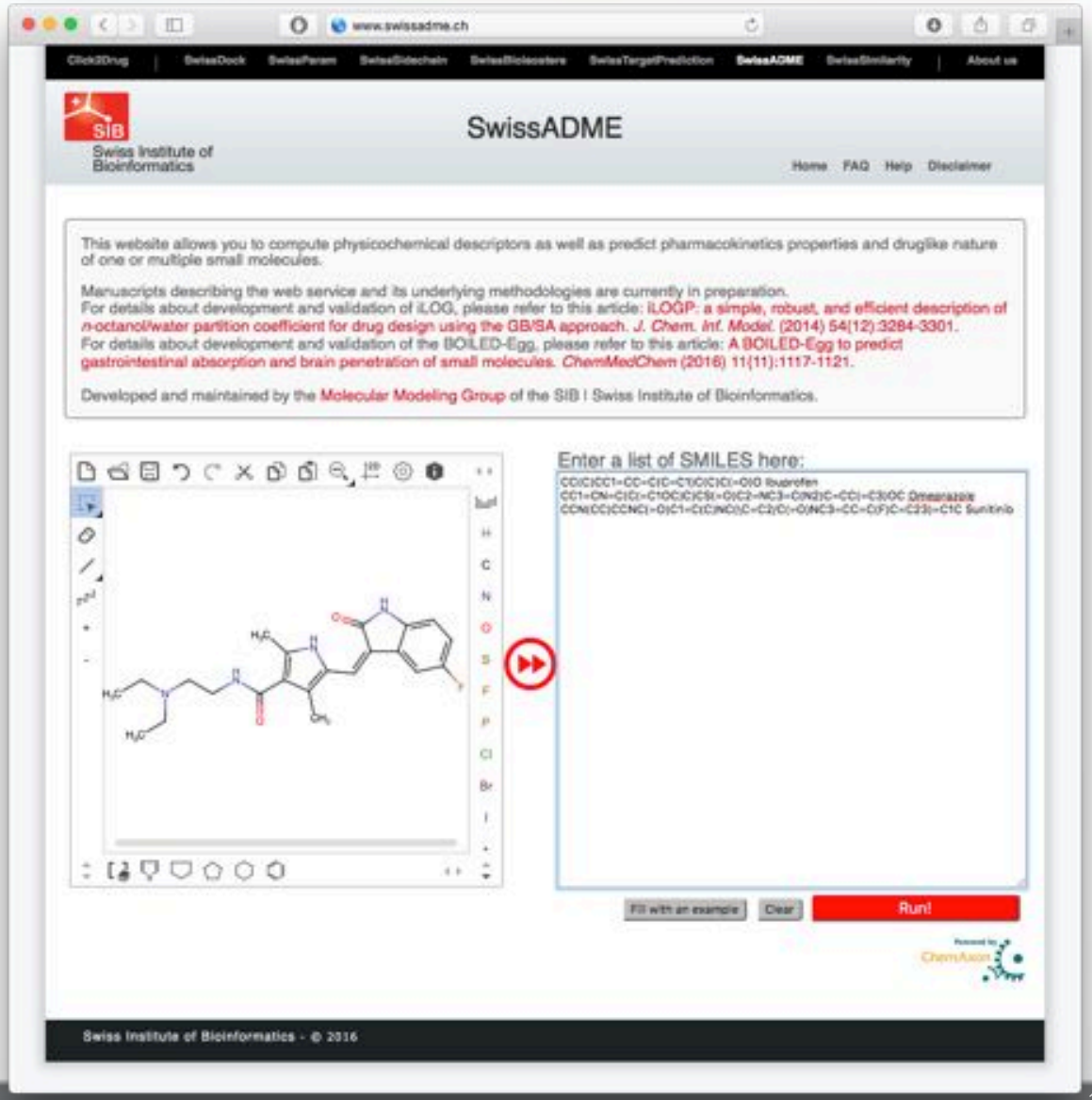
Olodaterol
FA 10-20%
P-gp efflux[2]

