

Future trends in Drug Discovery: The New Drug Metabolism Scientists

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Outline

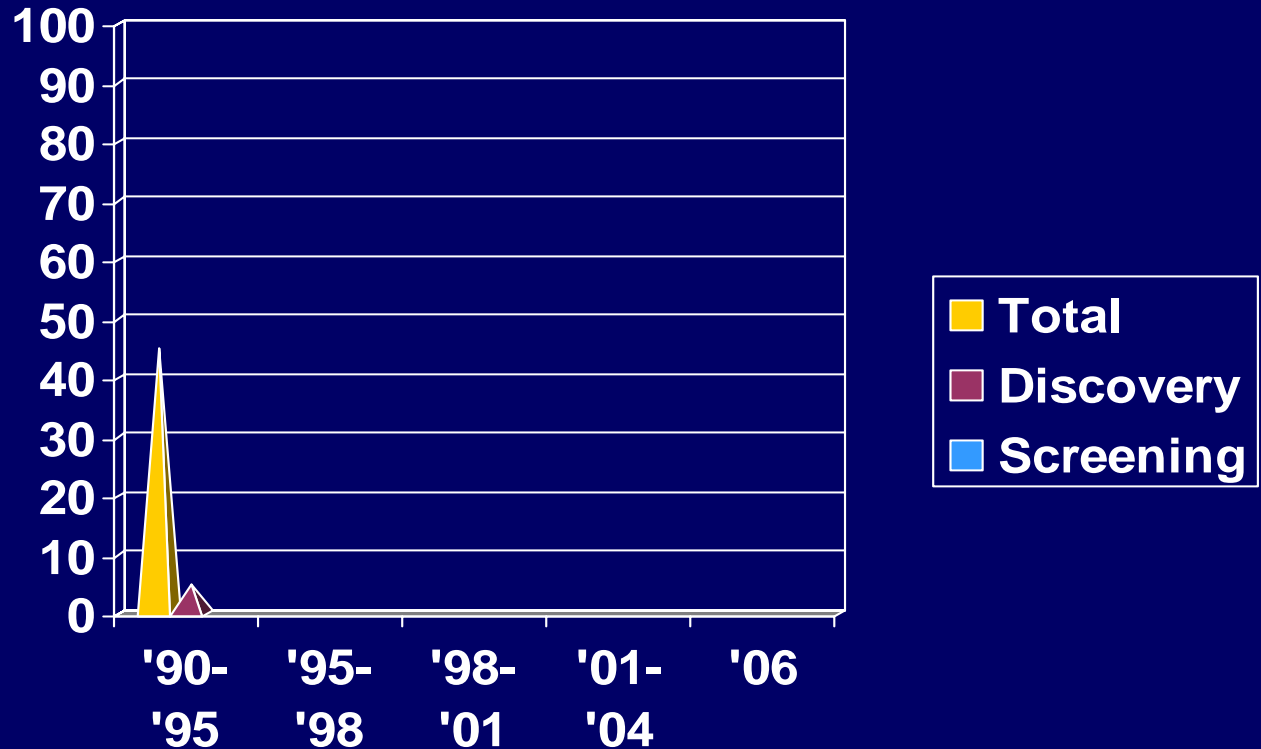
- A short retrospective of investments in the drug metabolism discipline at Pfizer's Groton, CT site

- Where the focus currently is
 - In silico
 - PK/PD

- Projected future trends and direction

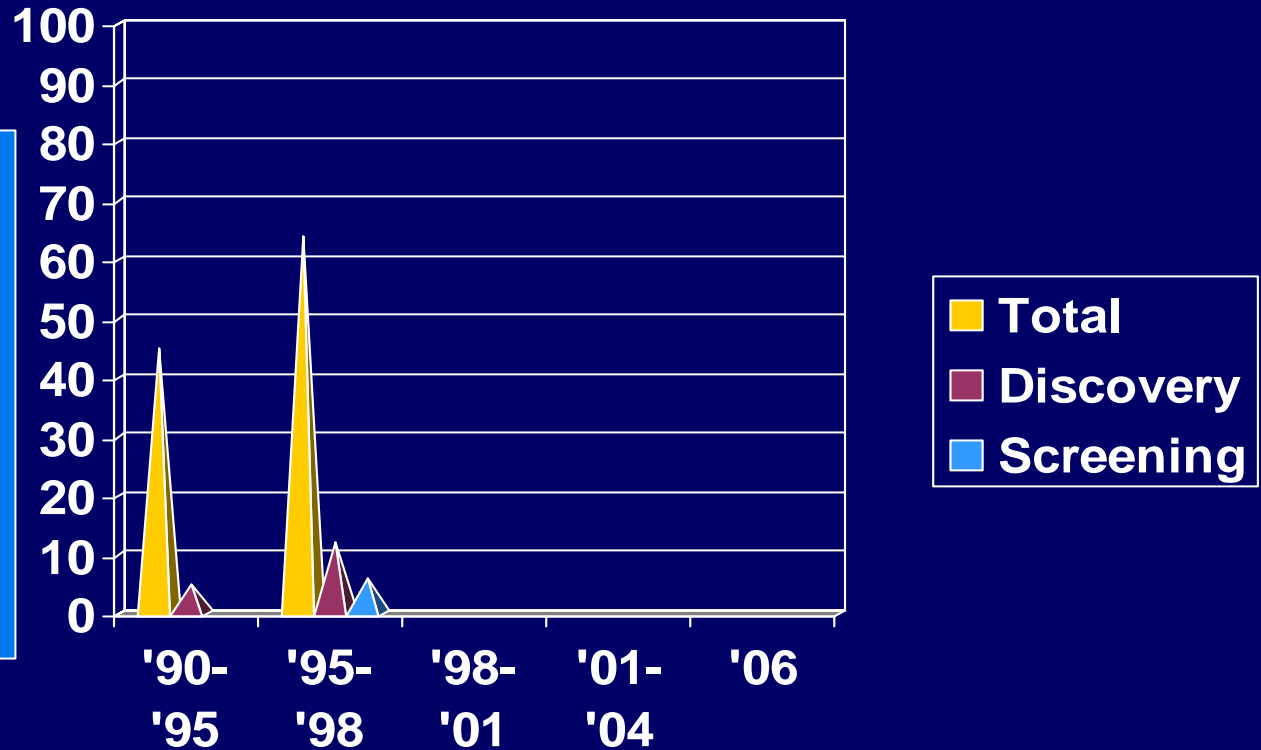
Growth and shifts in focus in Drug Metabolism at Pfizer's Groton, CT site 1990-2006

- Bioanalytical skills focus
 - HPLC-UV, GC
- Development focus
- > 90% investment post-nomination



