The Journey from Drug Discovery to Drug Design: How far have we travelled?

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SMI *In Silico* ADMET

16-17 May 2007

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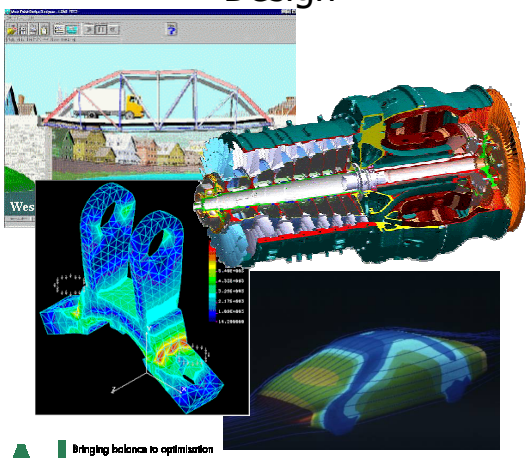
Overview

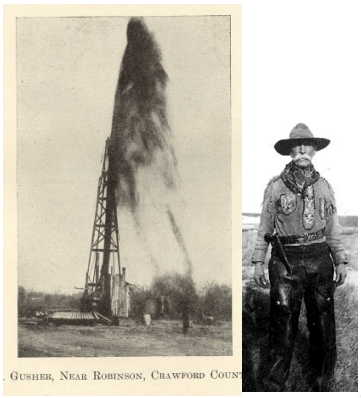
- Design vs. Discovery
- Analogy of drug design – The Boeing 777
  - Why does this analogy break down?
- An alternative analogy – Card counting in blackjack
- Applying predictions to support decision-making
  - Estimating probabilities
  - Balancing diversity and likelihood of success – spread your risk
- Interpreting models to guide design
- Illustrative example
  - Focussing resources in hit-to-lead/lead optimisation
- Conclusion

Design vs. Discovery

Design



Discovery



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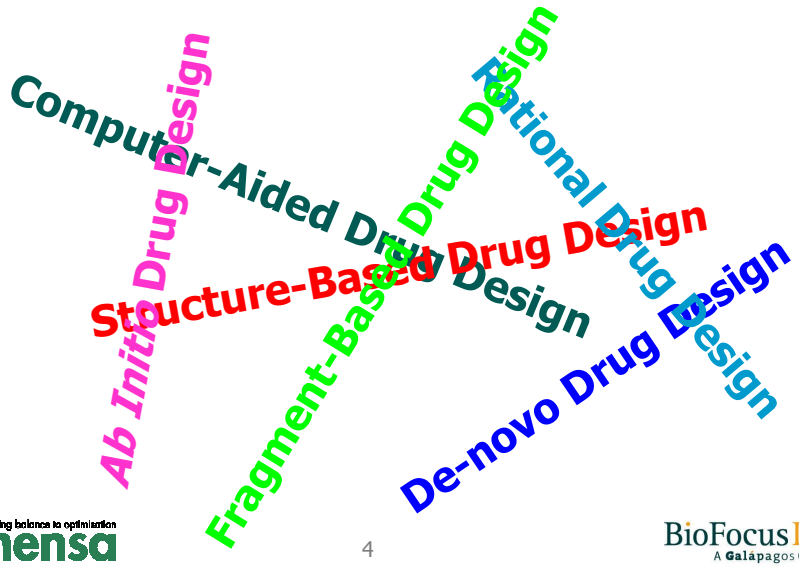
Are We Doing Drug *Design*?



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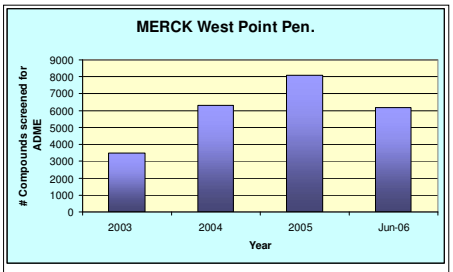
Are We Doing Drug *Design*?

