Predictive ADME Models in Drug Discovery: Can You Trust Them? Can You Afford Not To?

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11 October 2007

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A Galápagos Company

ADMEnsa
Bringing balance to optimization

Drug Discovery: Requires Prediction

Potent
Selective
Effective
Safe

Med Chem

Novel
Pure
COG
Safe

ADMEt

Appropriate
PK
Safe

Drug Discovery: ADME Prediction

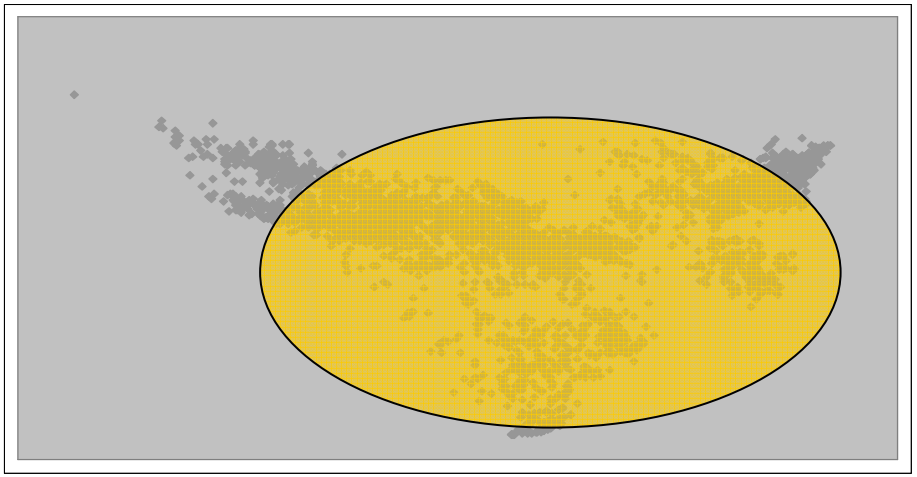
In Silico

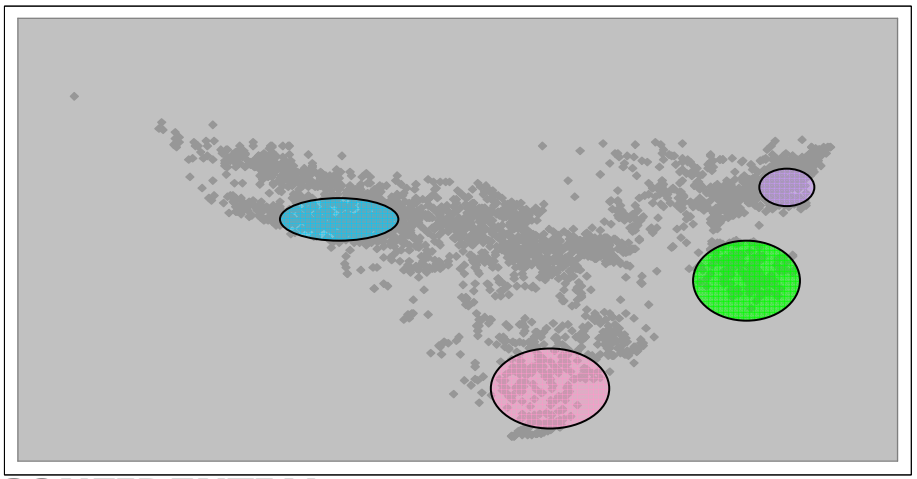
Throughput

Credibility?

Drug Discovery: ADME Prediction

In Silico





Credibility?

Global Models

- Cover as much chemical diversity as possible
- Capture 'long-range' trends in properties
- May not differentiate between close analogues

Local Models

- Based on data for specific chemistry
- May provide higher resolution for that chemistry
- Outside of 'chemical space' may rapidly lose predictive power

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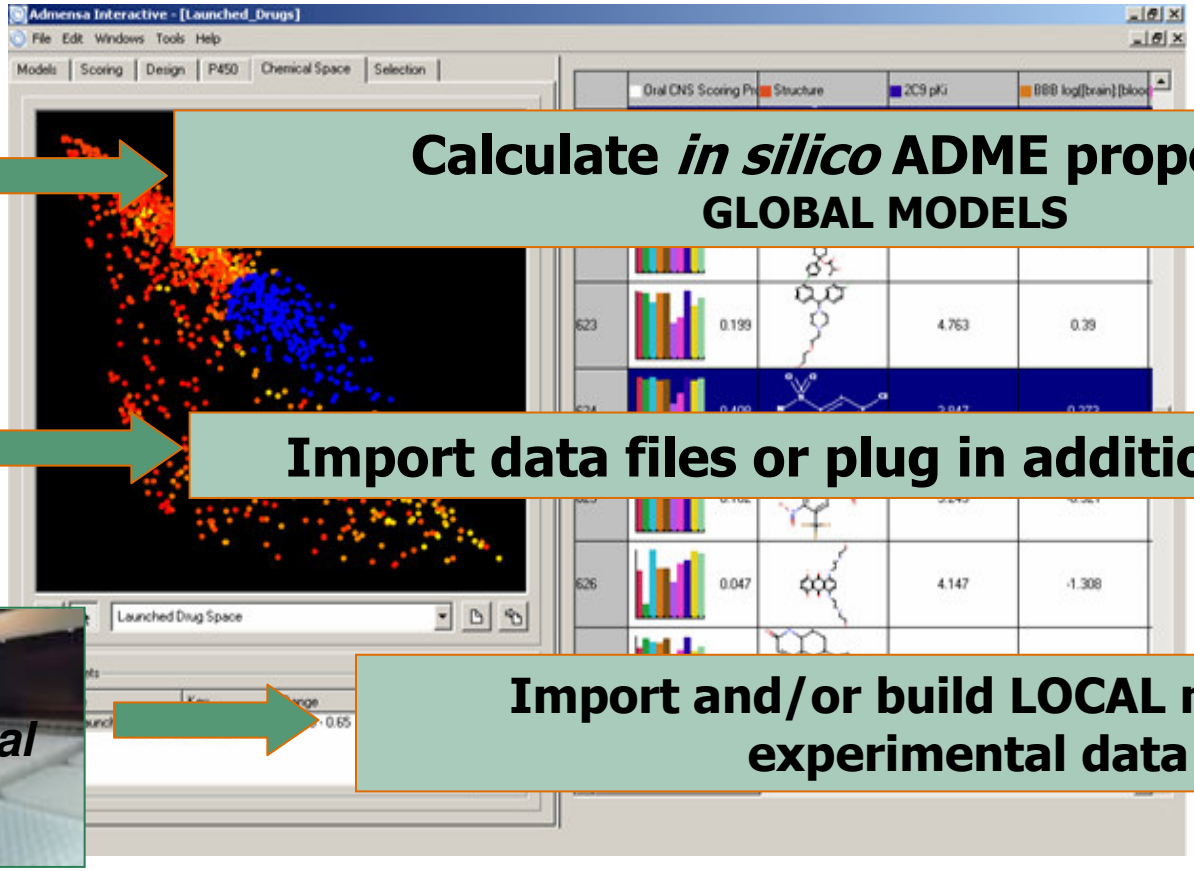
Drug Discovery: ADME Prediction

In Silico

SMILES or SDF



Calculate *in silico* ADME properties:
GLOBAL MODELS

Import data files or plug in additional models

Import and/or build LOCAL models on experimental data

User Interface: ADMEnsa Interactive™

Drug Discovery: ADME Prediction

In Silico

CYP1A2 Local Model build

- Training Set Results:
  - 55 compounds
  - 89% of the training compounds are correctly classified.
  - 18% false negative i.e. observed low predicted high.
  - 4% false positive i.e. observed high predicted low.

Training	*Predicted Low*	*Predicted High*	*%correctly classify*
Observed Low	**25**	5	0.83
Observed High	1	**24**	0.96
% Compounds correctly assigned within a predicted class.	0.96	0.82	

Likely error in prediction is "known"

- 79% validation compounds correctly classified
- 82% tests compounds correctly classified
- No false positive:
  - Highly confident in prediction Low
- Average false negative = 32%
  - ~32% of the predicted high could be observed low.

Validation	*Predicted Low*	*Predicted High*	*%correctly classify*
Observed Low	**8**	4	0.67
Observed High	0	**7**	100
% Compounds correctly assigned within a predicted class.	100	0.63	

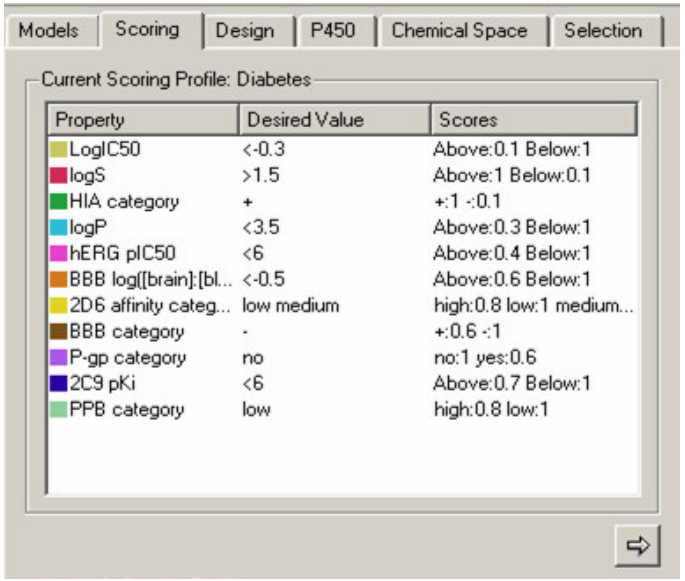
Test	*Predicted Low*	*Predicted High*	*%correctly classify*
Observed Low	**6**	3	0.67
Observed High	0	**8**	100
% Compounds correctly assigned within a predicted class.	100	0.73	