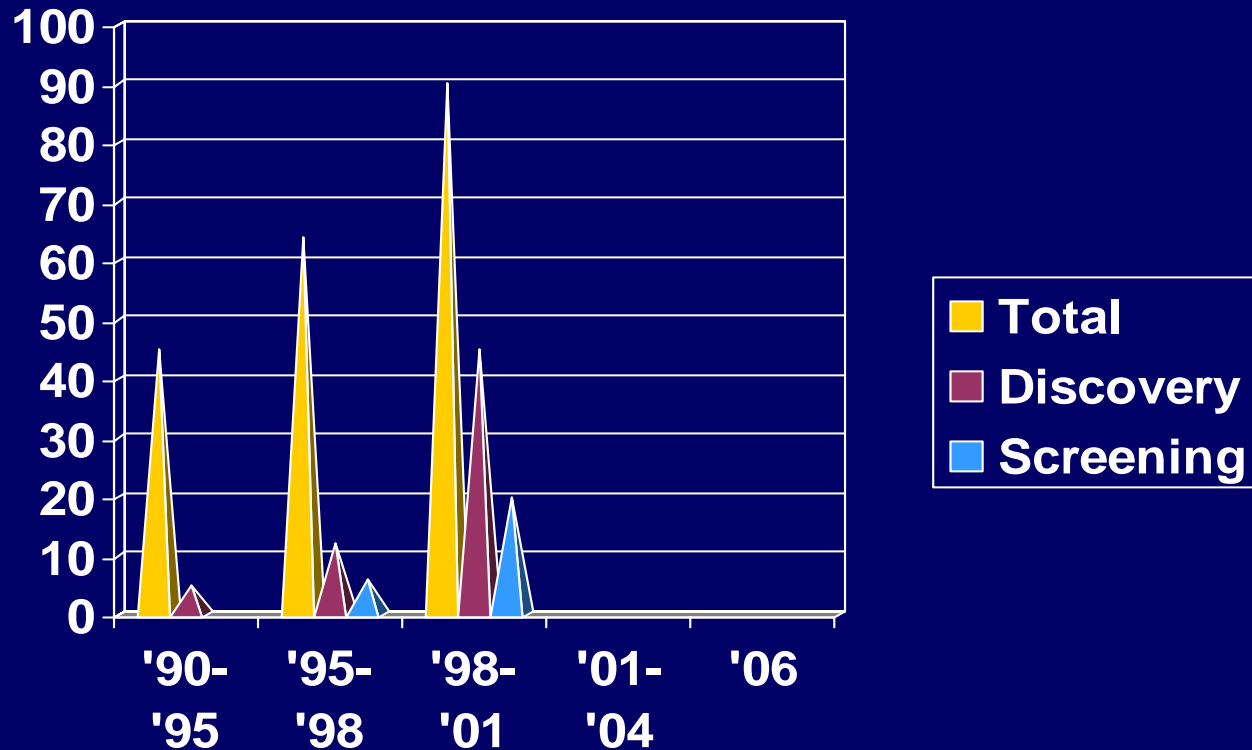
Growth and shifts in focus in Drug Metabolism at Pfizer's Groton, CT site 1990-2006

- Rapid advances in
 - in vitro tools
 - human PK predictions
- >75% effort invested post-nomination
- MS revolutionizing bioanalysis



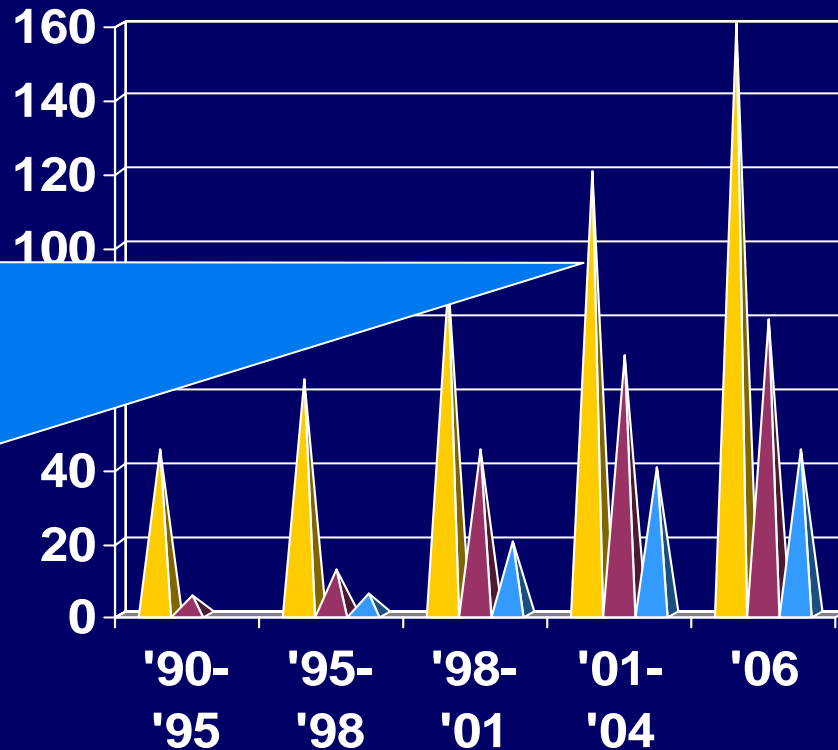
Growth and shifts in focus in Drug Metabolism at Pfizer's Groton, CT site 1990-2006

- 45+ scientists dedicated to discovery – widespread discovery experimentation
- ADME screening group in place
- Mass spec utilized by all generalists