"Around 15,000 samples are generated each week for LC-MS/MS analysis….This analytical capacity and speed is pivotal in facilitating the rapid data turn round times required for our discovery customers"

Kenneth Saunders & High Throughput ADME Team

Pfizer Global R&D, Sandwich, Kent

Advancing Drug Discovery conference, Seattle, Sept 2006



Scott D Mosser

Drug Discovery Technology conference, Boston, Aug 2006

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An Analogy of Drug Design The Boeing 777*

* Selick *et al.* Drug Disc. Today, **7**, pp. 109-116 (2002)

- Designed entirely on computer
- Full-scale prototype built
- Successfully flown first time
- Compared with the "crash test" paradigm of drug discovery

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Why Does this Analogy Break Down?
Complexity of Design Goals?

Airplane	Drug
• Cost	• Potency
• Efficiency	• Selectivity
• Range	• Absorption
• Capacity	• Metabolic Stability
• Safety	• Safety
• …	• ….

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Why Does this Analogy Break Down?
Precision of Models

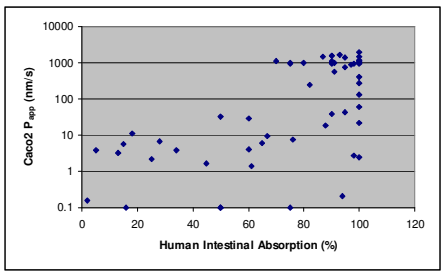
Airplane

$$\frac{D\rho}{Dt} + \rho\nabla\cdot\mathbf{v} = 0$$
$$\rho\frac{D\mathbf{v}}{Dt} = -\nabla\rho + \nabla\cdot\mathbf{T}' + \rho\mathbf{f}$$
$$\rho\frac{De}{Dt} = -\rho\nabla\cdot\mathbf{v} + \Phi - \nabla\cdot\mathbf{q} + \rho r$$

Drug

$y = h_1 x_1 + h_2 x_2 + h_4 x_4$

Caco2 vs. Human Intestinal Absorption*



* Irvine et al., J Pharm Sci 1999, 88, 28

R^2=0.81, RMSE=0.8 log units

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An Alternative Analogy
Card Counting in Blackjack*

- Uniquely among casino games, the outcome of a Blackjack hand is, to some degree, predictable
- The cards that have been dealt and discarded define the probabilities of drawing cards in the future
- High cards (10 through Ace) favour the player over the dealer
- Card counters use this information to *bias the odds* in their favour
- N.B. This is not a recommendation of card counting, it may be illegal in some jurisdictions.

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* Bringing Down the House, Ben Mezrich

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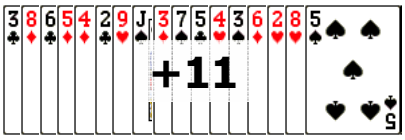
An Alternative Analogy
Card Counting in Blackjack

Discarded **Remaining**



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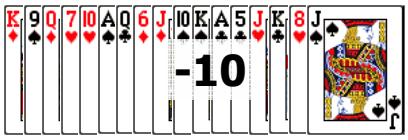