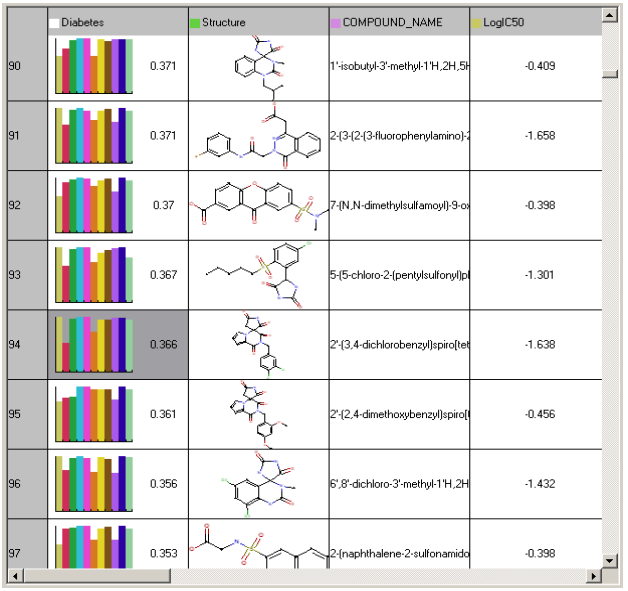
Drug Discovery: ADME Prediction

In Silico

Score and rank compounds against Target Product Profile

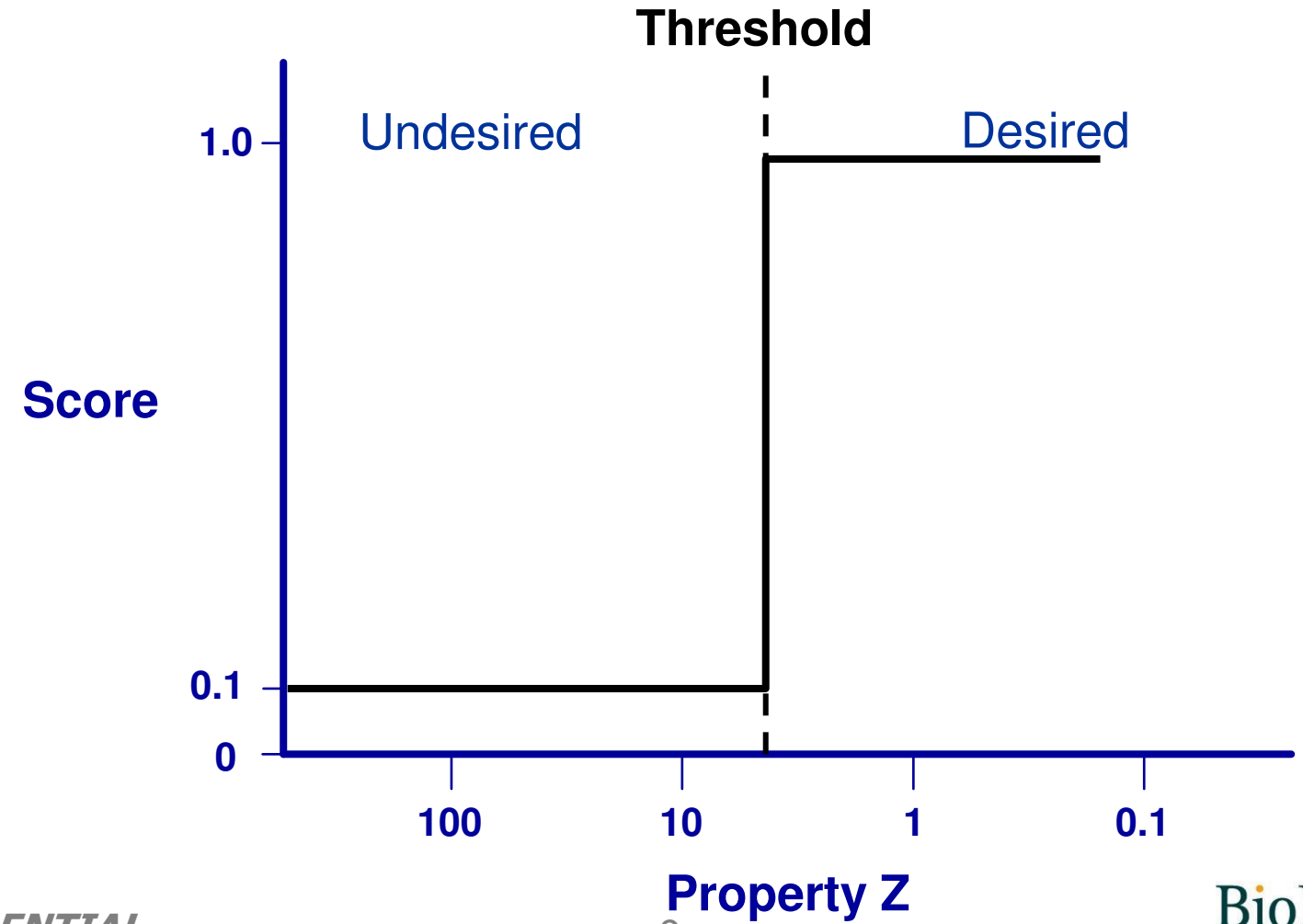
User-defined scoring profile



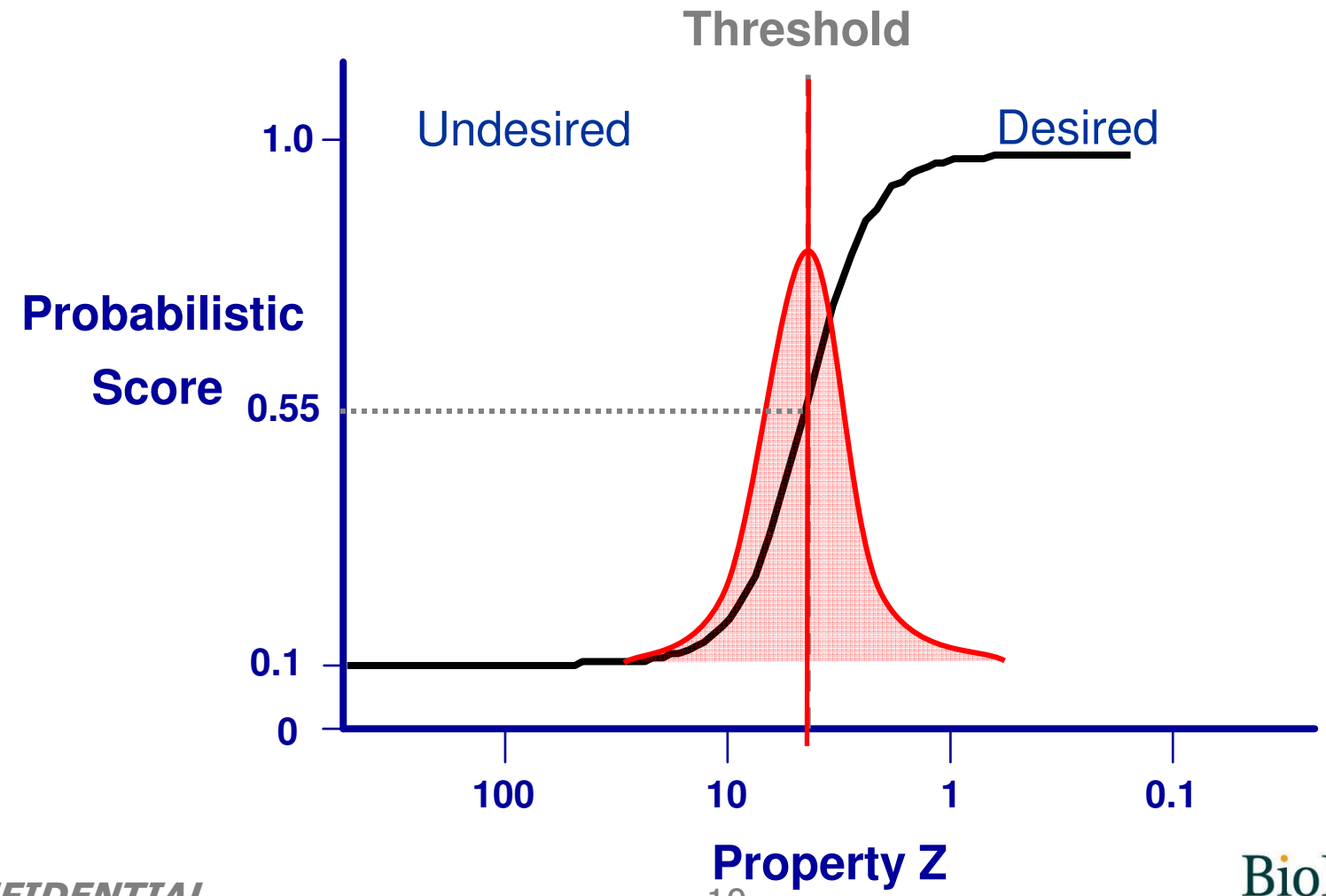


User Interface: ADMEnsa Interactive™

Filtering


Threshold
Undesired
Desired
1.0
0.1
0
Score
100
10
1
0.1
Property Z

Probabilistic Scoring

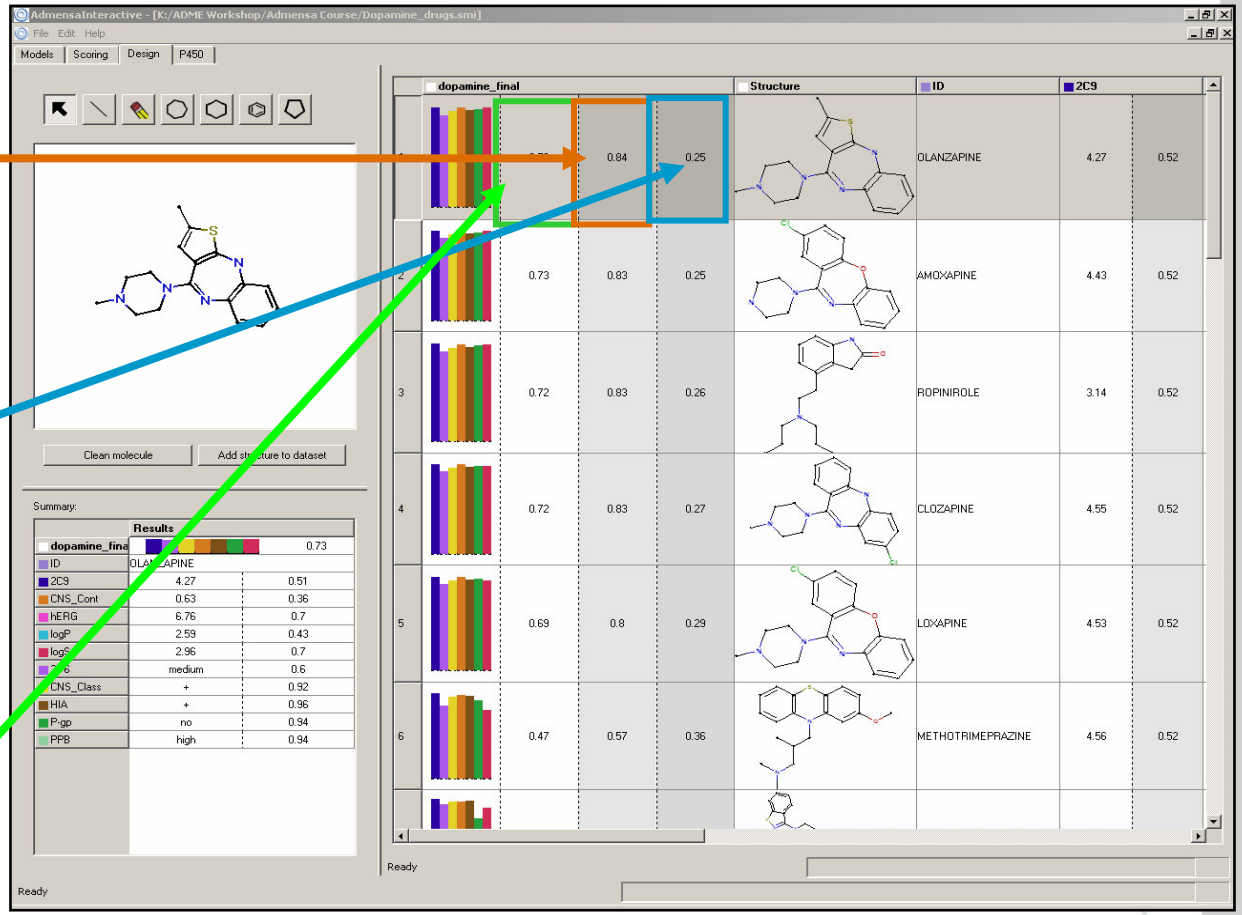


Probabilistic Scoring
Score, Uncertainty and Rank

Score: The best estimate of the likelihood of success of a compound against the scoring criteria.

Standard deviation: A measure of the uncertainty in this estimate.

Rank: A 'utility value' enabling compounds to be ranked in order of priority, based on a combination of score and uncertainty