- Oral administration
- ✚ Other routes only (i.v., inhalation, transdermal, ...)
- CNS indication

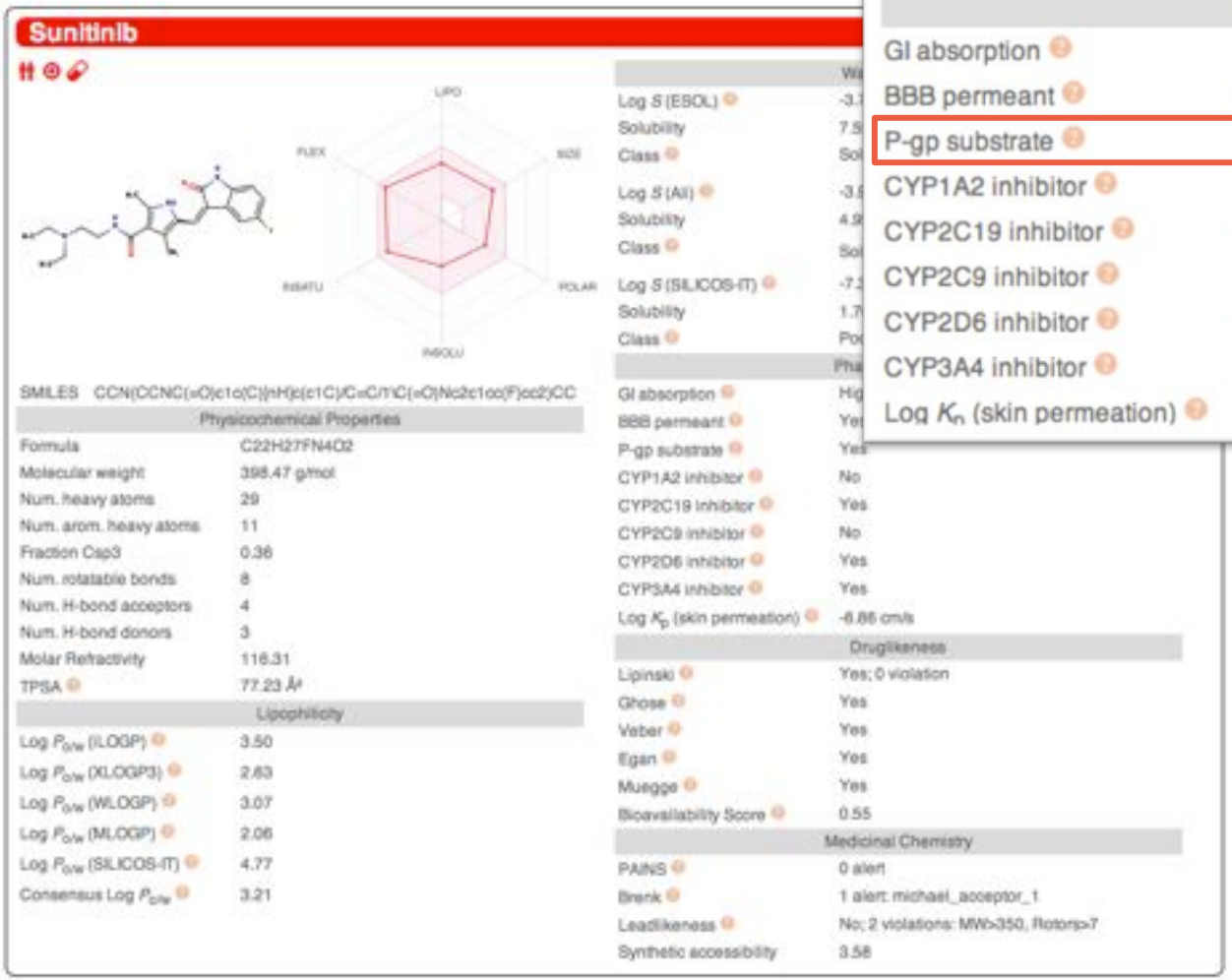
1. FDA, Clinical pharmacology reviews **2014**
2. Health Safety Regulation (Aus), **2014**