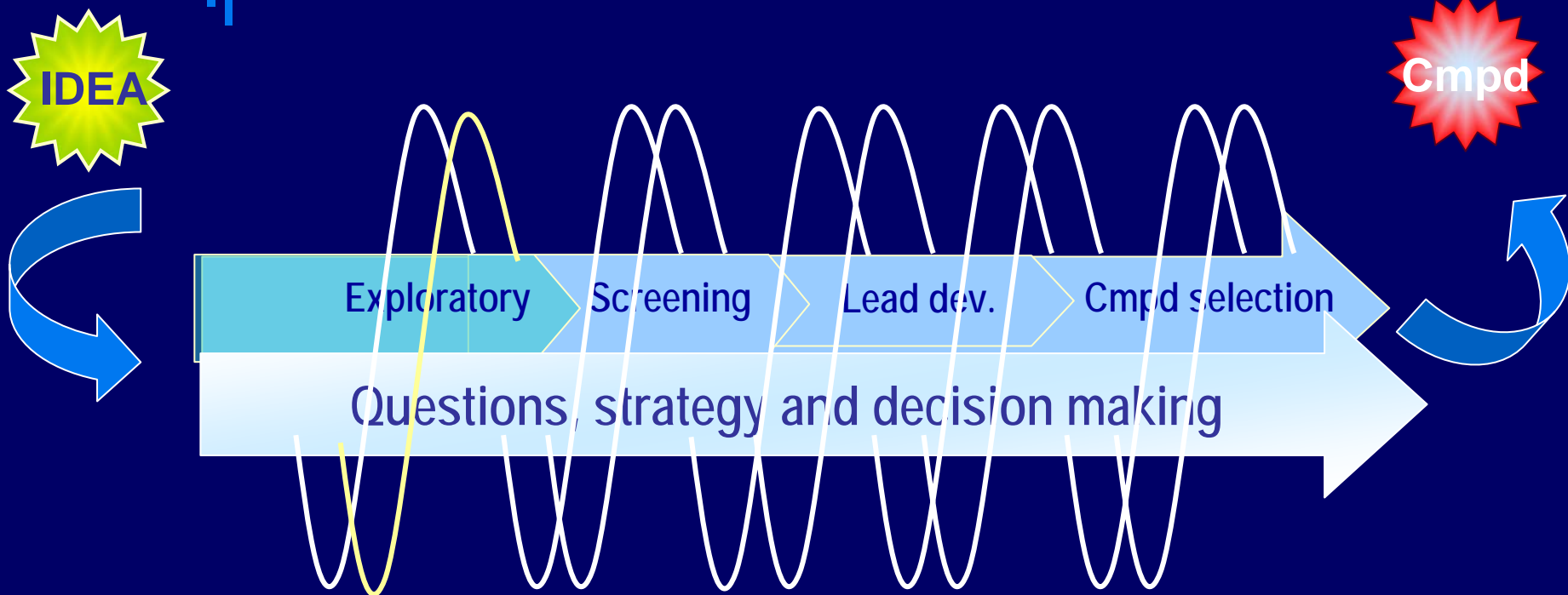
Growth and shifts in focus in Drug Metabolism at Pfizer's Groton, CT site 1990-2006

- 70 scientists dedicated to discovery
- Large ADME HTS group
- Team formed to focus pre-LD
- In silico model experimentation aided by large HTS data sets
- ADME attrition low



■ Total
■ Discovery
■ Screening

The Discovery Loop



Each loop should build on an hypothesis:

The better the questions the lower number of iterations required!

What questions should we ask and when?

Hits

Chemical space corresponding to target potency and
good ADME properties – develop tools for POC
- early IVIVC

Achieve preclinical efficacy
Understand target specific
ADME attributes and PK/PD