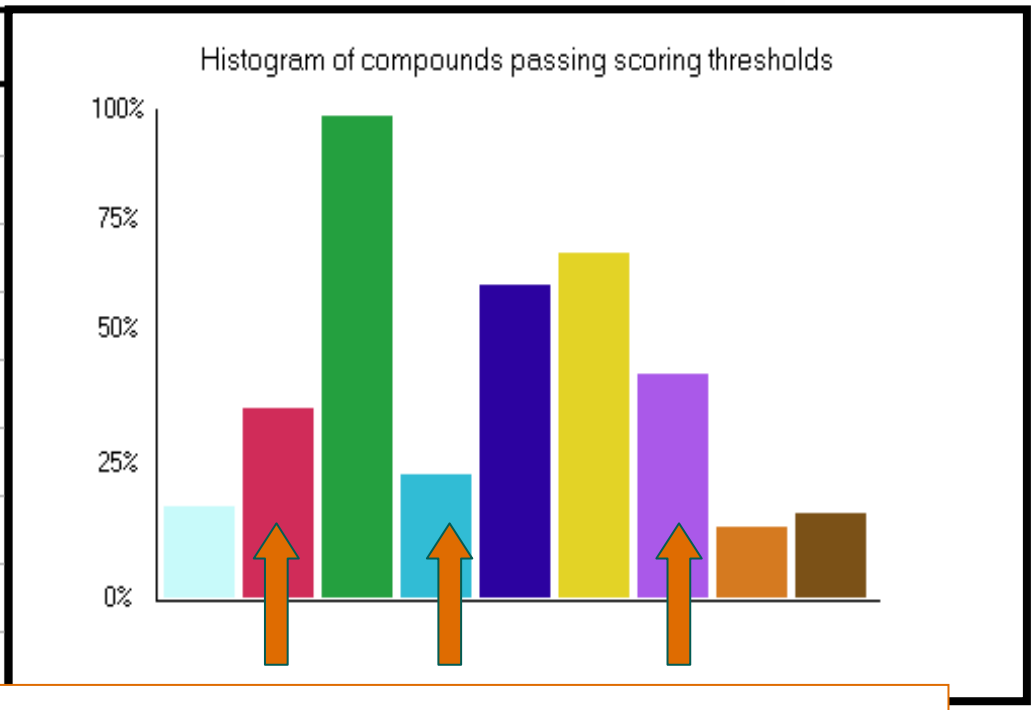


Drug Discovery: ADME Prediction

In Silico

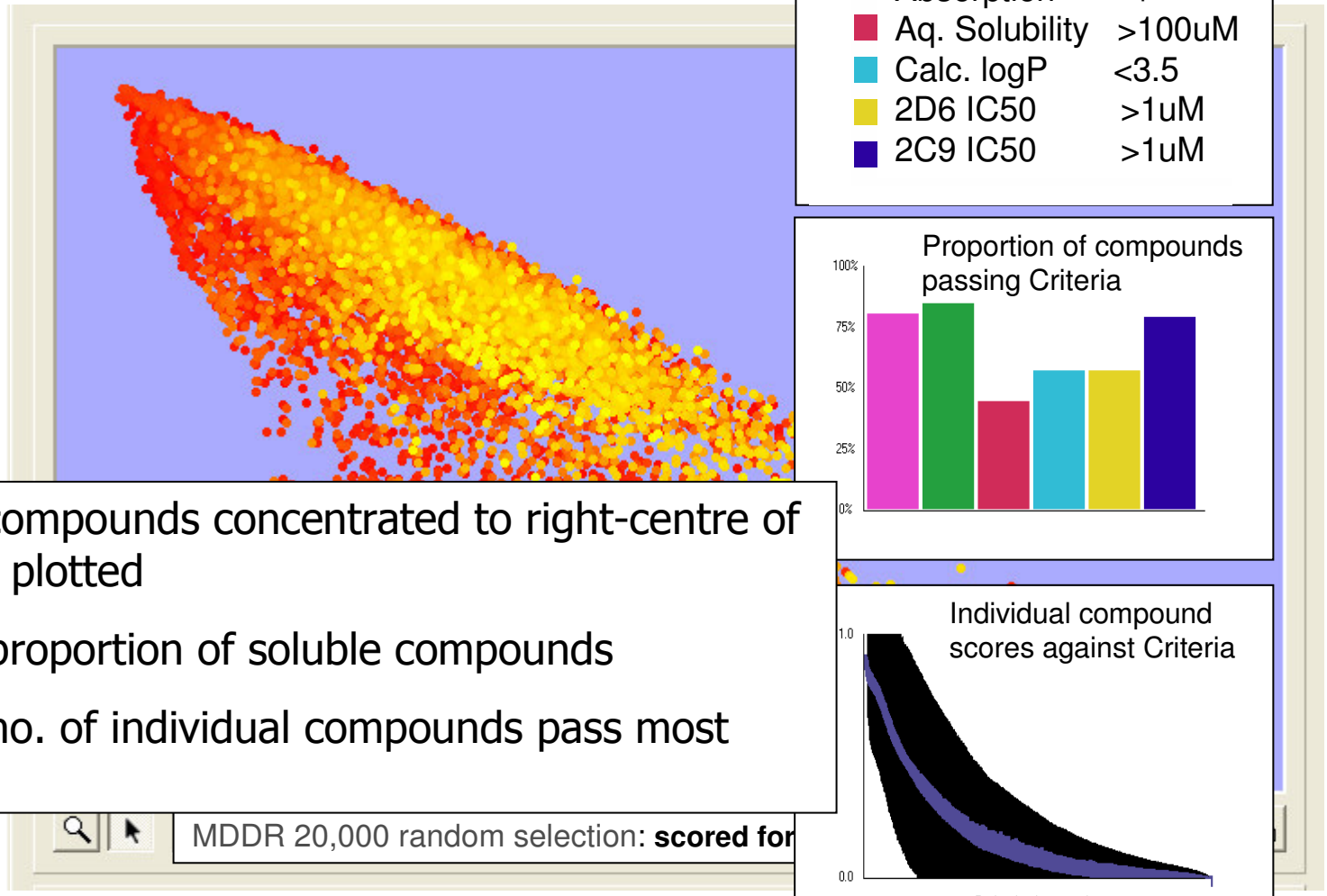
Overview of Entire Library against Target Product Profile

Property
Activity (%inhibition)
Solubility
HIA
logP
CYP2C9 Affinity
CYP2D6 Affinity
P-gp
BBB log([brain]:[blood])
BBB category



Risk of poor oral bioavailability?

Colour-coded Rank Order in "Chemical Space"

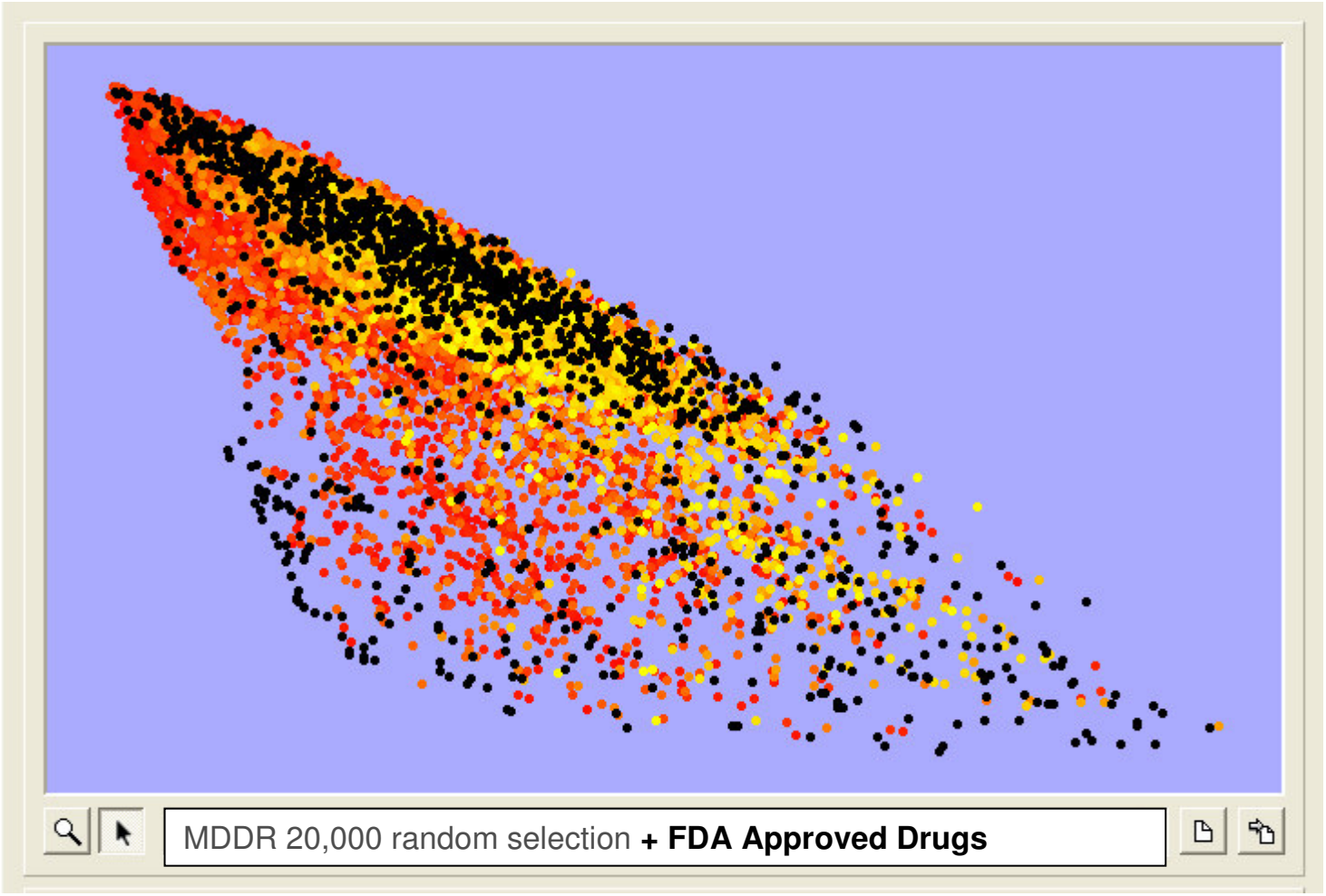


"Good" compounds concentrated to right-centre of space as plotted

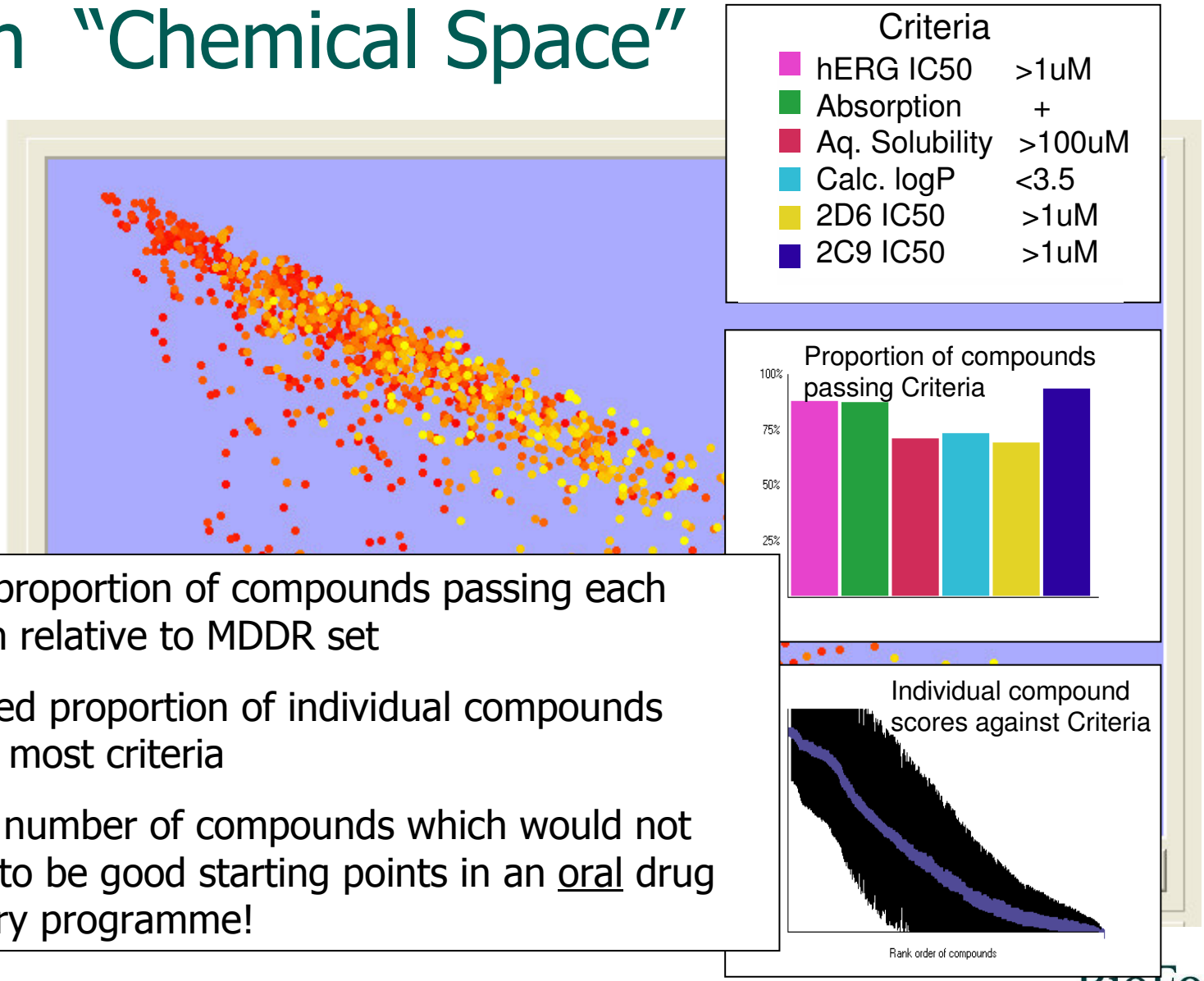
Limited proportion of soluble compounds

Limited no. of individual compounds pass most criteria

Colour-coded Rank Order in "Chemical Space"



Colour-coded Rank Order in "Chemical Space"