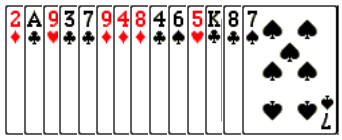

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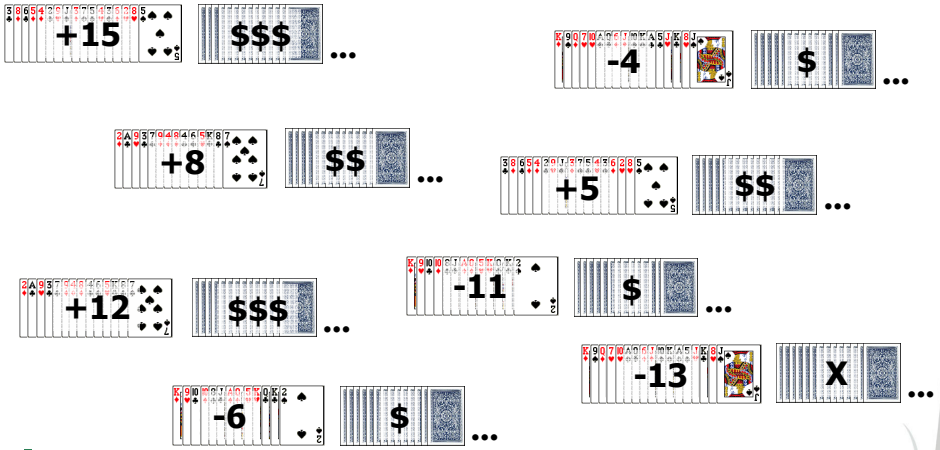
An Alternative Analogy
Card Counting in Blackjack



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Applying Predictions to Decision-Making in Drug Discovery

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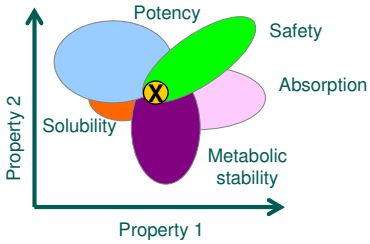
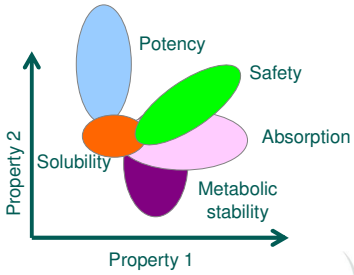
The Objectives

- Identify chemistries with an optimal **balance** of properties
  - "Hot decks"
- Quickly identify situations when such a balance is not possible
  - "Cold decks"





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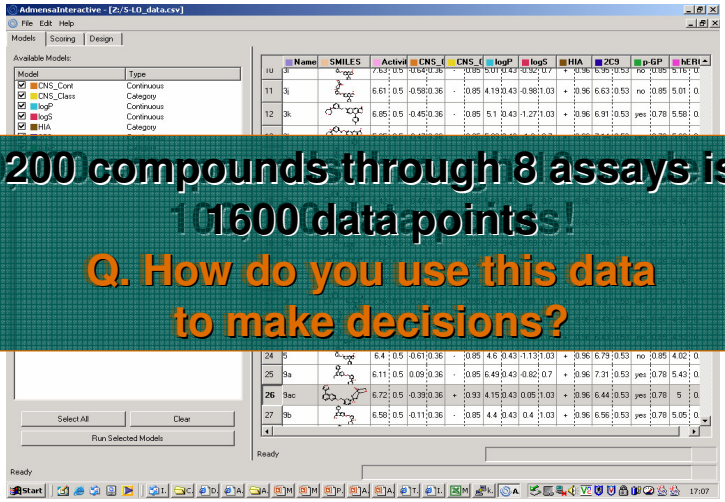
The Challenge



200 compounds through 8 assays is 1600 data points

Q. How do you use this data to make decisions?

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Applying Data to Making Decisions

Value created by good decisions, not data

Data	Prioritise	Selection
In silico *In vitro* *In vivo*	Relevance Uncertainty	Quality Diversity 'Manual'