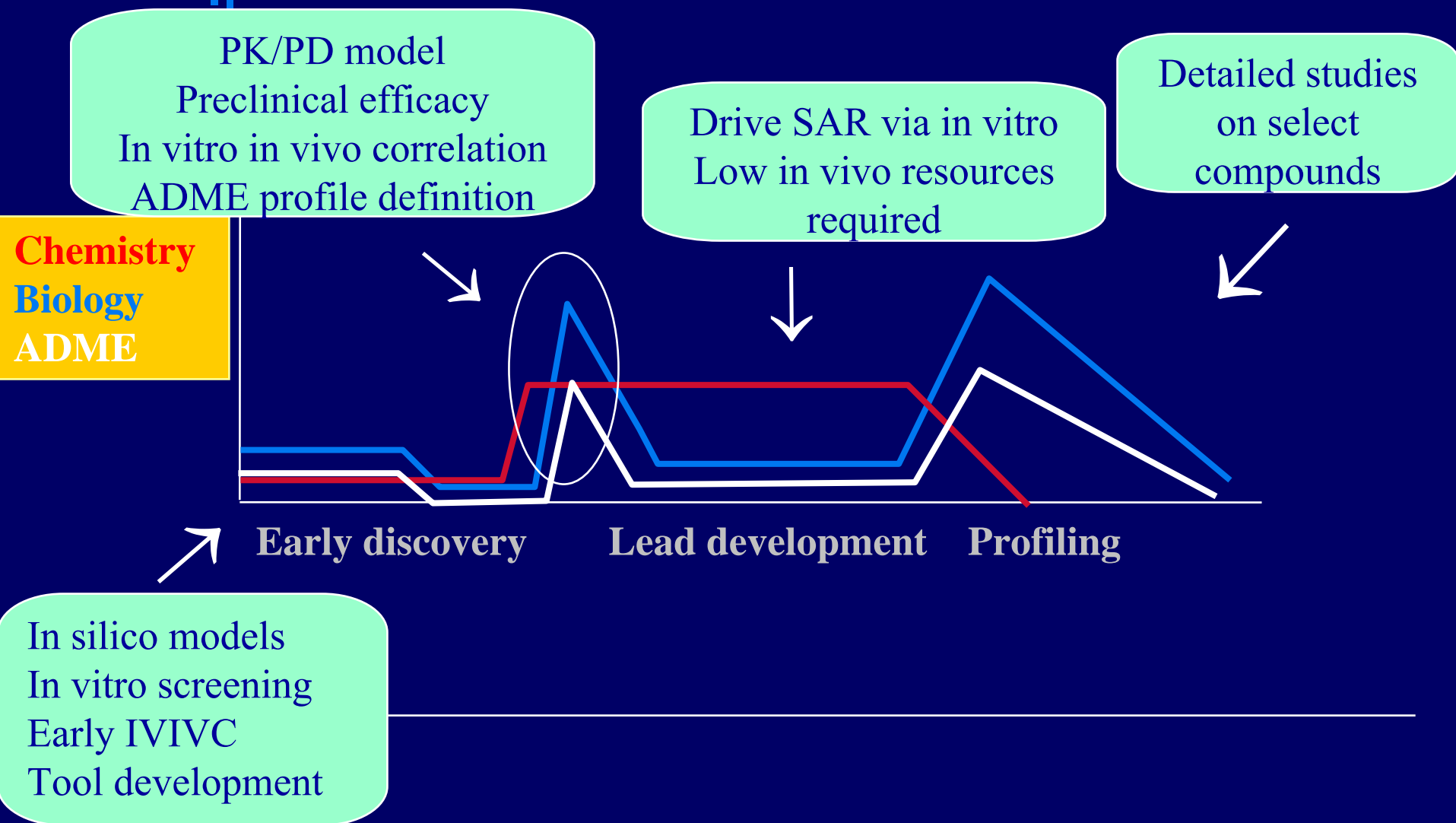
Refine and fine tune

Selection studies

Increasing cost

Compound selection

Aligning discipline investments to maximize knowledge development





Changes in Data Generated

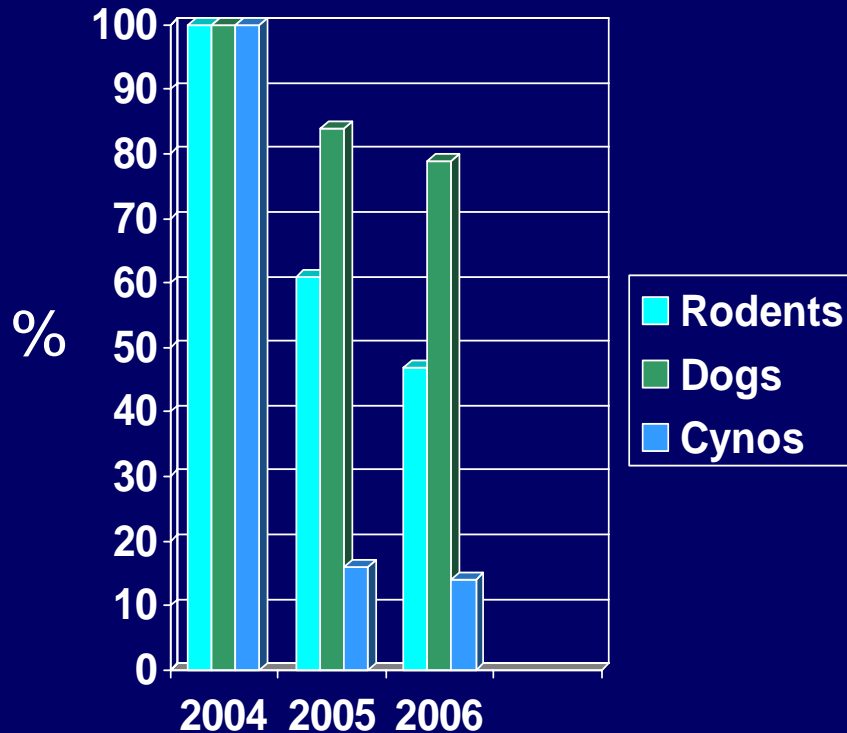
□ Reduced conduct of:

- In vivo studies
- “Routine” in vitro measures
 - Microsomal lability
 - Caco-2
- Biology screening exposure support

□ Enhanced focus on:

- In silico
- Specialized in vivo studies – tissue exposure, portal etc
- Free exposure determination – tissue and plasma
- Transporters; induction, reactive metabolites, metabolism studies
- PK/PD studies; early proof of mechanism

Reductions in Animal Use 2004-2006



- Reductions driven via
 - Increased application of in silico tools
 - Greater use of in vitro data to predict in vivo outcome
 - Reduced reliance on allometry (dogs & cynos) for human PK predictions
 - Enhanced Biology partnership



What questions are asked and when?

- Early discovery – library/series questions
 - What chemical space corresponds to target potency?
 - Where is the overlap with druggable space?
- Goal: Answer this with as few cmpds and as few data points as possible
 - Explore broad chemical space, not just potent space
 - Exploit well understood relationships between ADME properties and physicochemical properties

In silico data complemented with targeted screening

ADME In silico Models

An *in silico* model is a computer-based tool that relates a chemical structure to an ADMET property

Compound structure
and
assay data

+

Molecular
descriptors

+



Prediction of
ADMET property



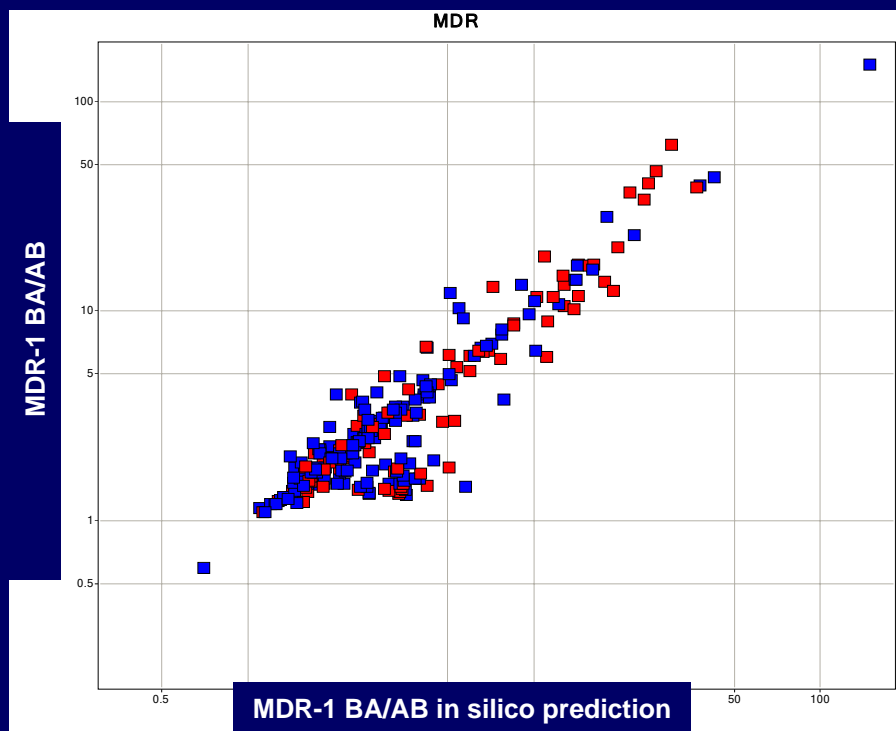
In silico models

- Widely applied across programs
 - Use of “global models” for early library generation
 - Development of series specific models for more advanced programs; provides enhanced predictability specific to chemical matter
- Can reduce the demand for High Throughput Screening (HTS)
 - Teams utilising in silico models require fewer cmpds screened
 - Data used to test hypotheses, enhance chemical space or confirm prediction

ADME HTS and individual labs generate data specifically for model development

In silico models: in vitro endpoints

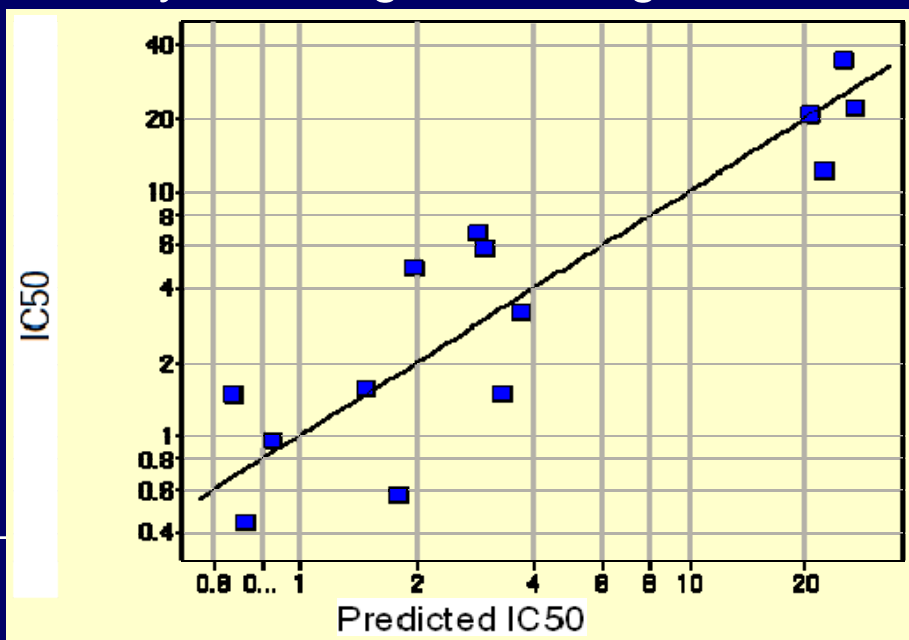
- Models are highly predictive of in vitro measures
 - >80% confidence in identification of Pgp substrates
 - >80% accuracy within 2 fold of in vitro measure for multiple models
 - Microsomal lability
 - Permeability
 - CYP 3A4 IC50 etc