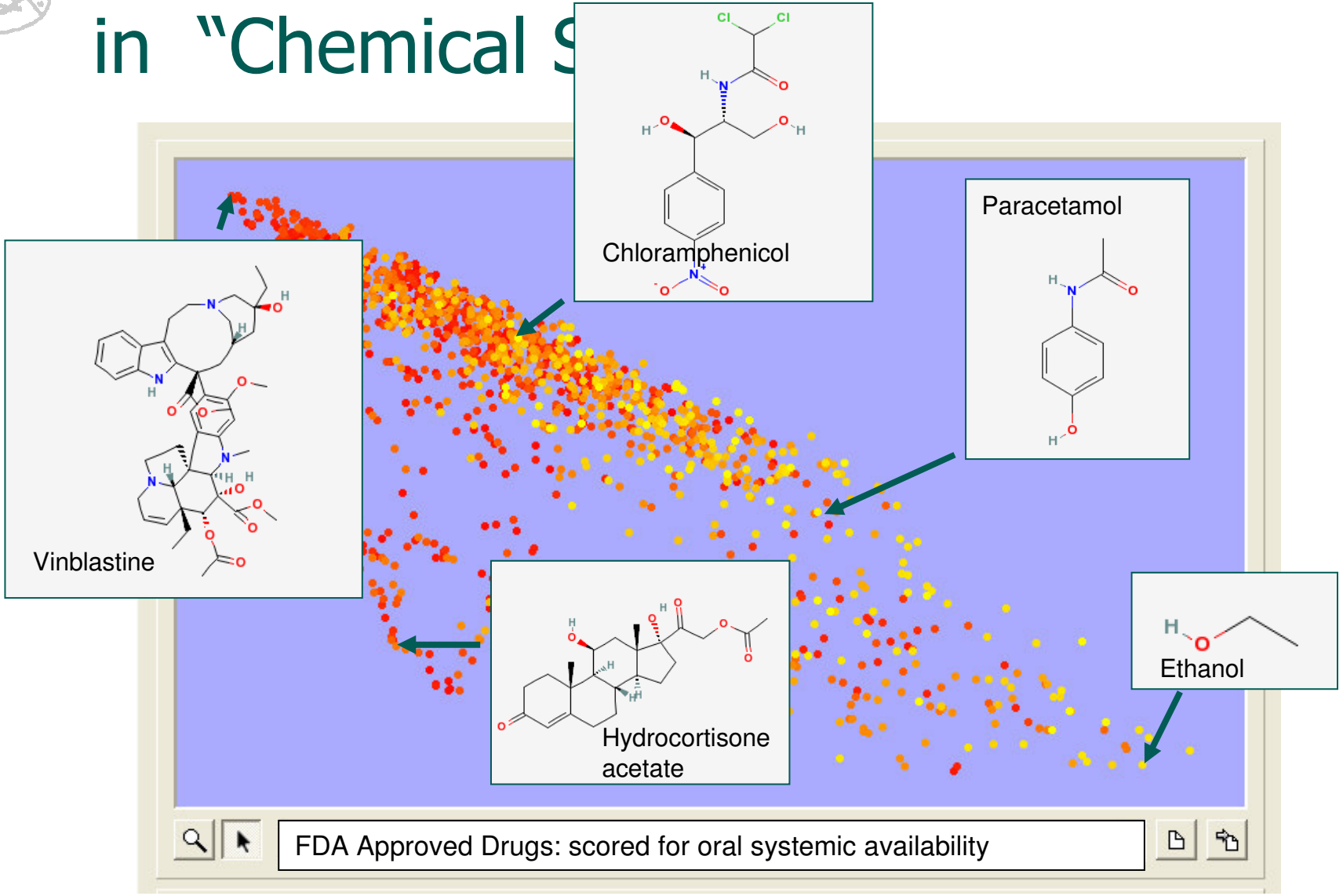


Higher proportion of compounds passing each criterion relative to MDDR set

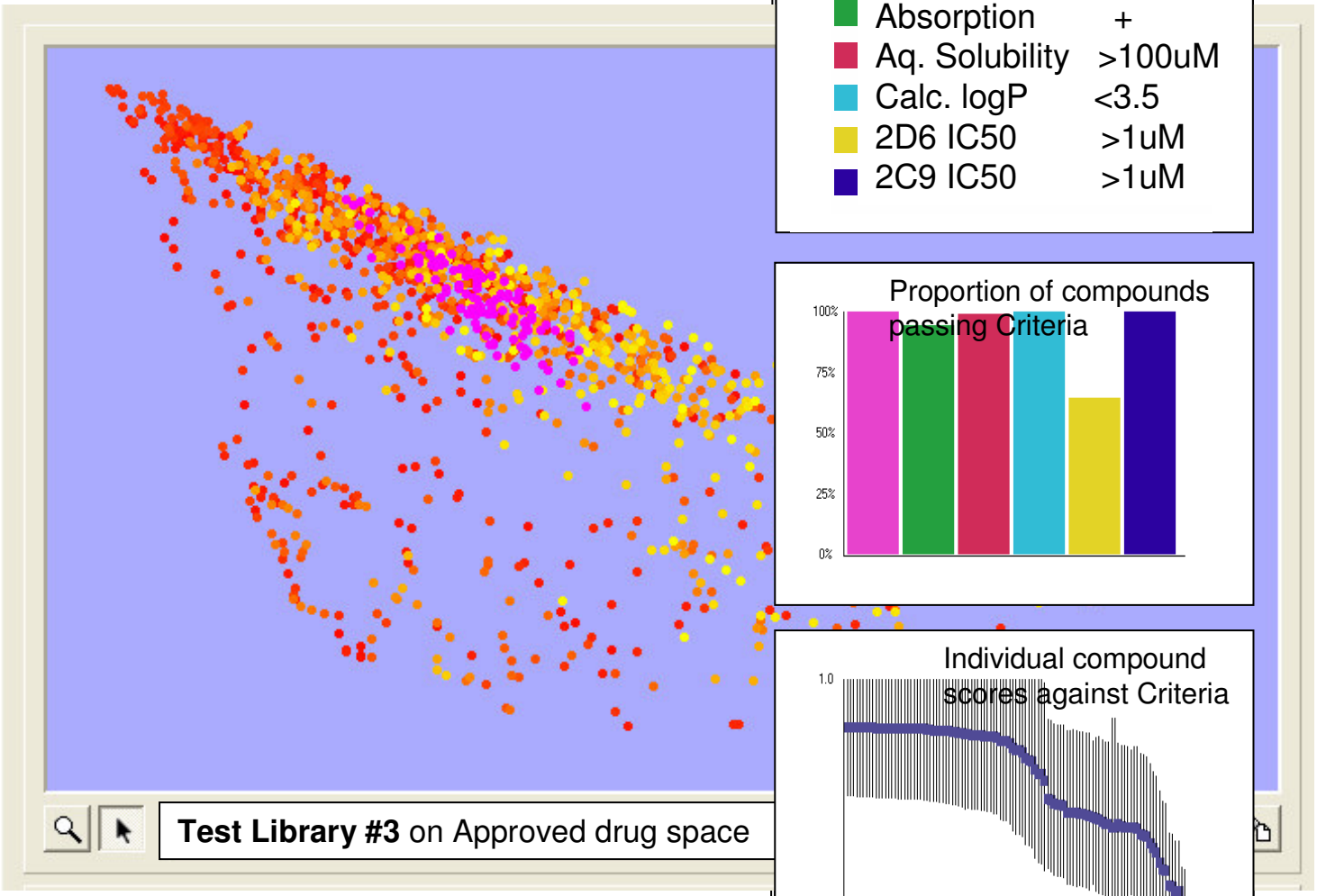
Increased proportion of individual compounds passing most criteria

But – a number of compounds which would not appear to be good starting points in an oral drug discovery programme!

Colour-coded Rank Order in "Chemical S

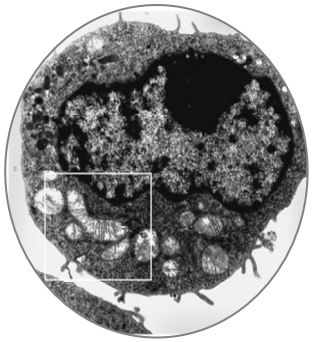


Library Design: ADME



Drug Discovery: ADME Prediction

In Vitro



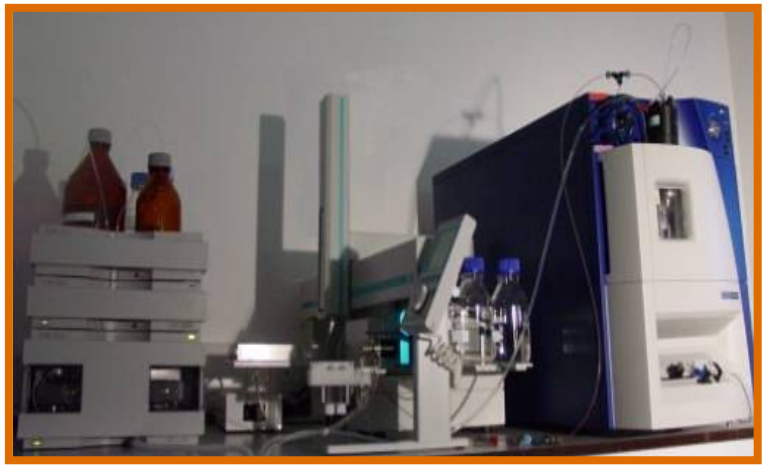
Throughput

Credibility?

