The Safety Related Attrition Challenge: A Medicinal Chemists Perspective

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AstraZeneca R&D, Global Safety Assessment

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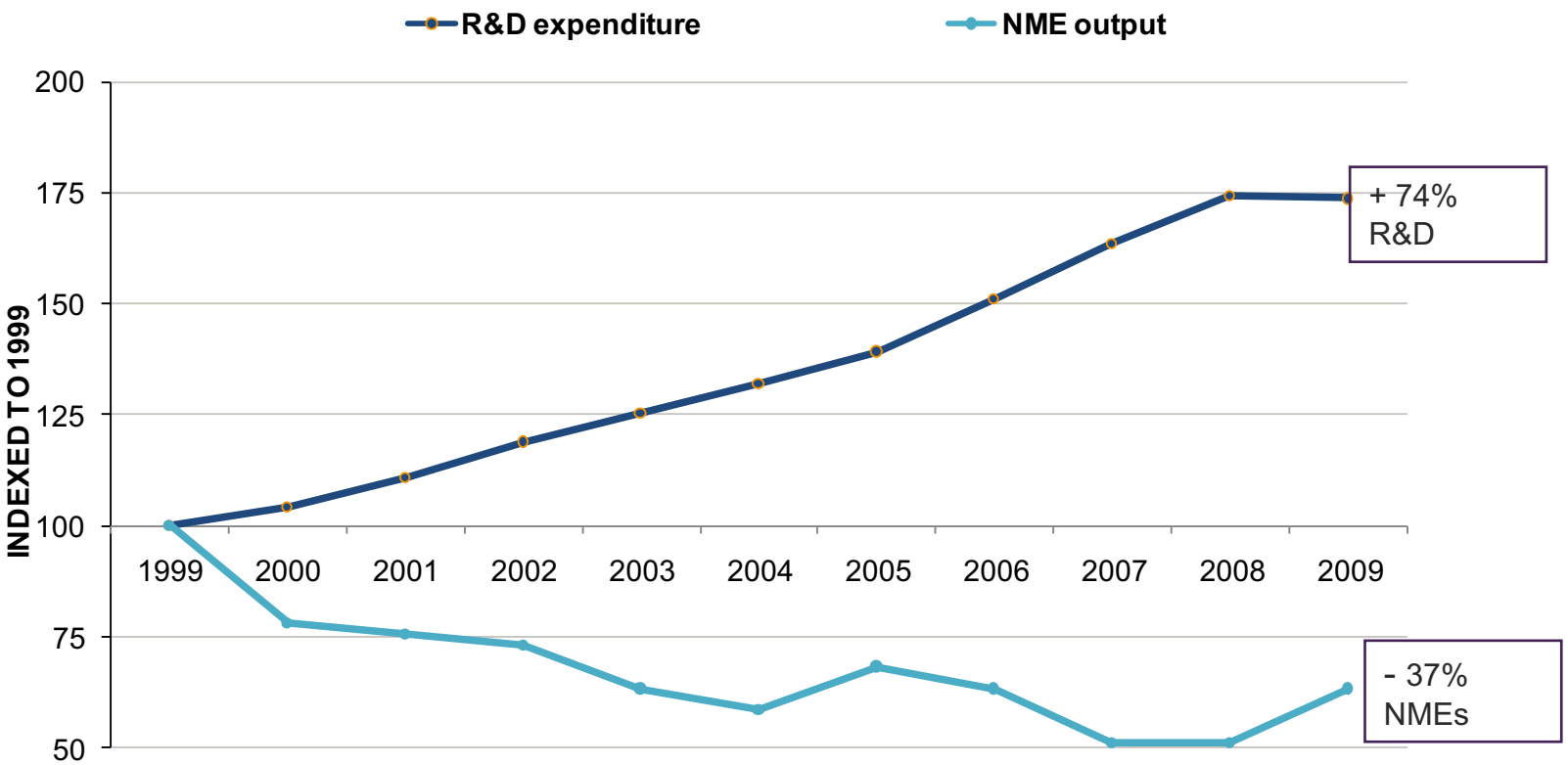
Introduction

- Pharmaceutical industry facing ever increasing challenge
- Rising costs & static productivity



Source: CMR International (2010 FactBook) & IMS Health

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Reasons for Attrition

- Shift in attrition from DMPK to toxicology
- No evidence of significant change in 2010