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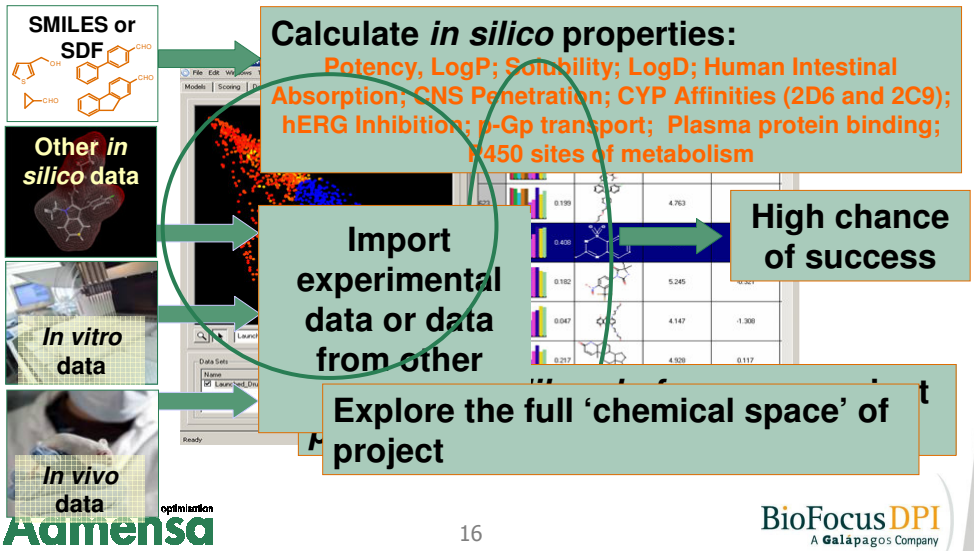
Integrating Data to Support Decisions Admensa Interactive™



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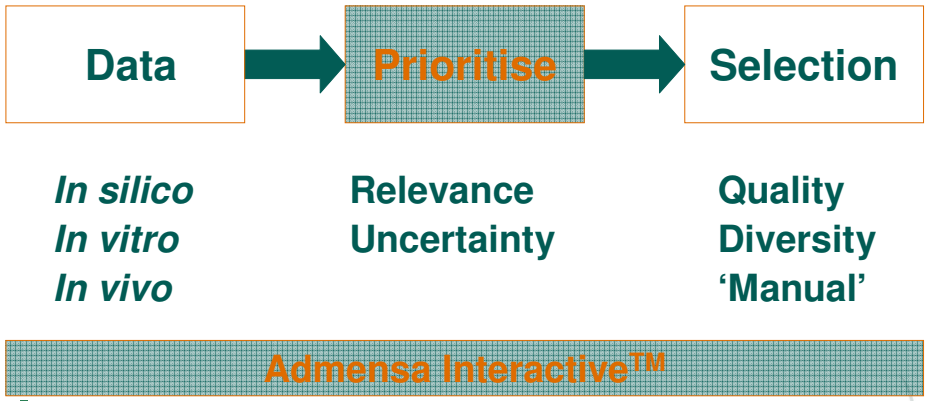
Applying Data to Making Decisions

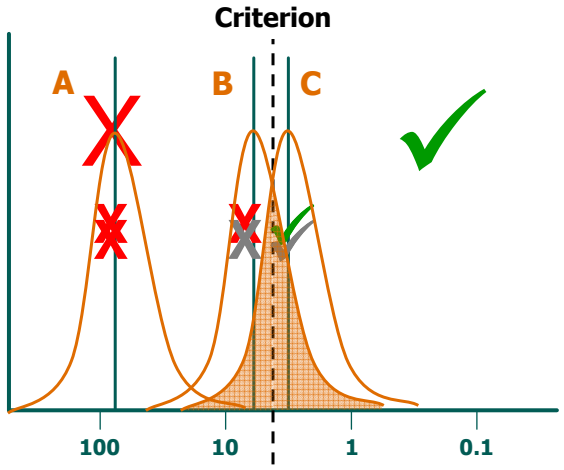


Applying Probabilities to Drug Discovery

- Property data
  - Experimental or predicted
- Criteria for success
  - Risk of failure
- Uncertainties in data
  - Experimental or statistical