In silico models: in vitro endpoints

Models can be used to determine:

- which cmpds to make/not make; define chemical space
- which cmpds to screen
- which cmpds are the most important and require data
- to test hypotheses
- for library and singleton design

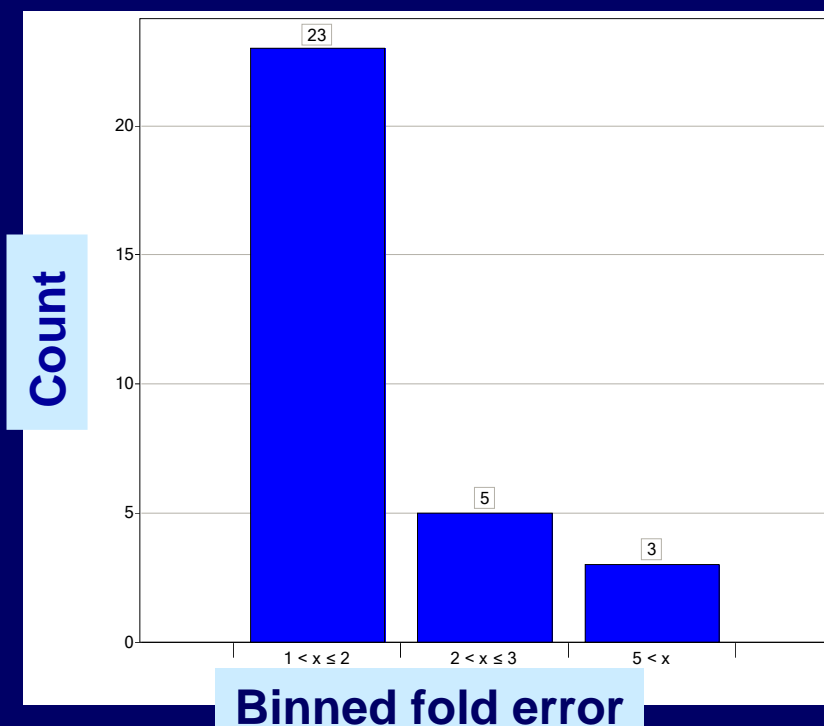
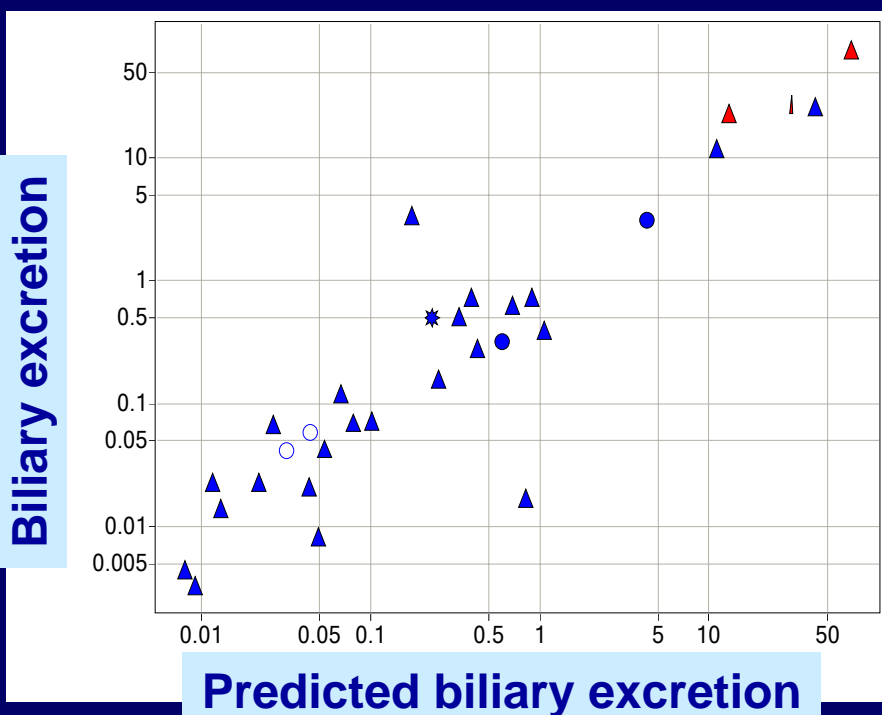


CYP 3A4 inhibition
Observed vs in silico prediction

Data courtesy of Hua Gao

In silico models: In vivo endpoints- Biliary Excretion

In silico models work for highly complex in vivo end-points



Teams early focus was on which cmpds to develop excretion data on to build model
- selection of cmpds driven by structural diversity and properties – not potency

Slide courtesy of Hua Gao

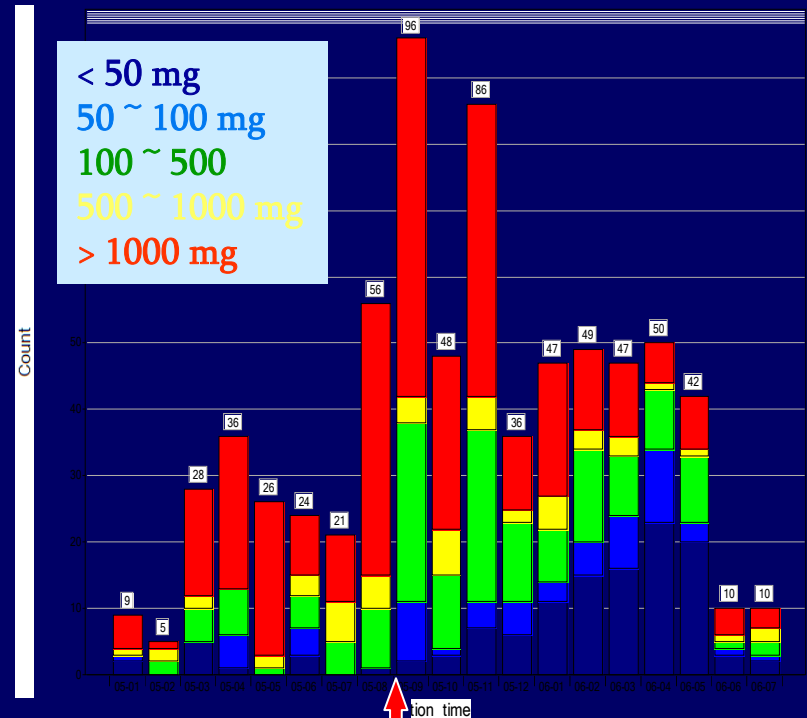
In silico models can be combined to predict dose

$$\text{Dose} \approx \frac{C_{\text{eff}} \cdot \text{CL} \cdot \tau}{F_a}$$

Combine in silico predictions of:

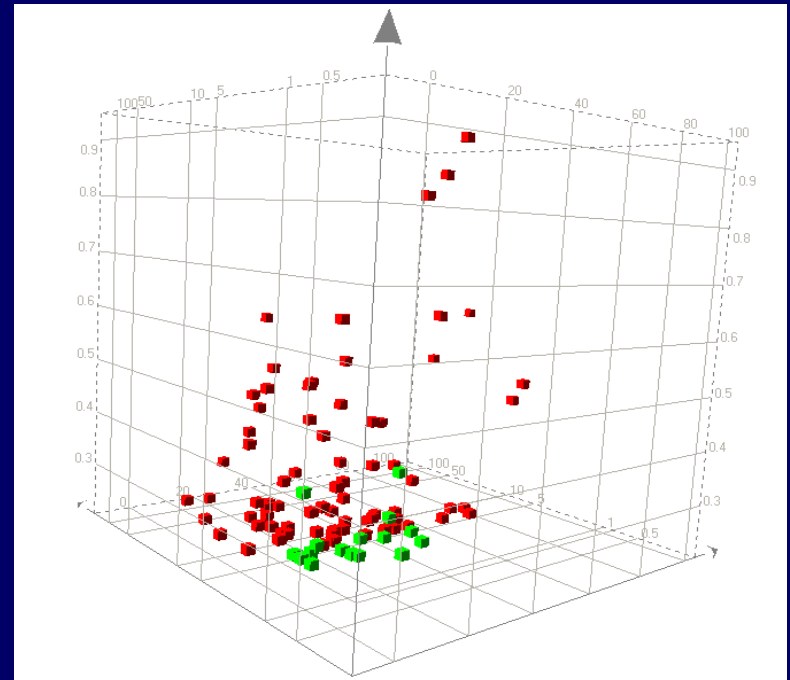
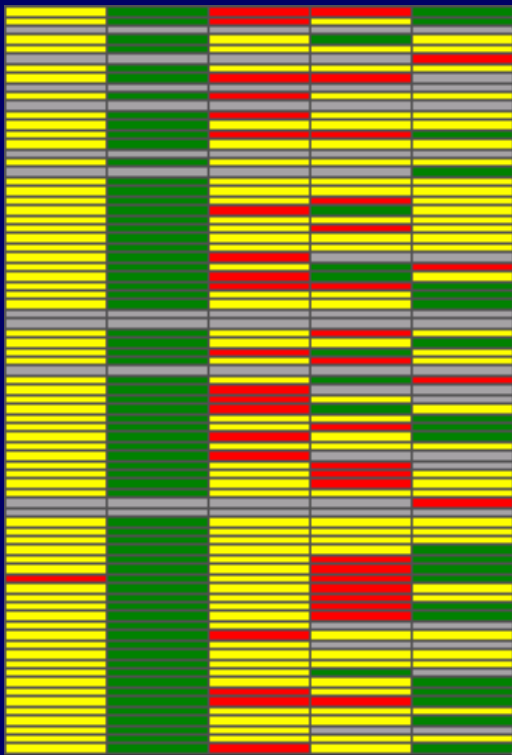
- Potency
- Permeability
- Intrinsic clearance
- Free fraction
- Tissue penetration

Projected human daily dose over project history



Use of in silico models begins

Decision making on large multi-parametric data sets



Simultaneous optimization of potency + ADME



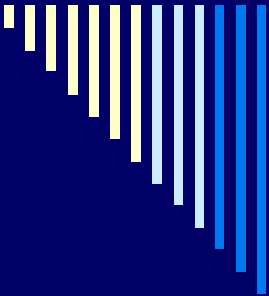
What questions are asked and when?

□ Prior to lead series selection

- What ADME properties are we really shooting for?
- With good tools in hand do we still have confidence in this target?

■ Goal: Increase confidence in mechanism for novel targets and identify requisite ADME properties

- Understand how in vitro potency translates to in vivo efficacy
 - Develop PK/PD understanding and use to drive ADME/potency targets
 - Select most appropriate series based on this knowledge
-



Maximizing the value of biology efficacy studies...

Compound A from series 1

- 870nM potency
- ED50 50 mg/kg in a rat

Compound B from series 2

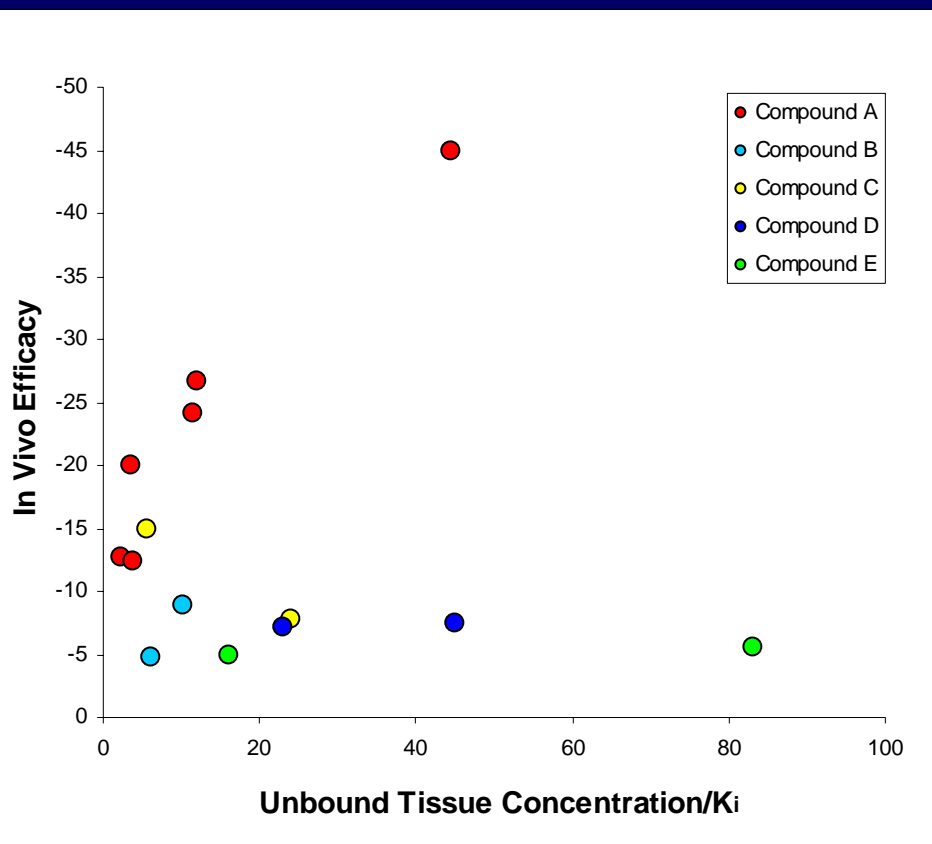
- 45nM potency
- ED50 25 mg/kg in a rat

Questions:

- 1) Is there a relationship between potency and efficacy?
- 2) Has improved potency in compound B translated into expected reductions in exposure for efficacy?