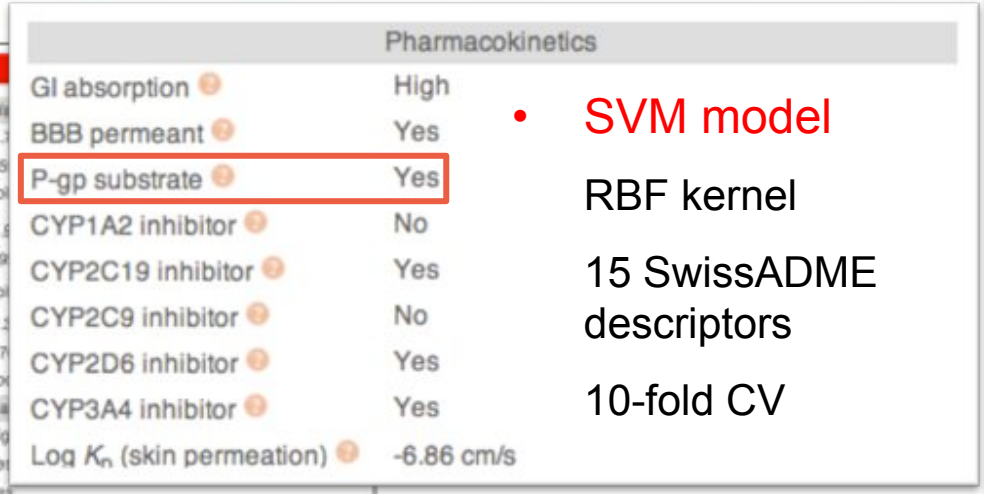
The BOILED-Egg within the SwissADME.ch web tool

- **SwissADME.ch** a free web tool to calculate pharmacokinetic, druglikeness and related parameters
- Standardized input and enahanced analysis
- Possibility to embed prediction of active transport