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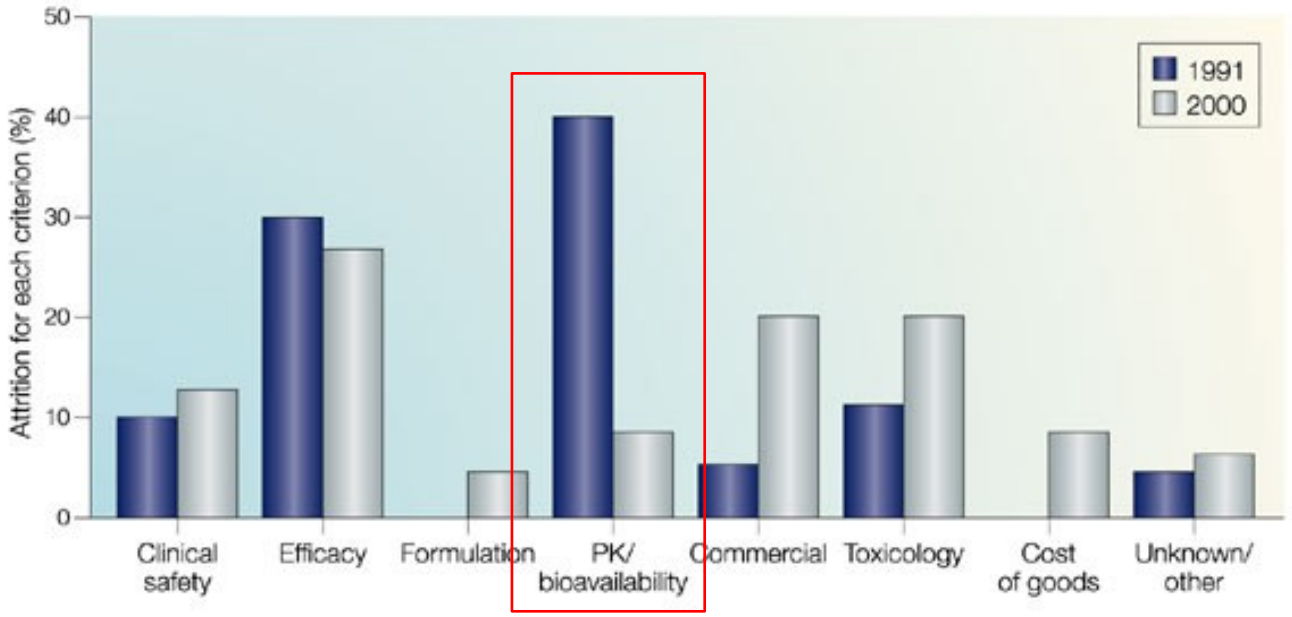
Discovery Toxicology Investment Needed



Kola *et al*, Nature Reviews Drug Discovery 2004, 3, 711

- Reduction in DMPK related attrition achieved through:
  - Investment in discovery DMPK
  - Development of assays
  - Sharing of data and analysis
  - Communication – integration into project teams

Close scientific collaboration between DMPK & medchem

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What is the problem?
Evidence, prevalence, occurrence

Phase	Preclinical	Non-clinical	Phase I	Phase I-III	Phase I-III	Phase III/ Approval	Post-Approval	Post-Approval
Information:	Causes of attrition	Causes of attrition	Serious ADRs	Causes of attrition	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale
Source:	ABPI (2008)	Car (2006)	Sibille et al. (1998)	ABPI (2008)	Olson et al. (2000)	BioPrint® (2006)	Budnitz et al. (2006)	Stevens & Baker (2008)
Sample size:	156 CDs stopped	88 CDs stopped	1,015 subjects	63 CDs stopped	82 CDs stopped	1,138 drugs	21,298 patients	47 drugs
Cardiovascular:	24%	27%	9%	35%	21%	36%	15%	45%
Hepatotoxicity:	15%	8%	7%	29%	21%	13%	0%	32%
Haematology/BM:	3%	7%	2%	3%	4%	16%	10%	9%
Nervous system:	12%	14%	28%	2%	21%	67%	39%	2%
Immunotox; photosensitivity:	7%	7%	16%	10%	11%	25%	34%	2%
Gastrointestinal:	5%	3%	23%	2%	5%	67%	14%	2%
Reprotox:	9%	13%	0%	5%	1%	10%	0%	2%
Musculoskeletal:	8%	4%	0%	5%	1%	28%	3%	2%
Respiratory:	1%	2%	0%	2%	0%	32%	8%	2%
Renal:	6%	2%	0%	5%	9%	19%	2%	0%
Genetic tox:	5%	5%	0%	0%	0%	0%	0%	0%
Carcinogenicity:	0%	3%	0%	3%	0%	1%	0%	0%
Other:	4%	0%	0%	2%	4%	16%	2%	2%

The various toxicity domains have been ranked first by contribution to products withdrawn from sale, then by attrition during clinical development. *Note* general agreement between pairs of equivalent studies.

0% 1-9% 10-19% >20%

Adapted from Redfern WS et al. The Toxicologist 2010; 114 (S-1), 1081.