Need to develop an understanding of exposure as a function of efficacy
- Essential to building confidence in mechanism early in a program

Connecting in vitro potency with in vivo efficacy

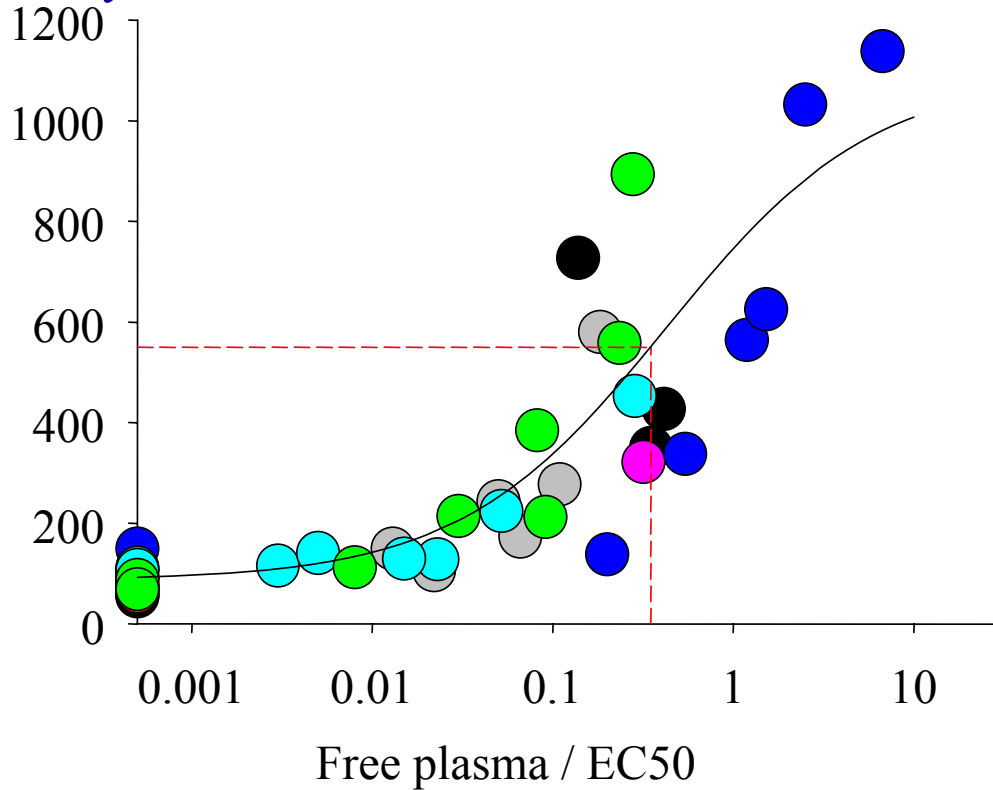


For this target in vitro potency does not appear related in a consistent way to in vivo efficacy....

- low confidence in mechanism or
- knowledge gap

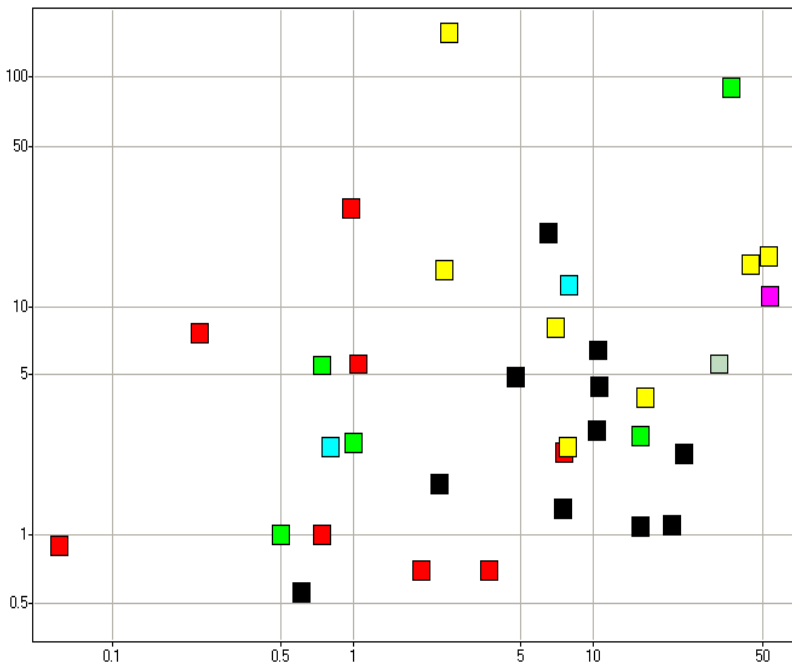
Connecting in vitro potency with in vivo efficacy

Efficacy



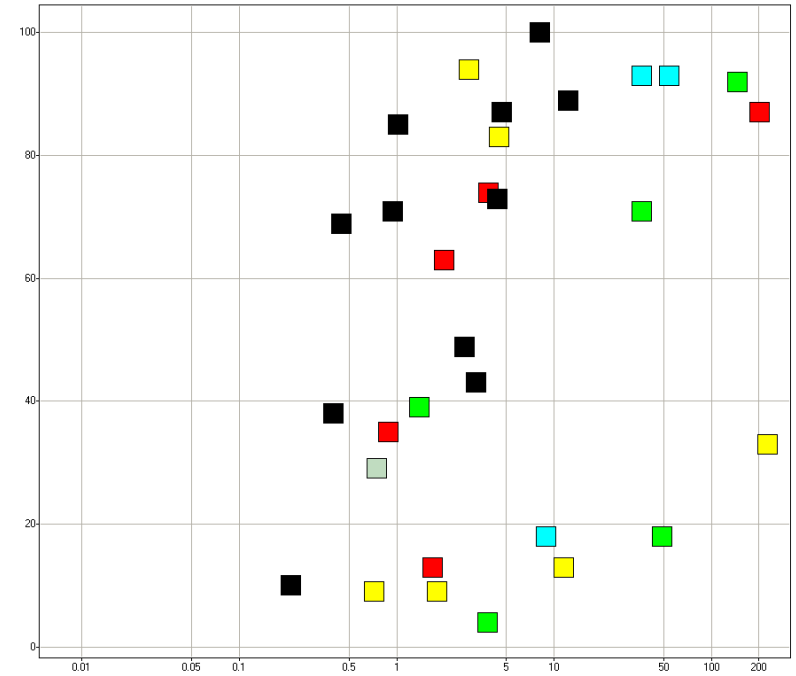
Identifying the assays to drive the program