SwissADME one-panel-per-molecule output

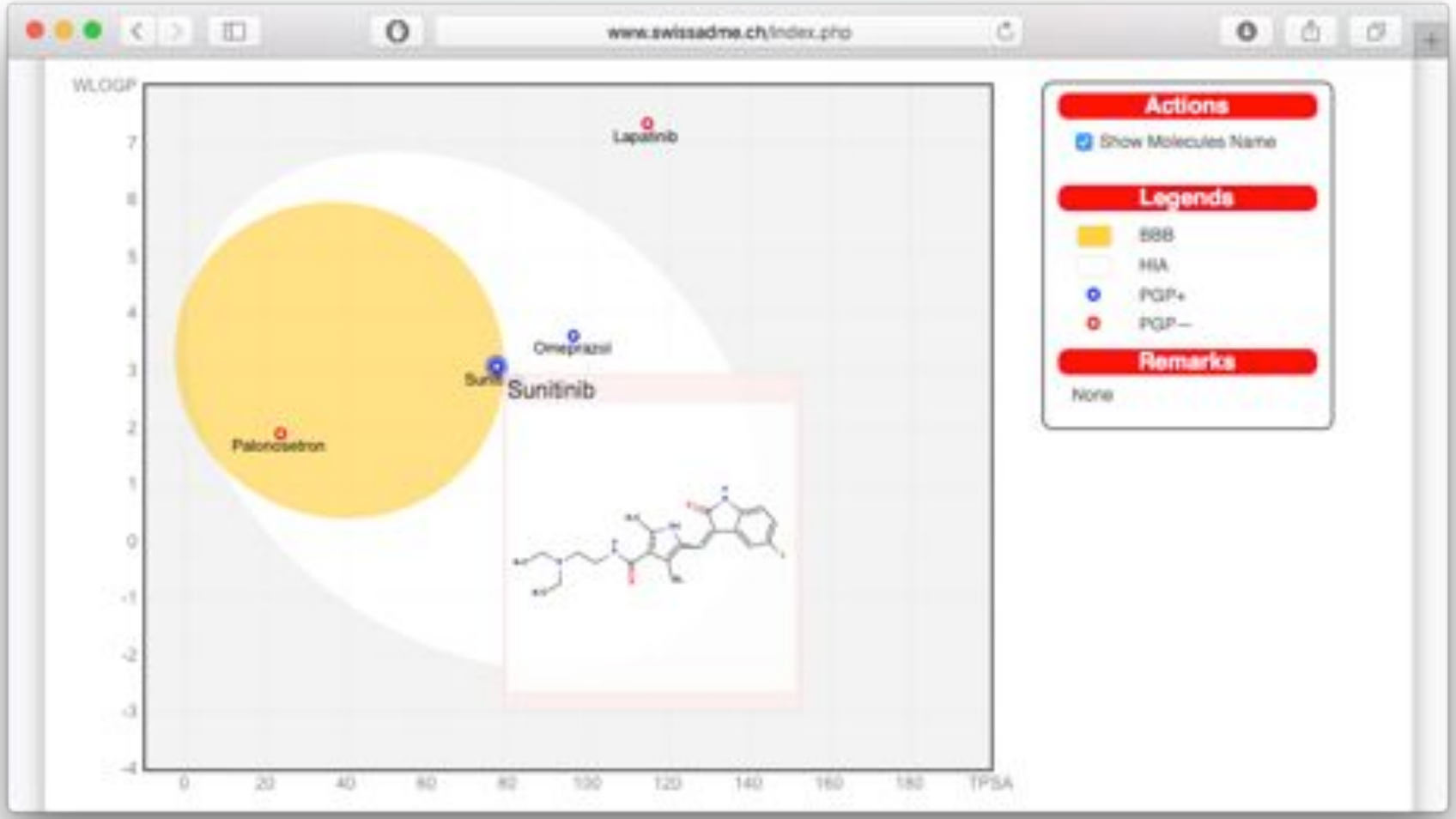




- SVM model
  - RBF kernel
  - 15 SwissADME descriptors
  - 10-fold CV
- Training: 564 substrates and 469 non-substrates[1]
- Test: 215 substrates and 200 non-substrates[2]
- Performance
  - $Accuracy_{CV}$: 72%
  - $Accuracy_{EXT}$: 89%