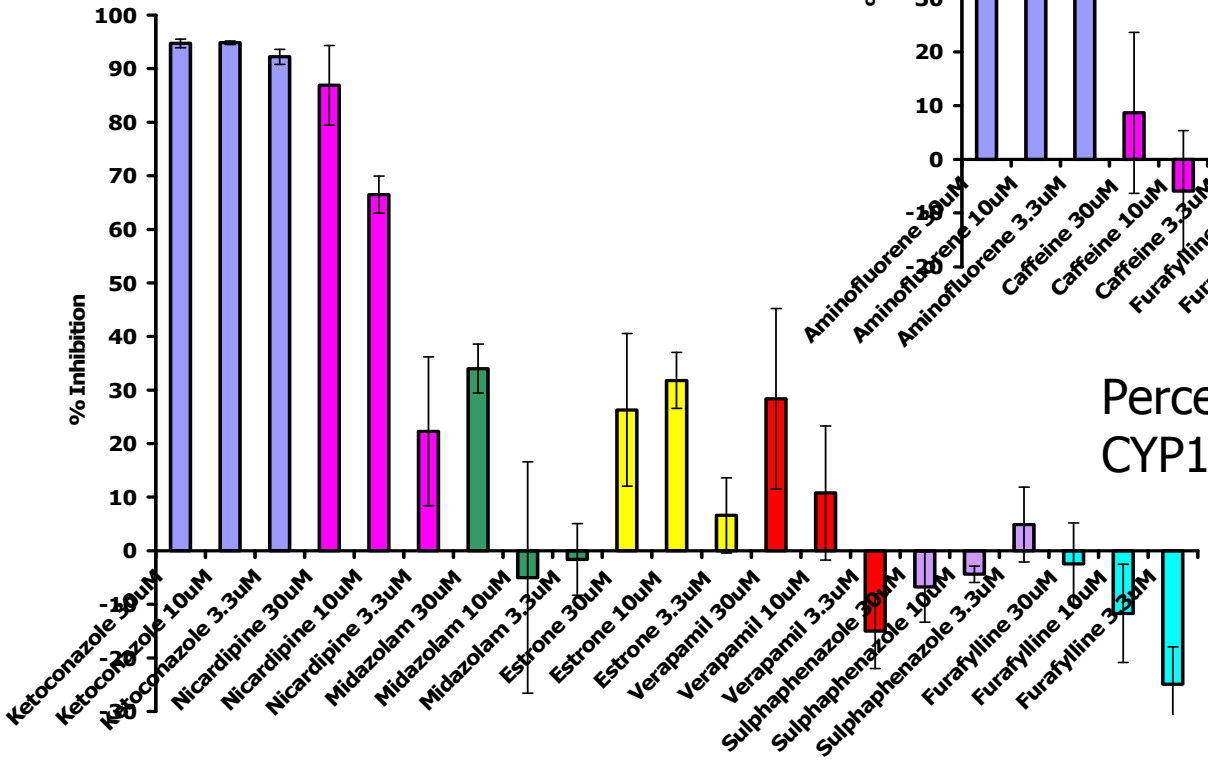
Drug Discovery: ADME Prediction

ADMEnsa Routine *In Vitro* Assays

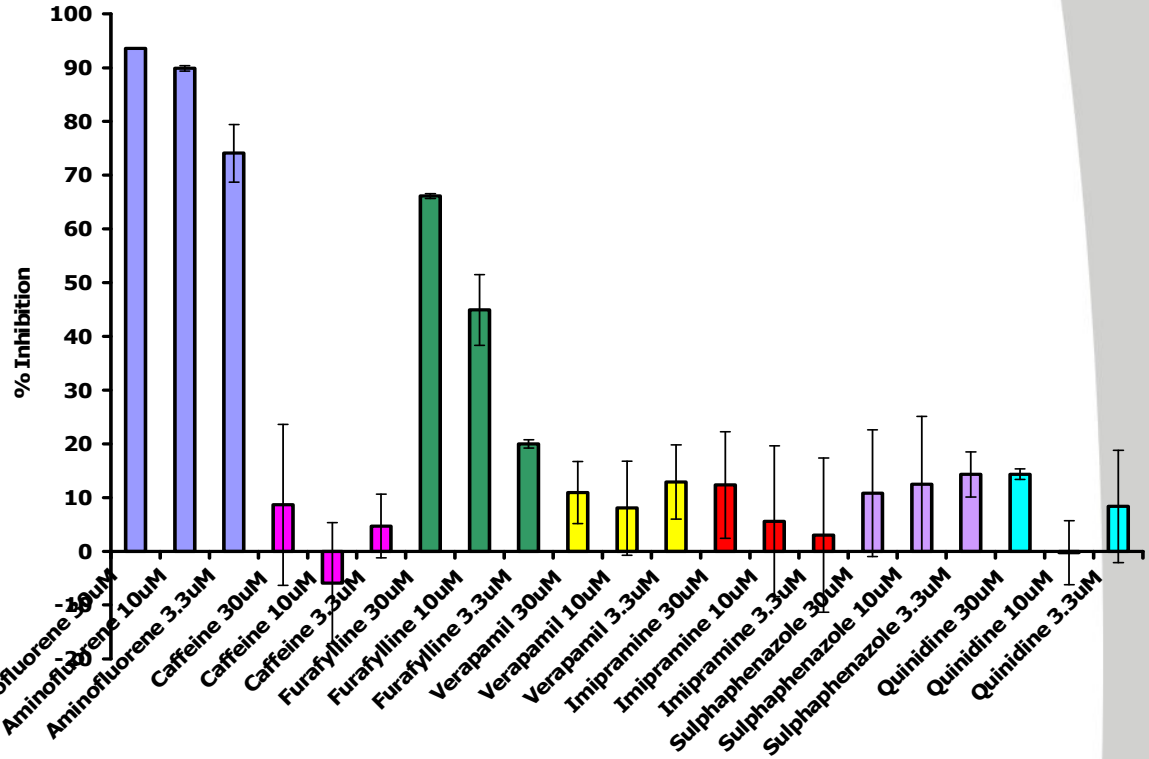
- Solubility
- LogD
- pKa
- CHI
- PAMPA
- Plasma stability
- Plasma protein binding
- Liver microsomal stability (Phase I and Glucuronidation)
- Liver S9 metabolism
- CYP450 metabolism
- UGT metabolism
- Enzyme kinetics
- P450 inhibition
- Time-dependent inhibition
- Hepatocyte stability
- Caco-2
- P-gp ATPase activity
- hERG
- Cytotoxicity



In Vitro Human P450 Inhibition



Percent inhibition and standard deviation:
CYP3A4 test set using testosterone as probe substrate