Likelihood of Success

The Importance of Uncertainty



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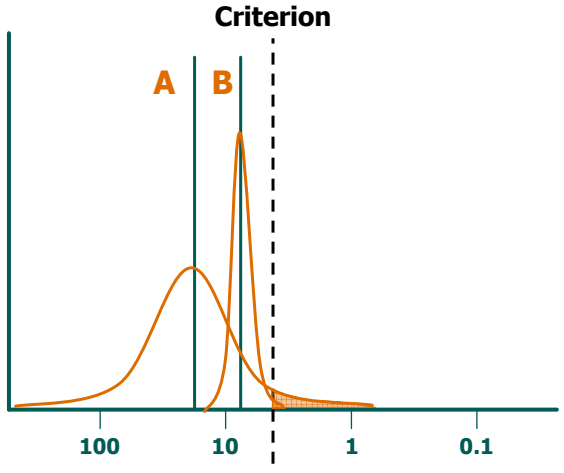
The Importance of Uncertainty



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Applying Data to Making Decisions

Data → **Prioritise** → **Selection**

In silico	**Relevance**	**Quality**
In vitro	**Uncertainty**	**Diversity**
In vivo		**'Manual'**

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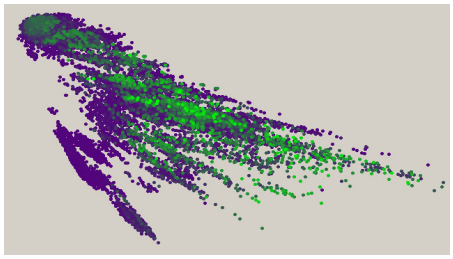
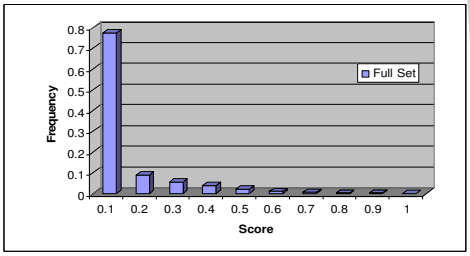
Selection:
Balancing Quality and Diversity





Objective: Select 200 compounds from scored library of 13,000 compounds

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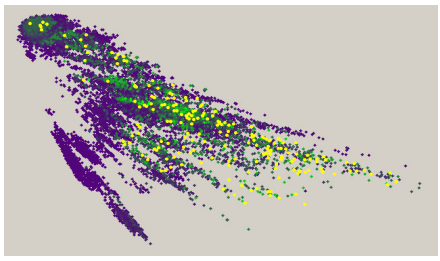
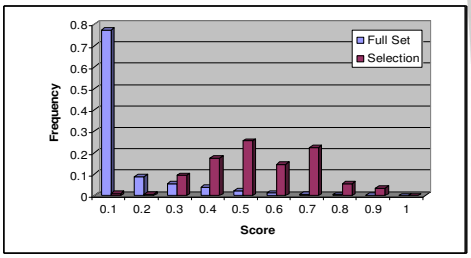
Selection:
Balancing Quality and Diversity





Balance Diversity and Quality: 80:20

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Interpreting Models to Guide Design

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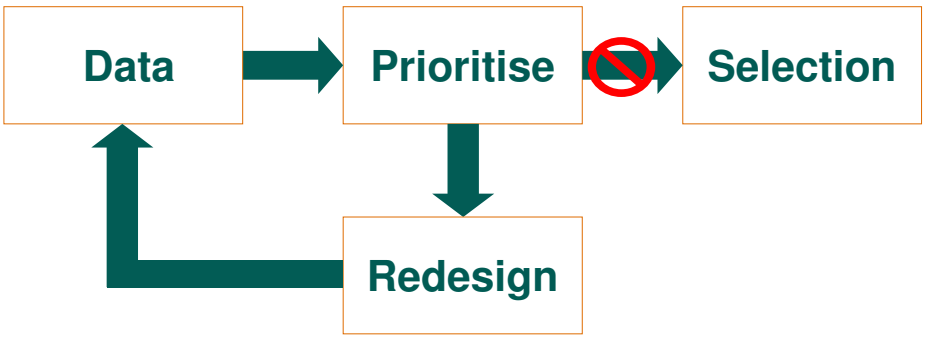
Guiding Redesign