1. J. Mak *et al*. *J. Cheminfor.* **2015**
2. V. Poongavanam, *Bioorg. Med. Chem.* **2012**

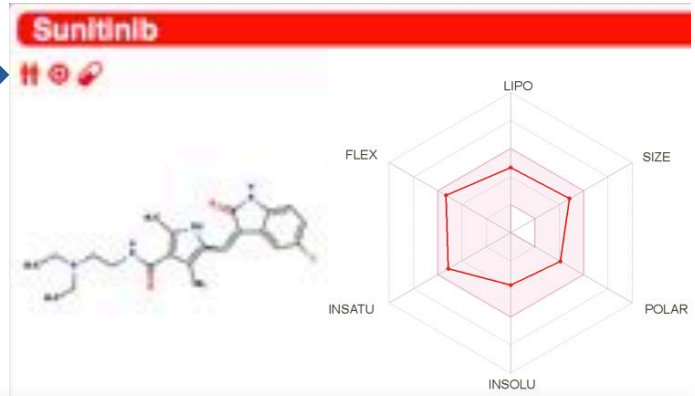
SwissADME graphical output

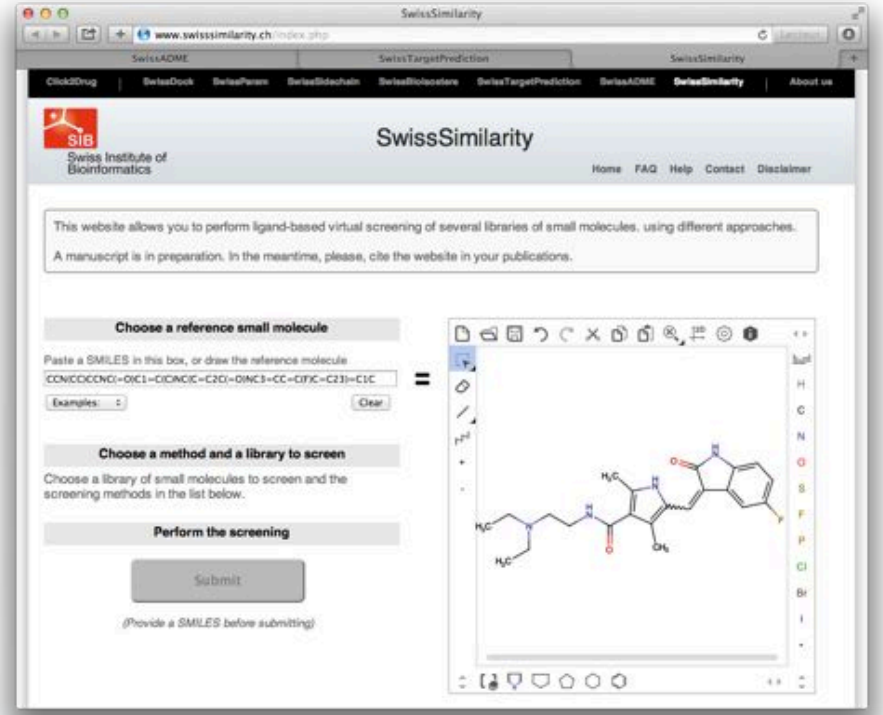


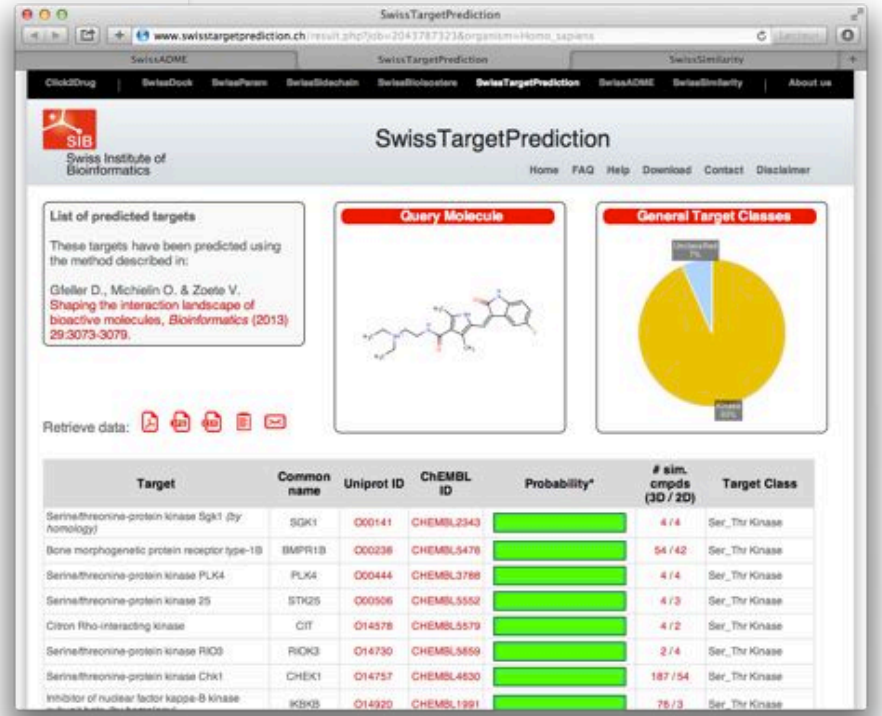
- SwissADME include an enhanced version of the BOILED-Egg, including
  - estimation of P-gp substrate (active efflux)
  - Interactive analysis capabilities

SwissADME: a module of SwissDrugDesign

- **SwissADME**:
  - Not published or communicated yet.
  - Promising start of 40+ jobs per day, on average.
  - Referenced in VLS3D.com or click2drug.org
- **Interoperability** with other tools of **SwissDrugDesign**