Ki nM



EC50 nM

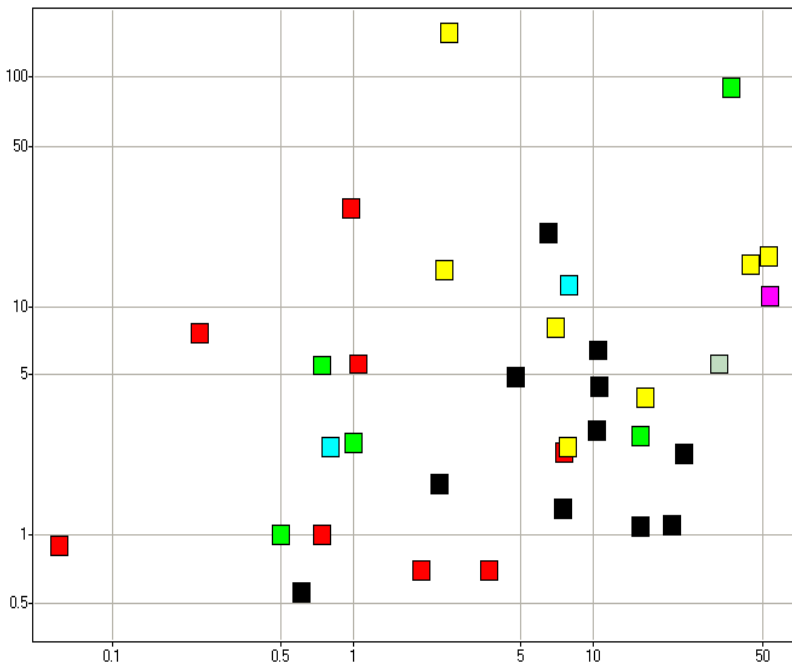
% Inhibition over 2 hr



Free brain/EC50

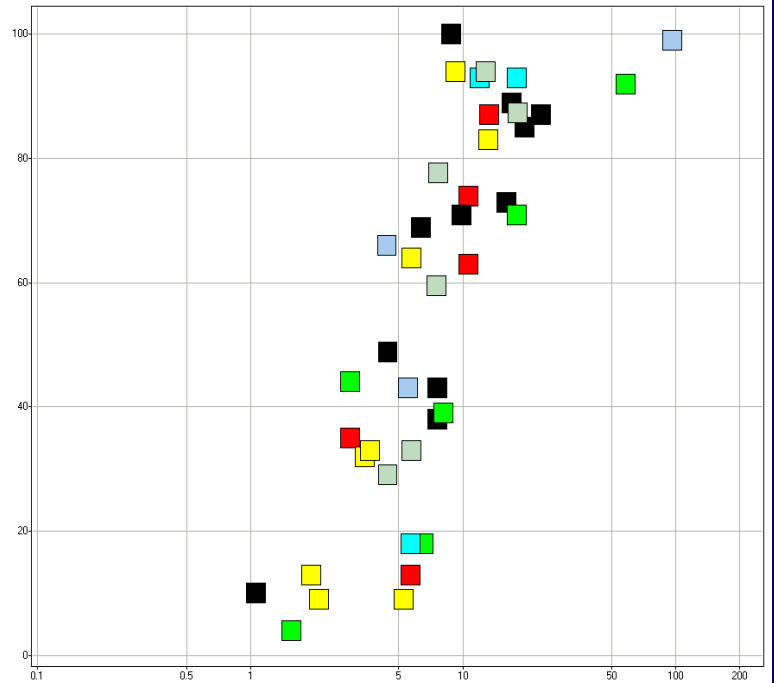
Identifying the assays to drive the program

Ki nM



EC50 nM

% Inhibition over 2 hr



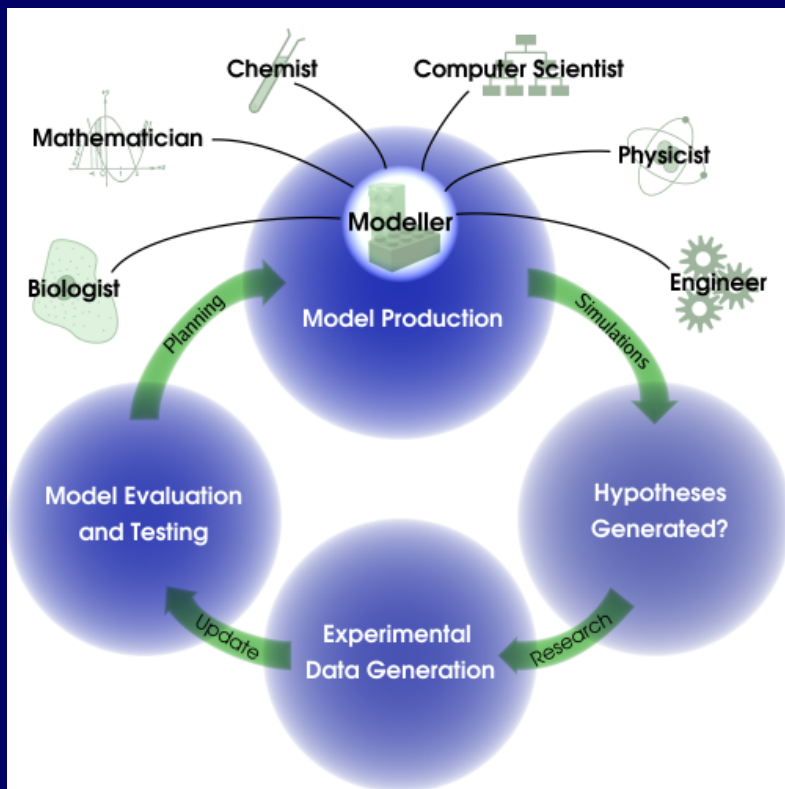
Free brain/Ki



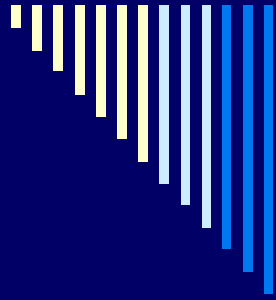
The Future...

- Biotherapeutics (here now!)
 - Antibodies, spiegelmers, oligonucleotides, proteins, peptides etc
 - Will drive different bioanalytical skills
 - Will drive new knowledge/science
 - in vitro tools/predictive tools to measure/predict disposition
 - Enzymology and transportation of biologics
 - Biomarkers
 - Obvious linkage with bioanalytical skills across discipline
-

The Future...



- Enhanced in silico capabilities
 - reduced need for current “Tier 1” ADME HTS screens
- Systems Biology/PK/PD
 - modeling of pathways enabling selection of best/safest point of intervention
 - integration of organ models to predict disposition
- Virtual Drug Discovery!
 - minimal synthesis/assay
 - data generated confirms prediction



Questions?