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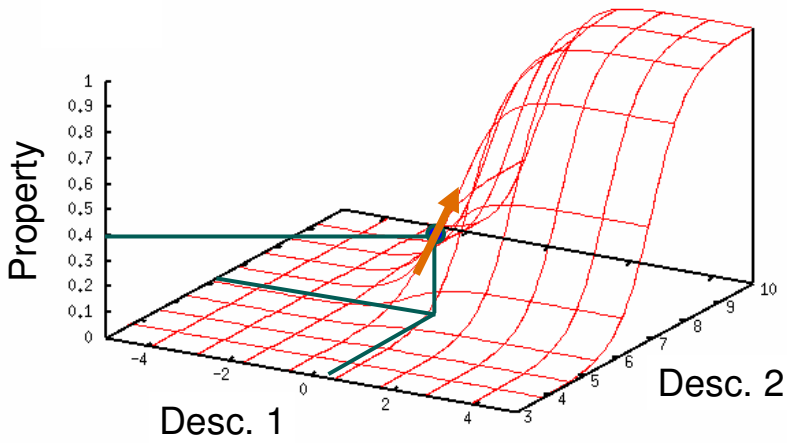
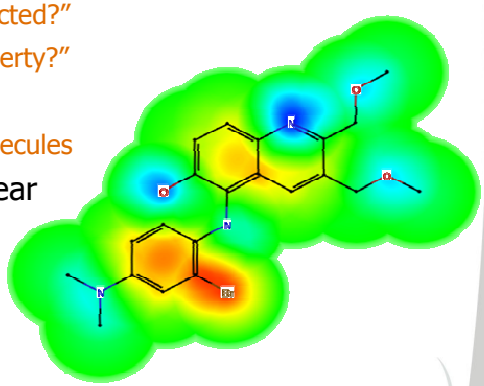
Interpreting Models Motivation



The "Glowing Molecule"*

- Provides visual interpretation of structural influences on predicted properties
  - "Why is a property value predicted?"
  - "Where can I change this property?"
  - Interpret SAR
  - Guide efficient redesign of molecules
- Applies to linear and non-linear models
  - No-more 'black box' models!
  - Individual properties or scores



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*Patent pending

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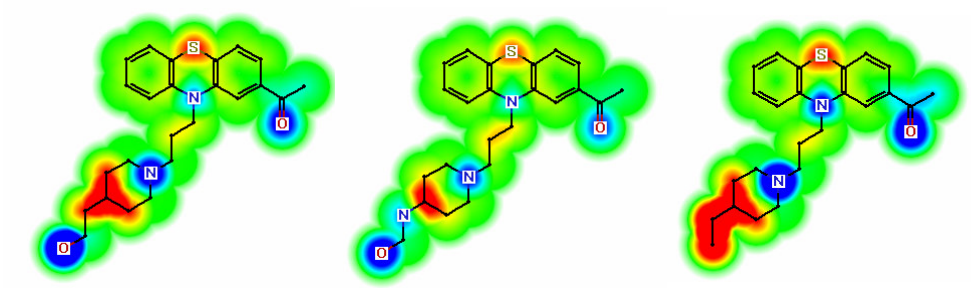
Example 1: logP



Piperacetazine
logP = 3.9

Analogue 1
logP = 3.0

Analogue 2
logP = 5.0

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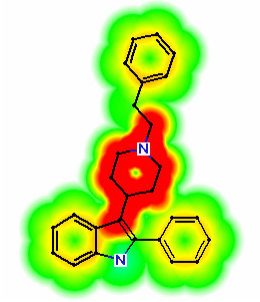
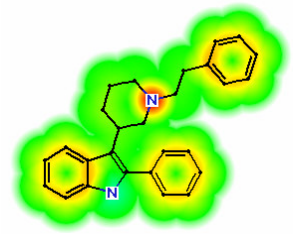
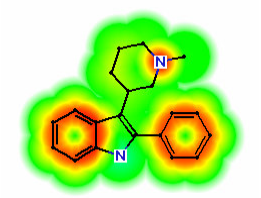
Example 2: hERG



IKr pK_i: 7.1
Predicted hERG pIC_{50}: 7.0
This figure suggests that the piperidine moiety is the largest contributor to the high observed hERG affinity.