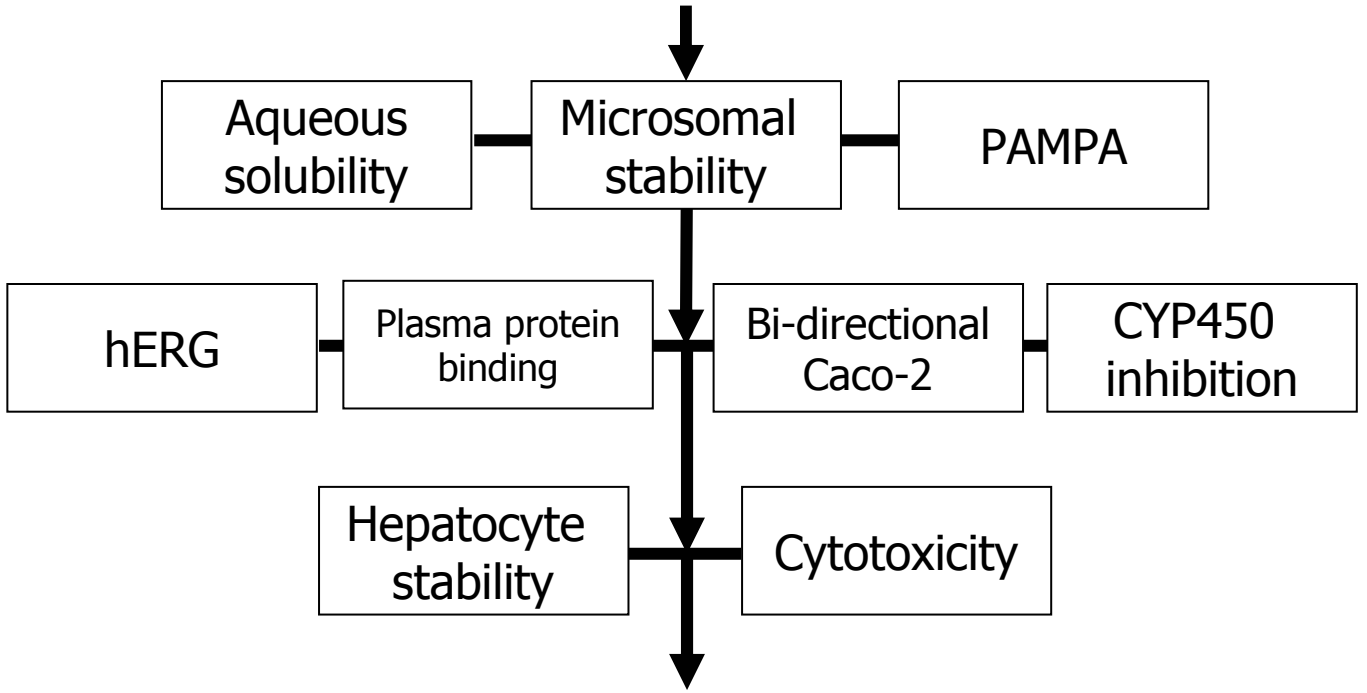


Percent inhibition and standard deviation:
CYP1A2 test set

Drug Discovery: ADME Prediction

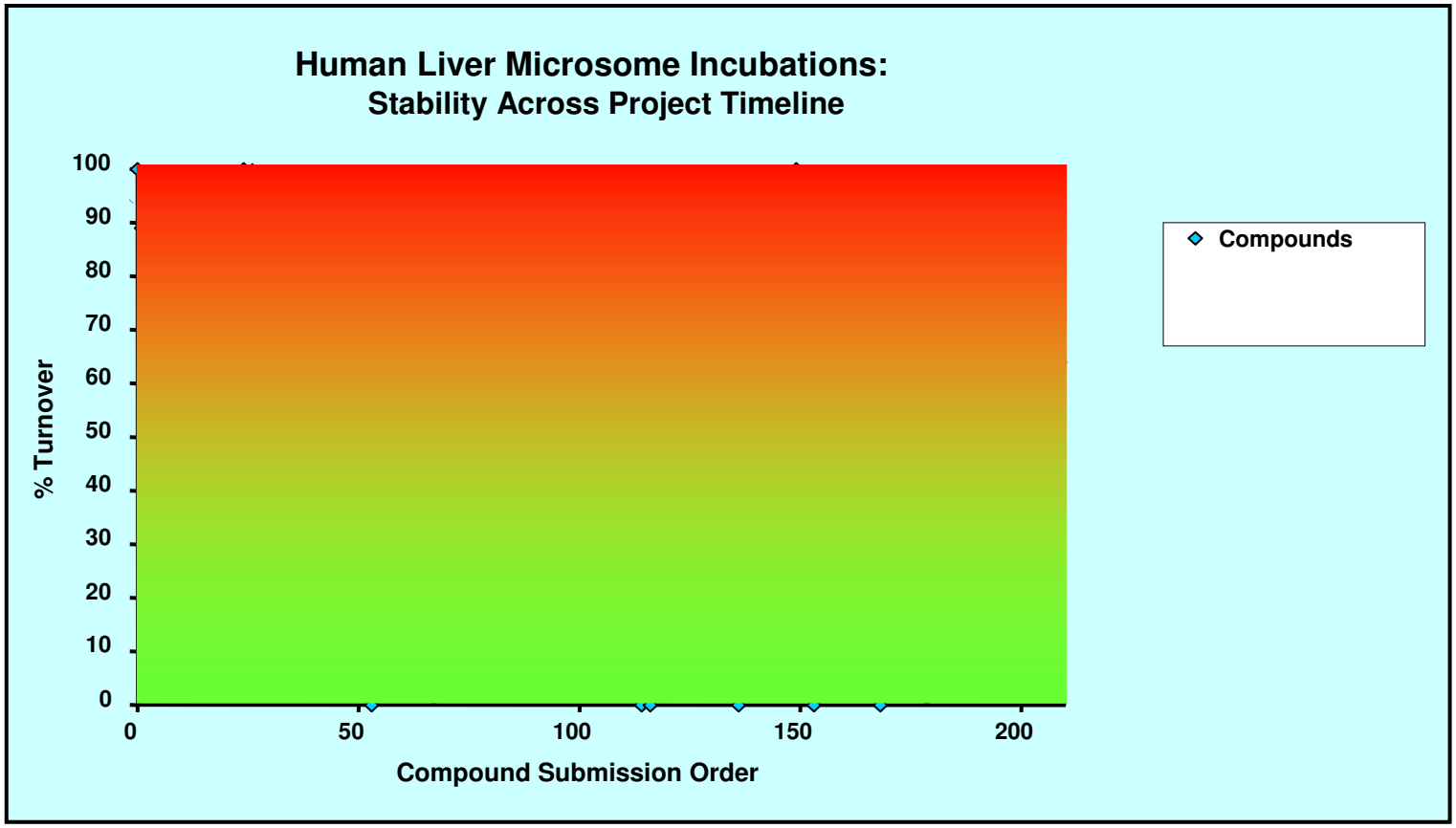
In Vitro

In vitro cascade to generate the most relevant data



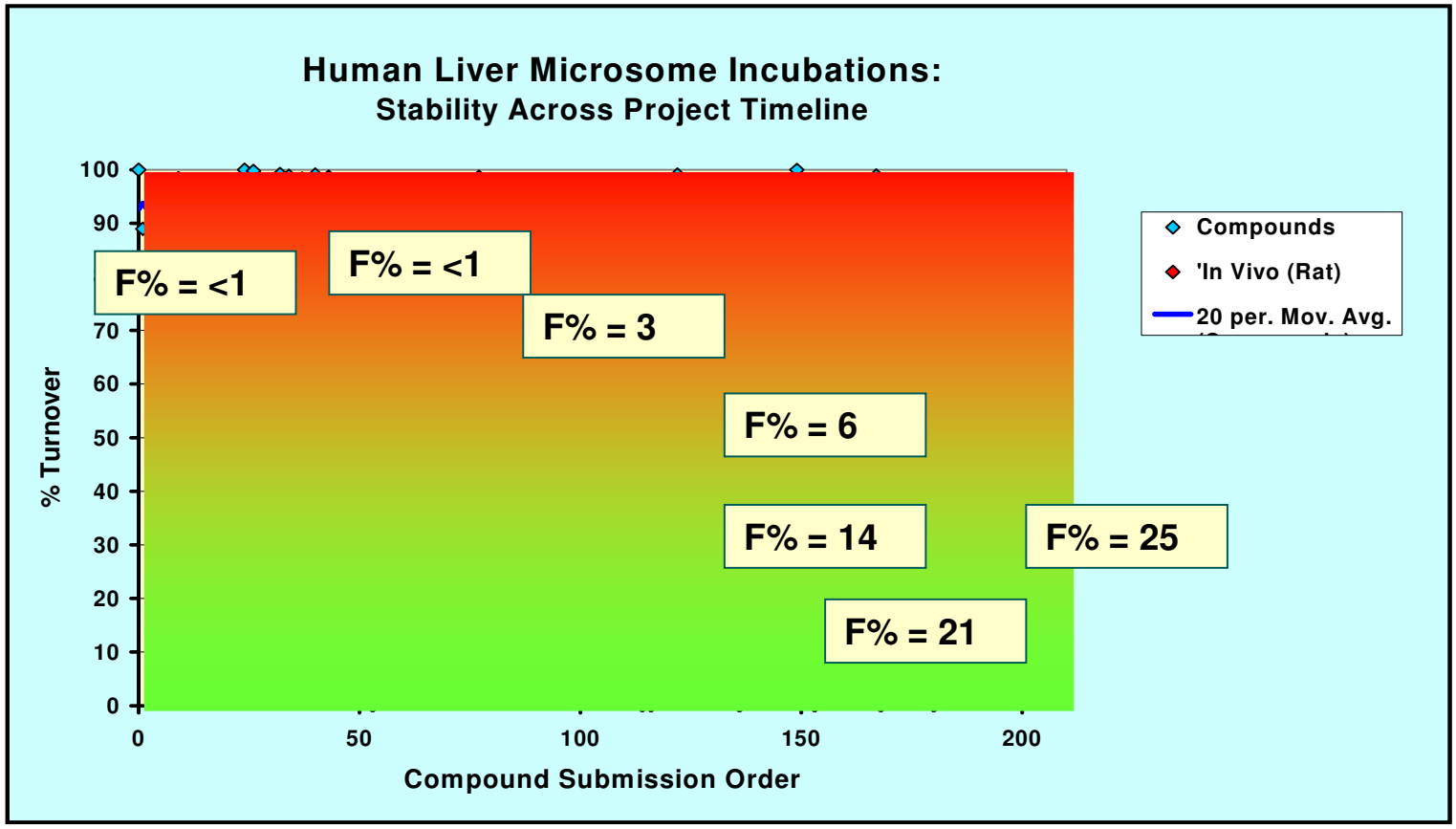
Drug Discovery: ADME Prediction

In Vitro

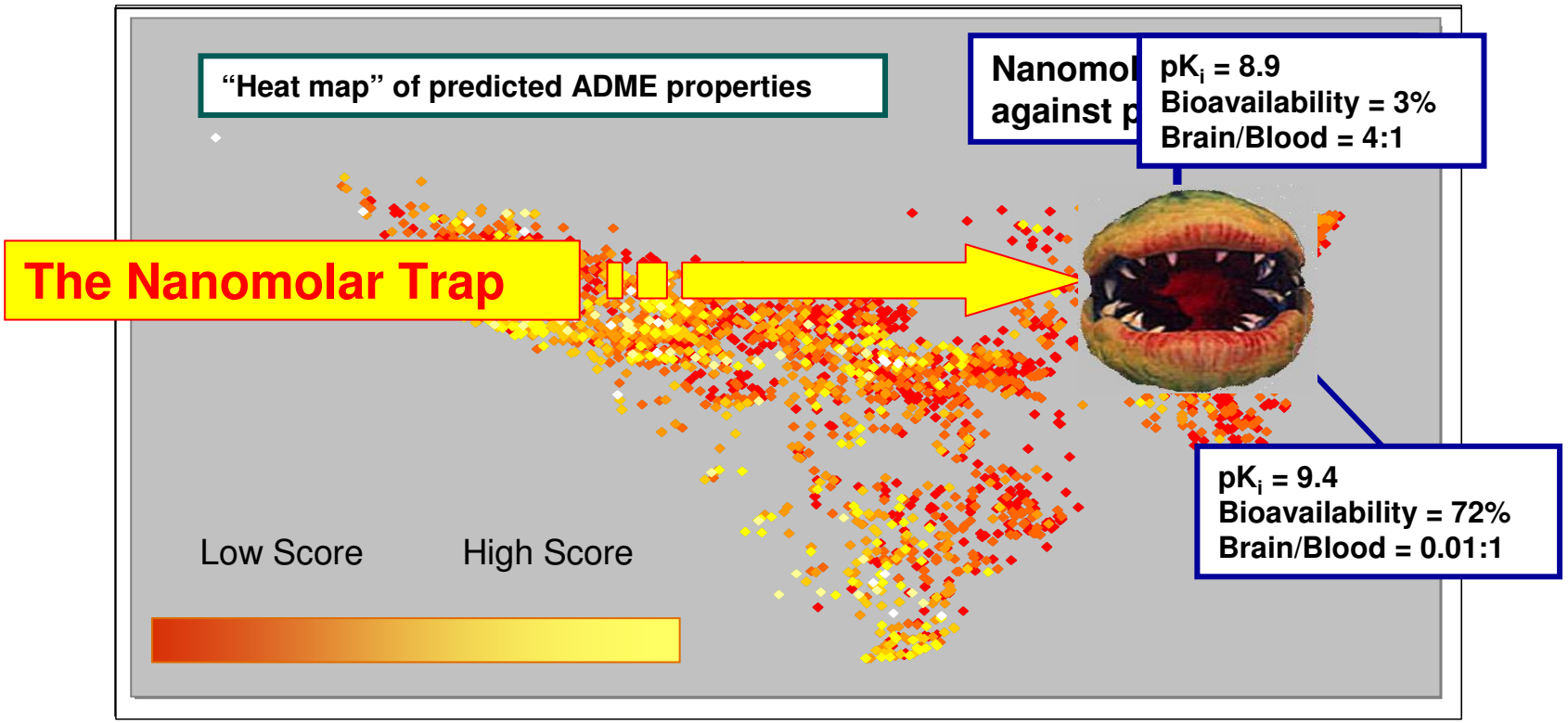


Drug Discovery: ADME Prediction

In Vitro



Screening cascade:
Oral dose, CNS target

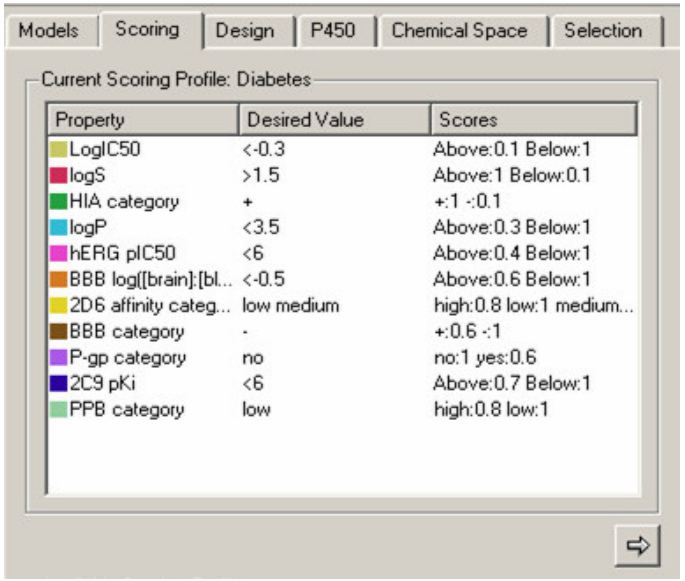


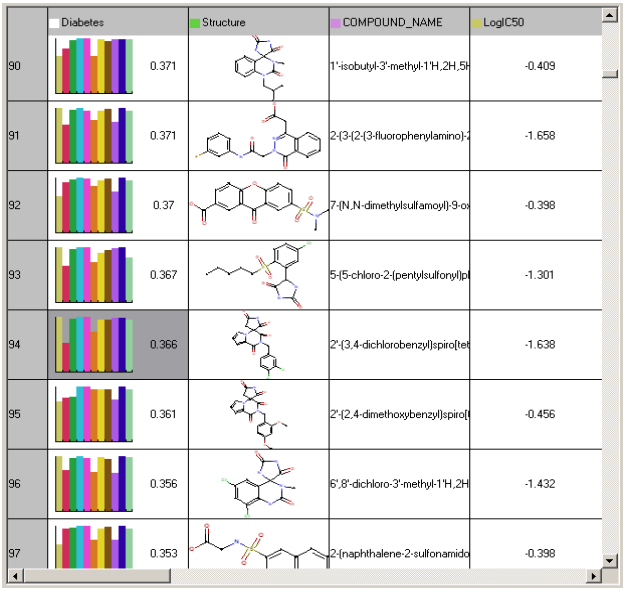
Drug Discovery: ADME Prediction

In Vitro

Score and rank compounds against Target Product Profile

User-defined scoring profile



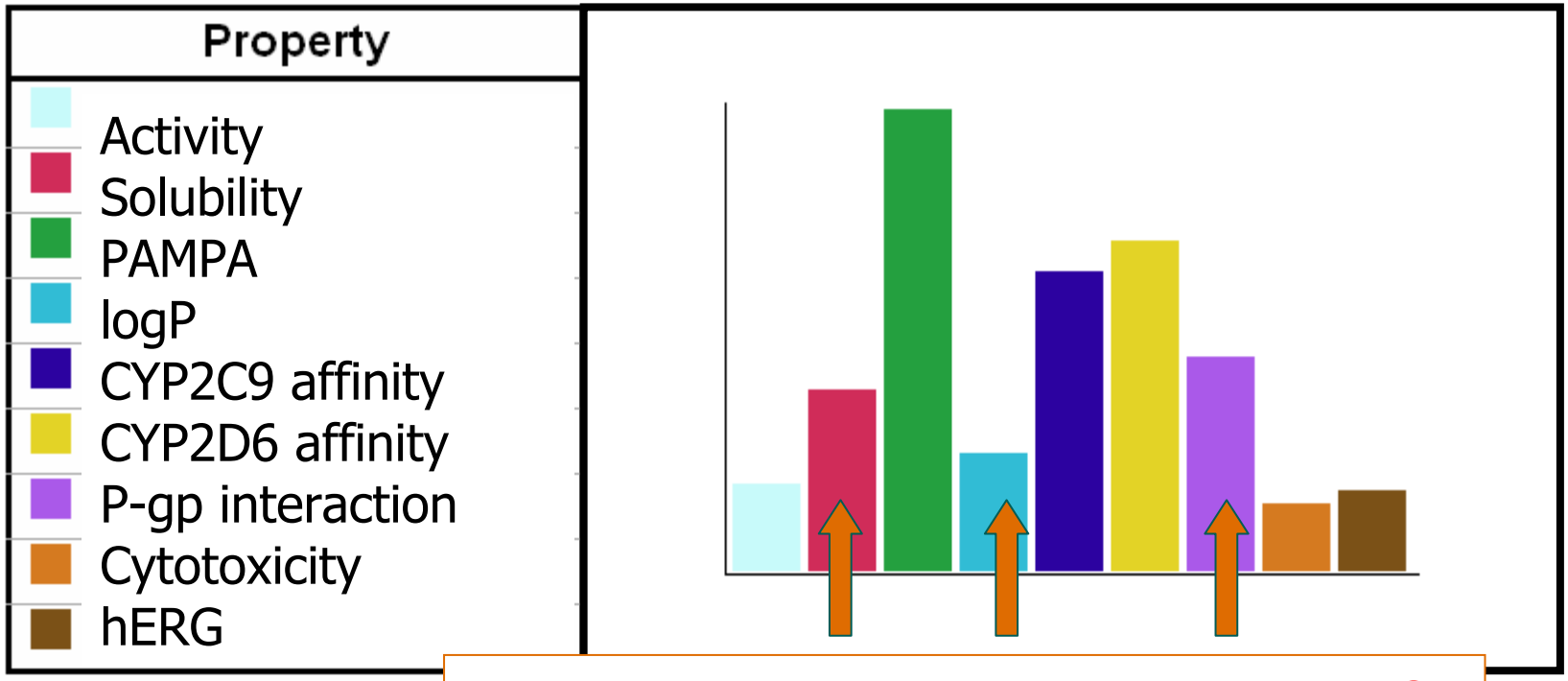


User Interface: ADMEnsa Interactive™

Drug Discovery: ADME Prediction

In Vitro

Assessment of ADME risk against Target Product Profile



Risk of poor oral bioavailability?