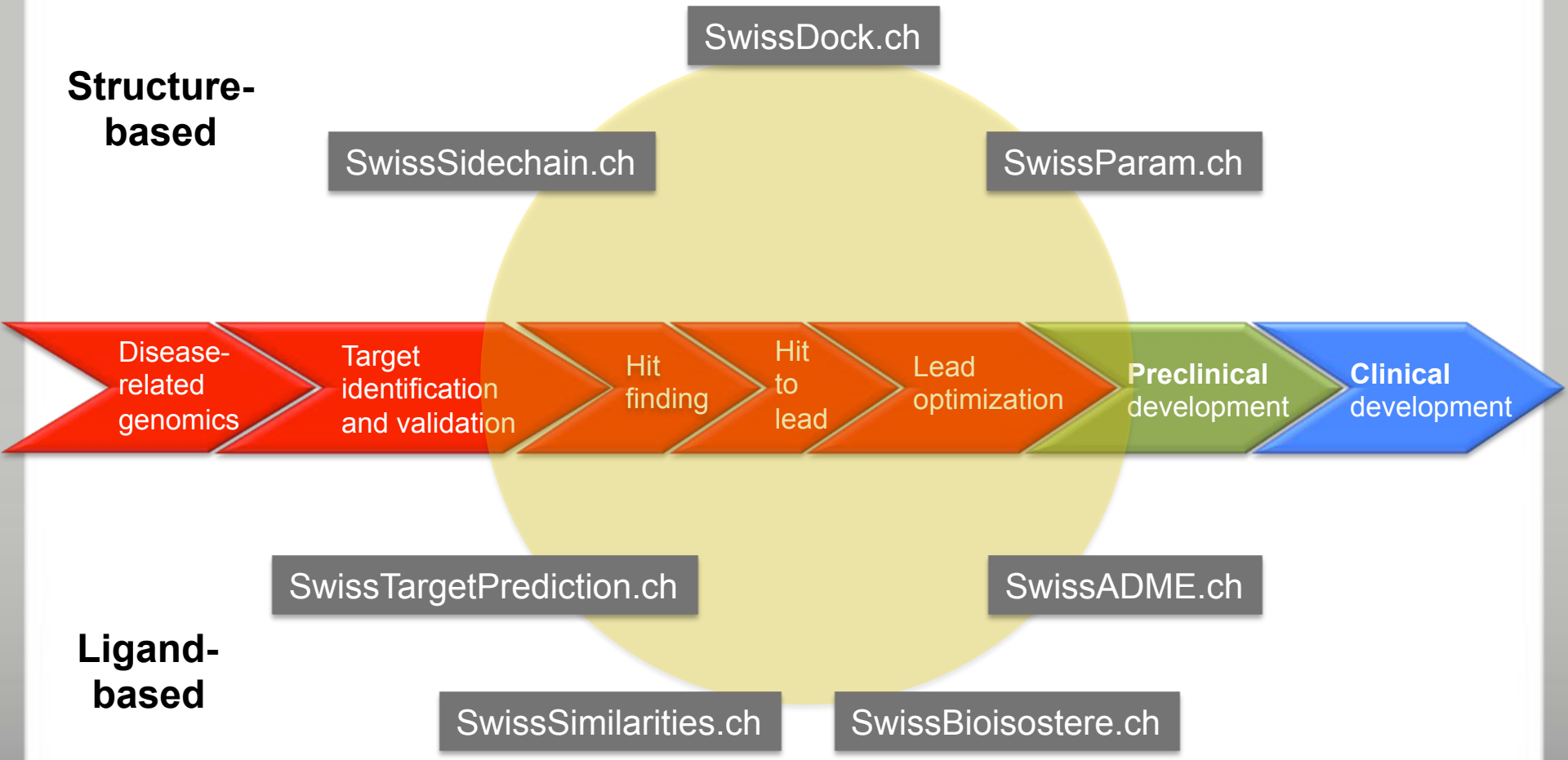




V. Zoete *et al. J. Chem. Inf. Model.* **2016**

D. Gfeller *et al. Nucl. Acids Res.* **2014**

SwissDrugDesign: SIB initiative in CADD



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