IKr pK_i: 6.3
Predicted hERG pIC_{50}: 6.6
Changing from para- to meta-substituted piperidine reduced hERG inhibition. The figure indicates that removal of a benzyl group would further reduce hERG affinity.



IKr pK_i: 5.0
Predicted hERG pIC_{50}: 6.0
Removal of this group has the anticipated effect.

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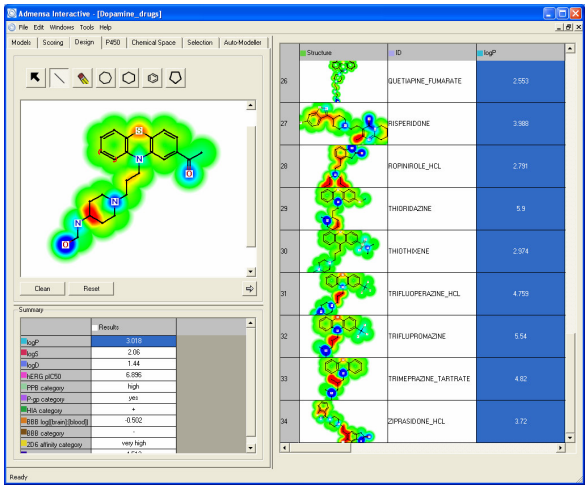
Interactive Redesign on the Desktop: Admensa Interactive



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Illustrative Example

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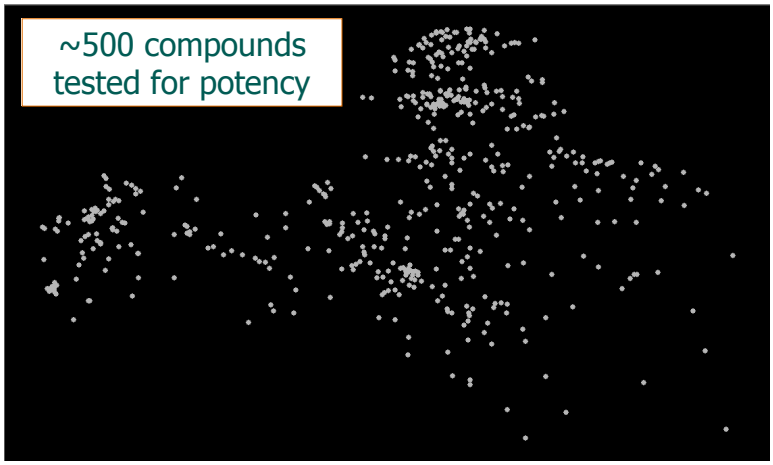
Case Study
Project Goal: Oral compound for CV disease



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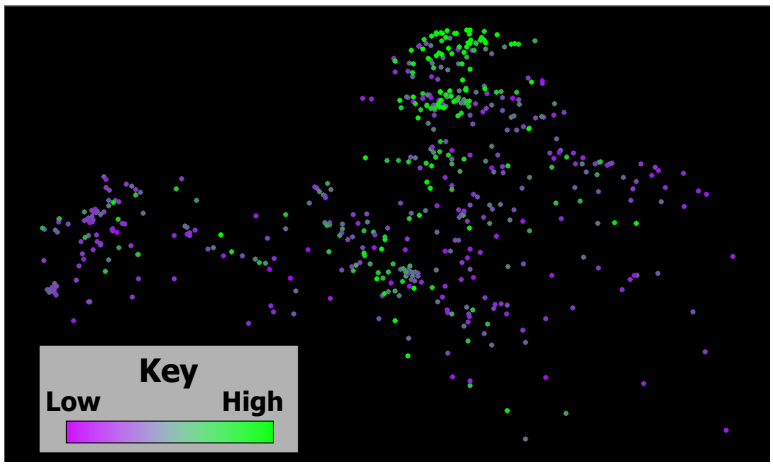
HTS Results
%Inhibition of Target