Drug Discovery: ADME Prediction

In Vivo

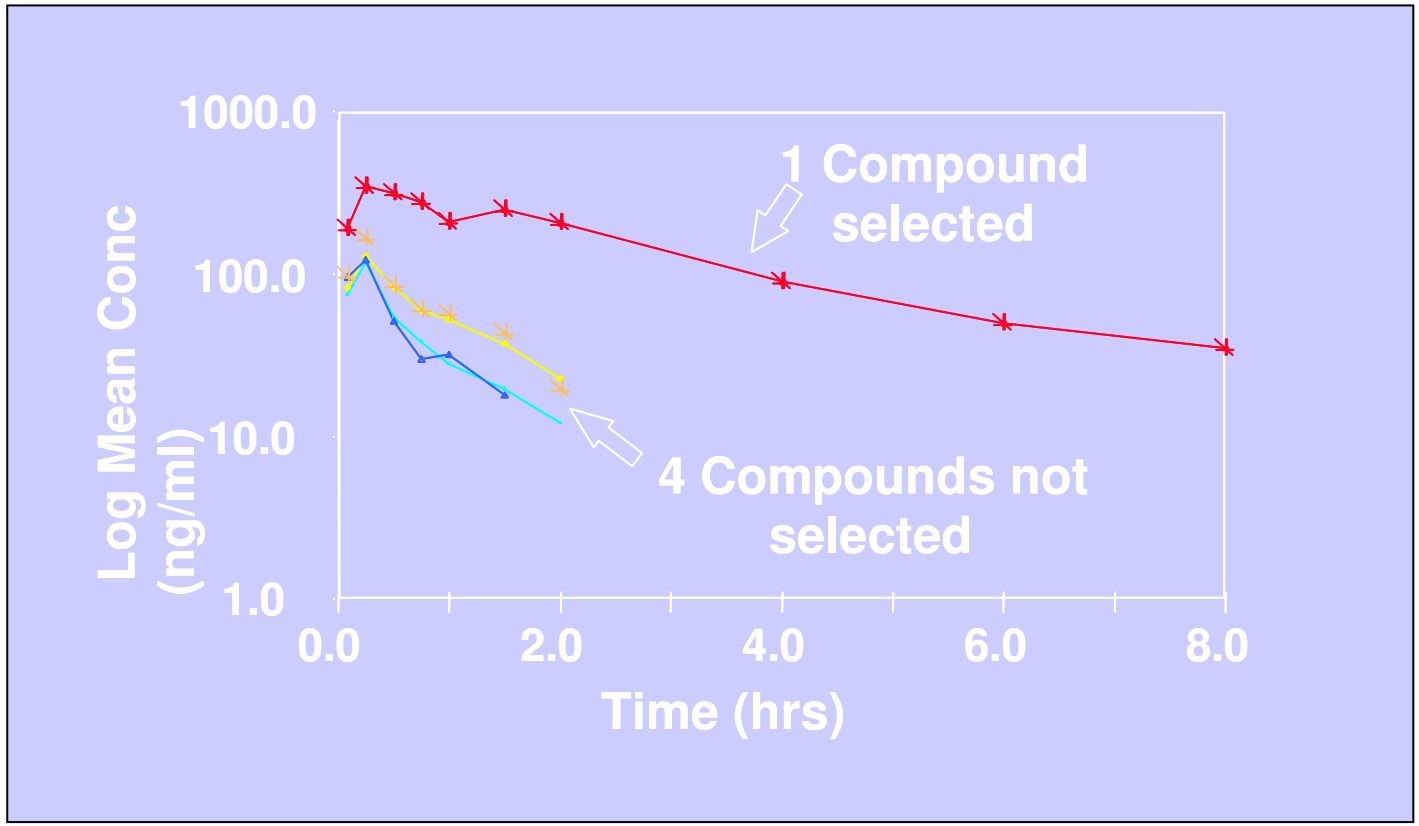
Throughput

Credibility?

Drug Discovery: ADME Prediction

In Vivo

Rat oral "cassette" dosing



Drug Discovery: ADME Prediction

In Vivo

LEAD MOLECULE SELECTED FOR PROGRESSION

	RAT	DOG	MAN
Cl (ml/min/kg)	40	6	8 (14)?
Vd (L/kg)	4	6	5 ?
T1/2 (min)	70	700	430 (250)?
F (%)	45	118	80?

Drug Discovery: ADME Prediction

In Vitro- In Vivo

	Half-Life (minutes)			
	Mouse	**Rat**	**Dog**	**Human**
Liver microsomes (1 µM)	**6**	**8**	**55**	**91**
Hepatocytes (1 µM)	**>200**	**>200**	**>200**	**>200**
In vivo	**35**	**70**	**700**	**?**
Oral bioavailability (%)	**35**	**45**	**118**	**?**

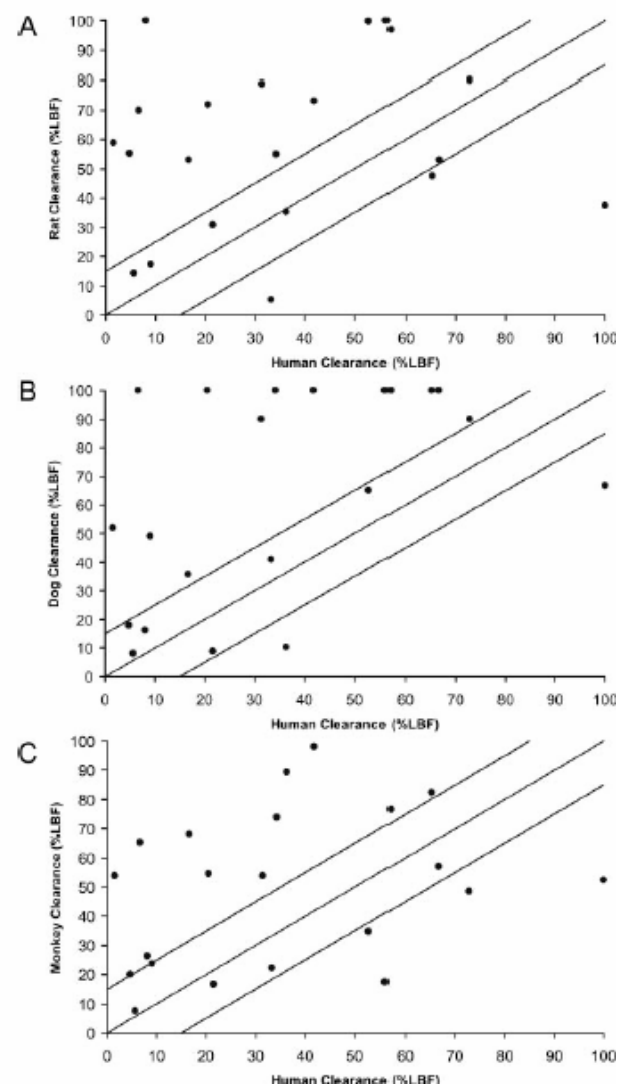
Allometric Scaling Credibility?

A = Rat

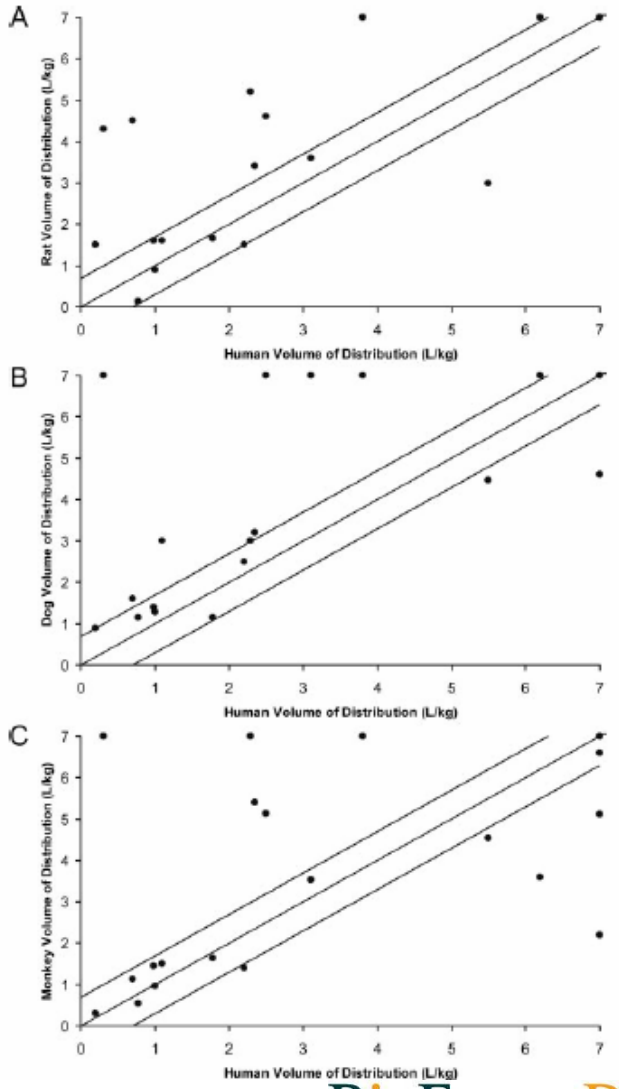
B = Dog

C = Monkey

Clearance / Liver blood flow



Volume of Distribution (L/Kg)

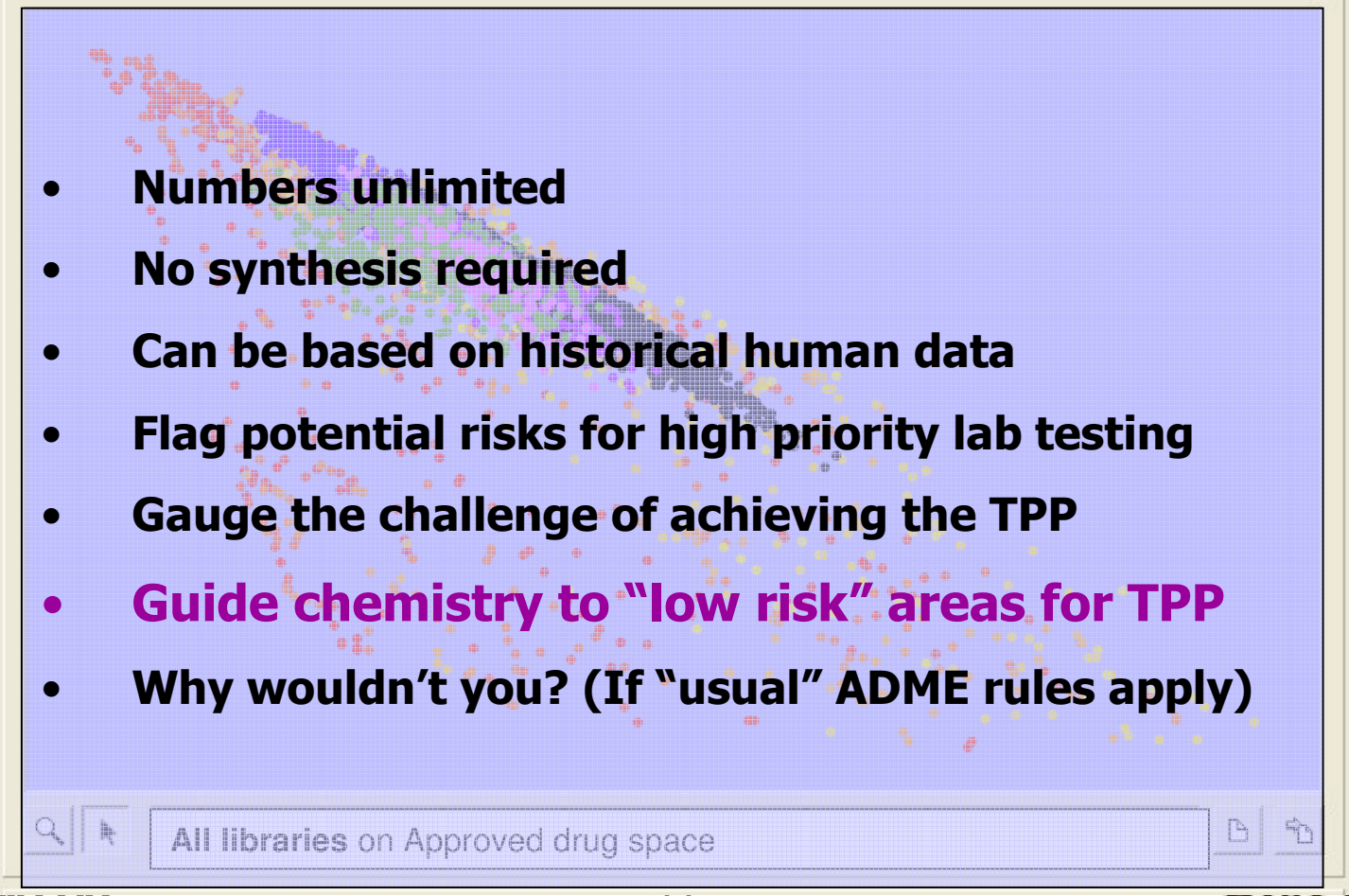


Evans et al., *Drug Met Dispos,* **34,** 1255-1265 (2006)

Drug Discovery: ADME Prediction

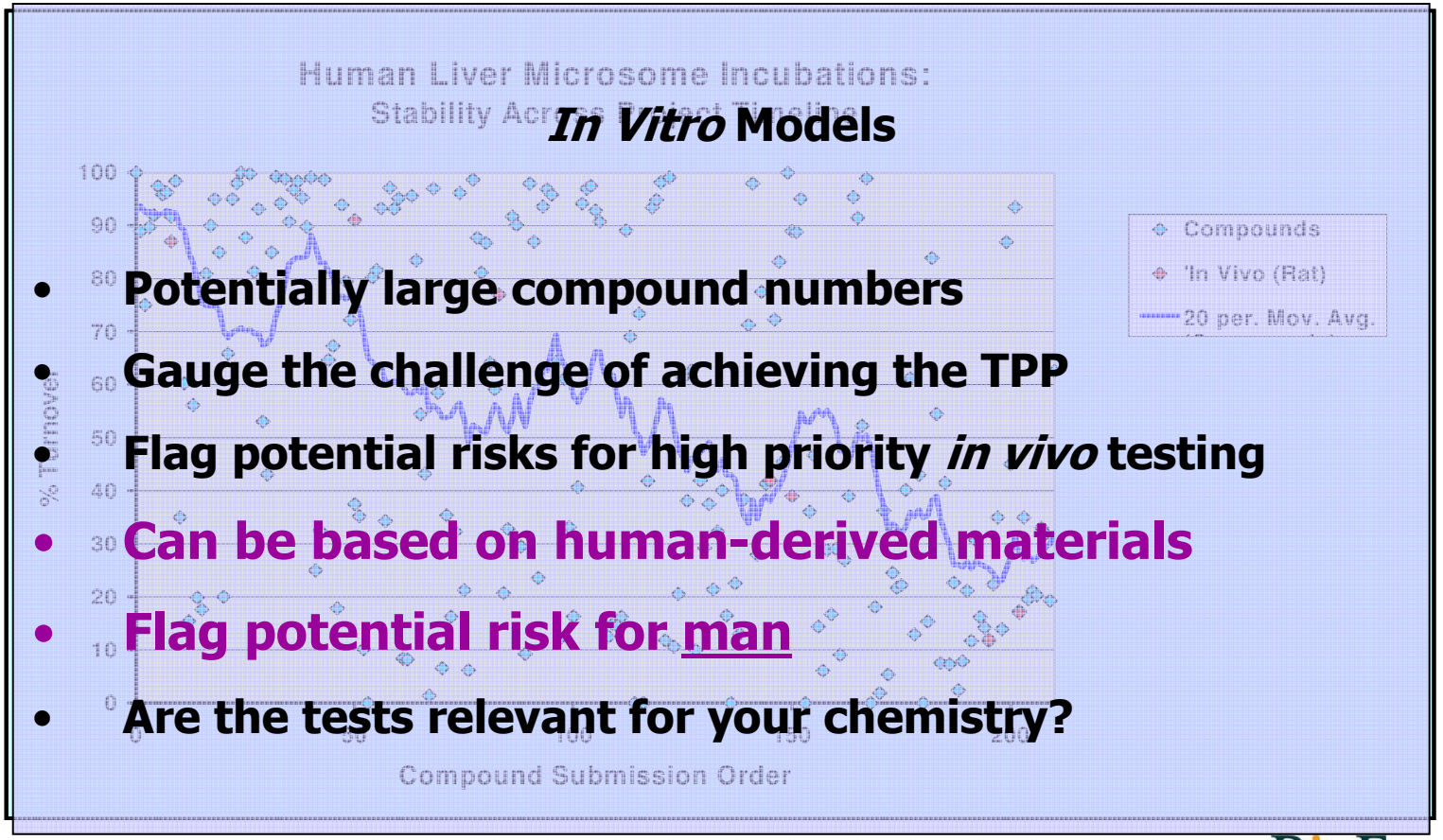
In Silico

- **Numbers unlimited**
- **No synthesis required**
- **Can be based on historical human data**
- **Flag potential risks for high priority lab testing**
- **Gauge the challenge of achieving the TPP**
- **Guide chemistry to "low risk" areas for TPP**
- **Why wouldn't you? (If "usual" ADME rules apply)**



Drug Discovery: ADME Prediction

In Vitro

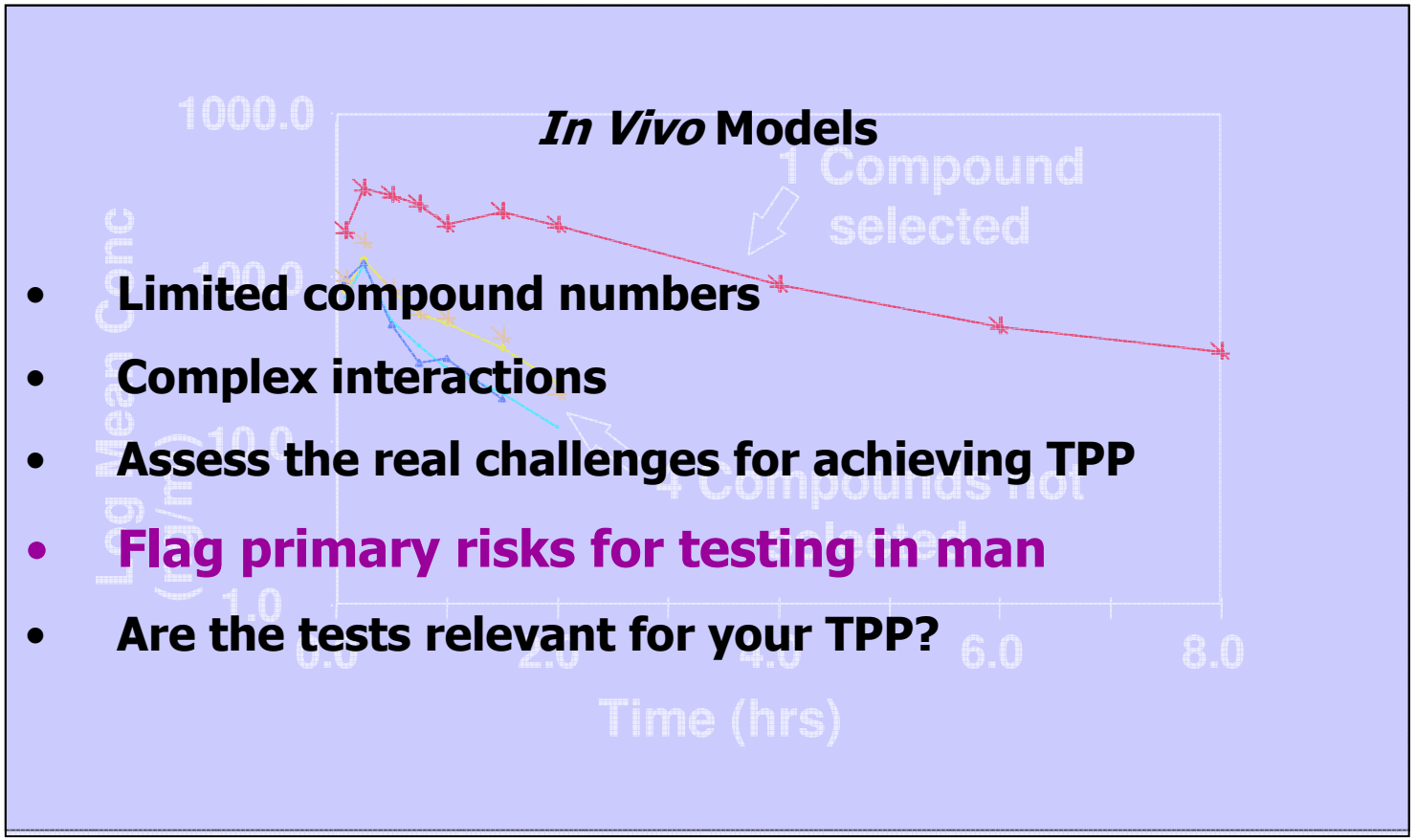


In Vitro Models

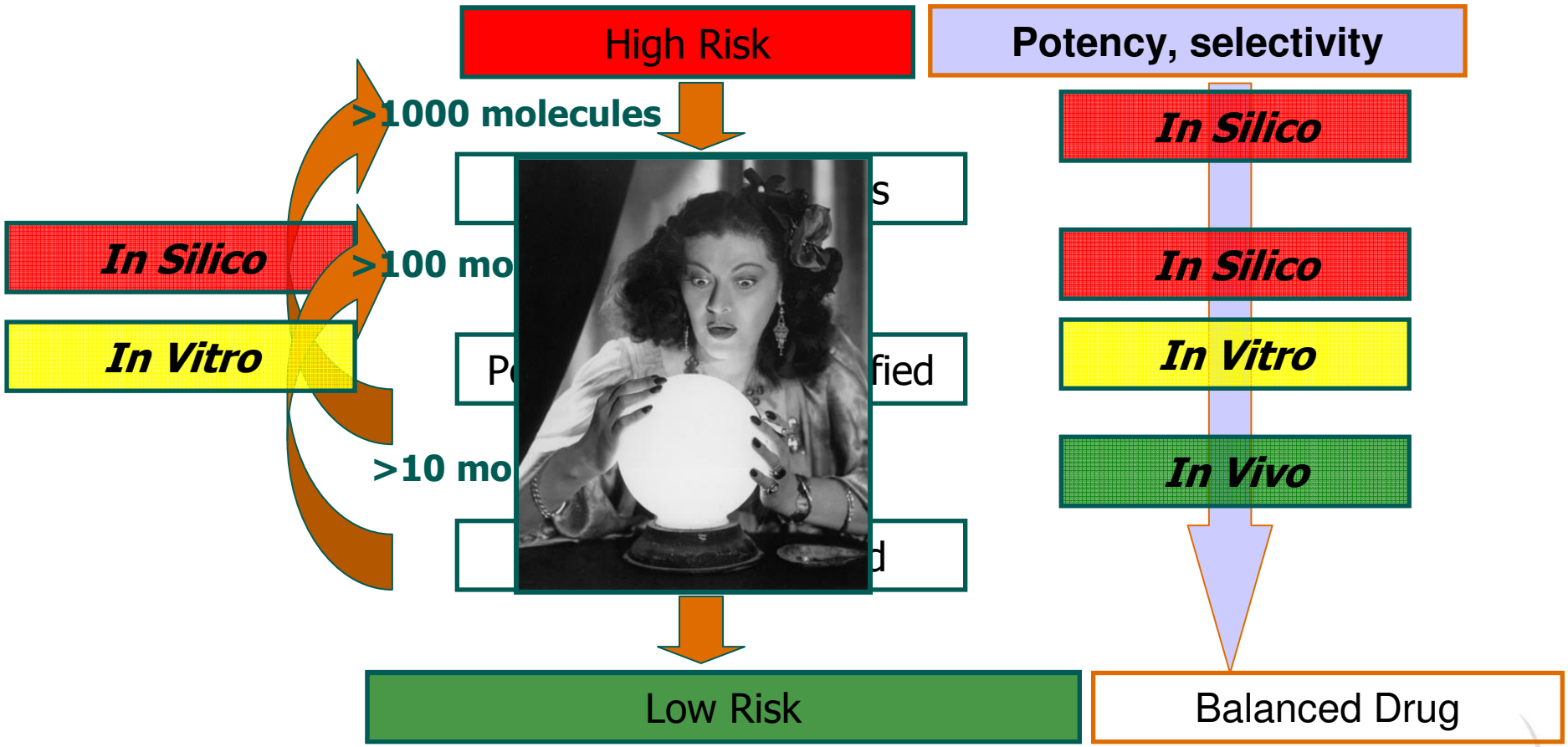
- **Potentially large compound numbers**
- **Gauge the challenge of achieving the TPP**
- **Flag potential risks for high priority *in vivo* testing**
- **Can be based on human-derived materials**
- **Flag potential risk for man**
- **Are the tests relevant for your chemistry?**

Drug Discovery: ADME Prediction

In Vivo



ADME Models in Drug Discovery



Acknowledgements:

Joelle Gola

Matt Segall

Dawn Yates

Thank You for Your Attention