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In Silico Analysis
Identify Low Risk Chemistry

Score and rank compounds against the target profile for a **balance** of properties

Property	Desired Value	Weight
Activity (%inhibition)	>80%	High
Solubility	>10µM	
HIA	+	
logP	<3.5	
CYP2C9 Affinity	<6 (pKi)	
CYP2D6 Affinity	low or medium	
P-gp	Non substrate	
BBB log([brain]:[blood])	<-0.5	
BBB category	out	Low

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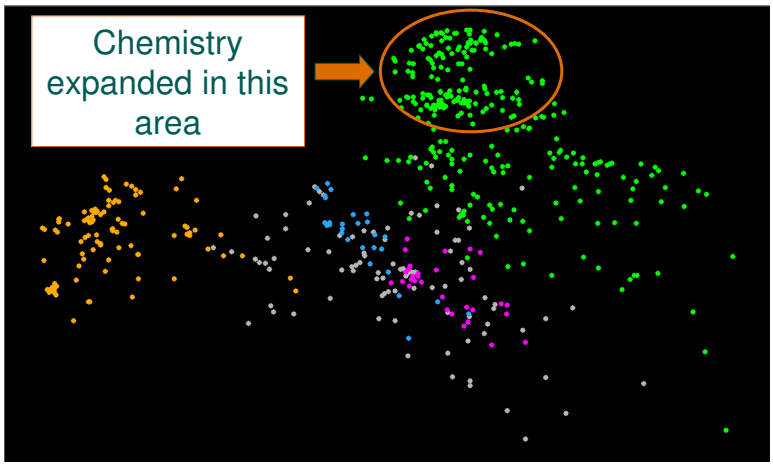
In Silico Analysis
Identify Low Risk Chemistry



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In Vitro Assessment of Risk

Risk of poor oral bioavailability

Primary *in vitro* screening

Activity
>80% inhibition of target @ 1µM

+

Solubility
>10µM in PBS:DMSO (98:2, v/v)

+

Metabolic Stability
>60% remaining @ 40min in human liver microsomes

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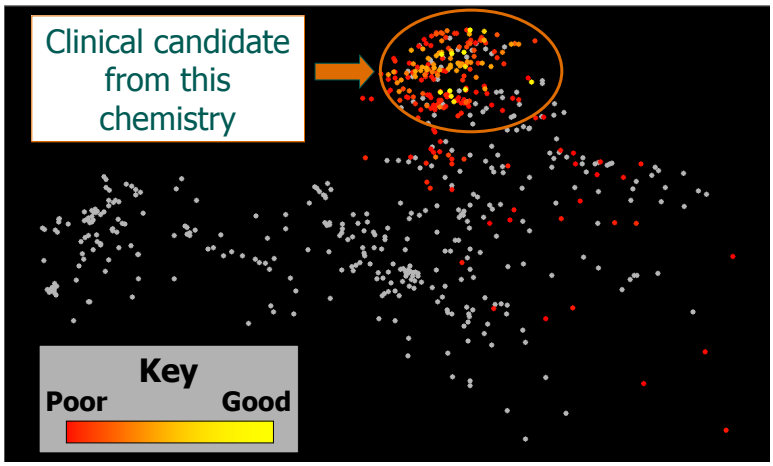
In Vitro Analysis
Confirmation of Low Risk Chemistry



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Conclusions

- Models of drug properties (potency, ADMET, physicochemical properties…) are not yet sufficiently accurate to enable a true drug *design* paradigm
- However, despite these shortcomings models may be used to achieve many of the efficiencies of drug design
  - Focus resources on chemistry that is most likely to succeed
  - Guide the design of new molecules through interpretation of SAR/docking
- Rather than focus on the properties of single molecules, models may be used to *bias the odds* of success by focussing on areas of chemistry most likely to yield a successful drug

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  - Yvonne Walker
  - Dawn Yates

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