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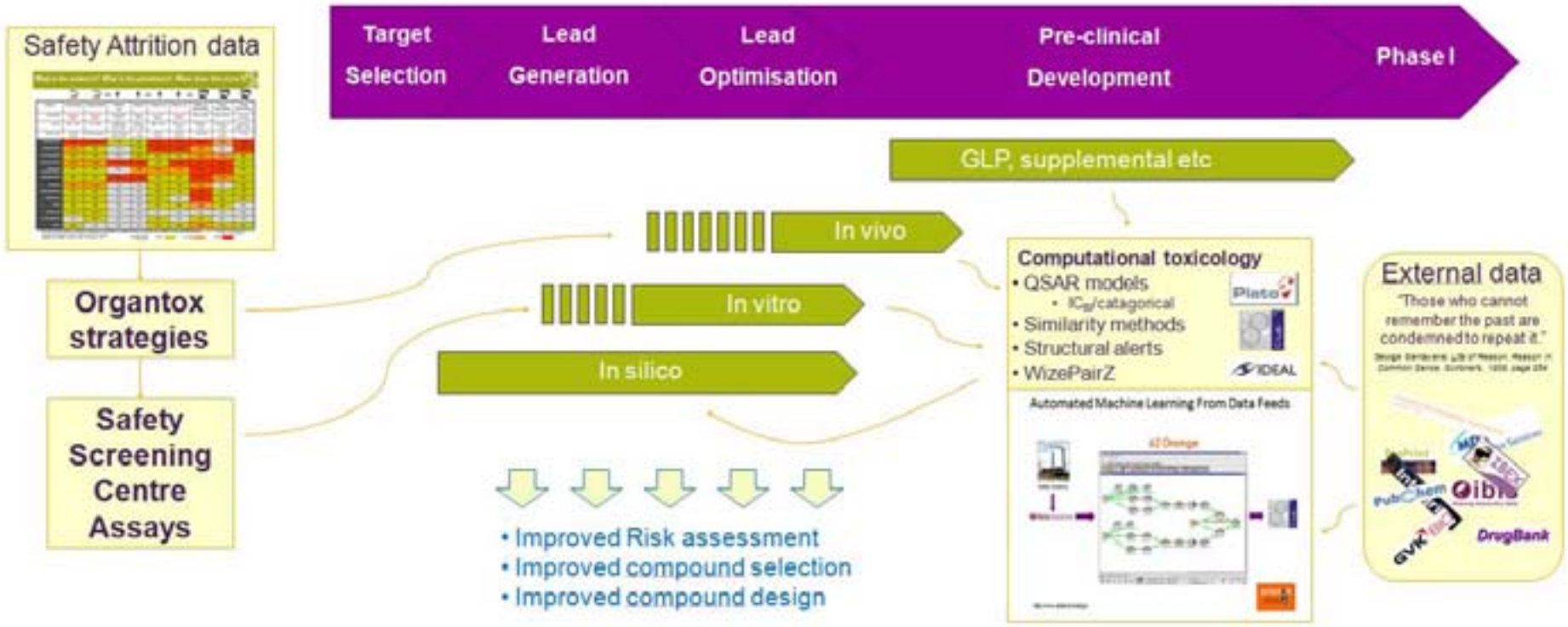

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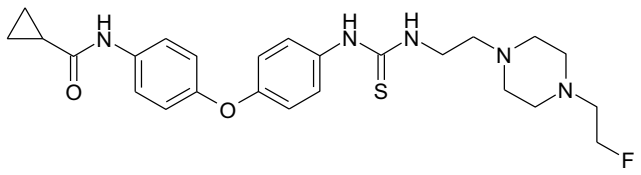
A chemists view of toxicology

Chemistry Related Toxicity



Target Related Toxicity

Reactivity & bioactivation

Off Target pharmacology

Physicochemical properties

Substructures

Whole molecule property (Typically)

Deeper understanding

Earlier Hazard identification

Chemist

Experimental Plan To mitigate risks

Toxicologist

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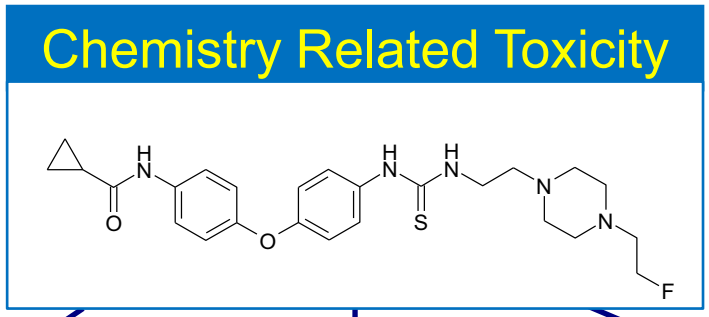
Earlier identification of chemical hazards



"Those who cannot remember the past are condemned to repeat it."

George Santayana: *Life of Reason, Reason in Common Sense, Scribner's, 1905, page 284*

Reactivity & bioactivation

Off Target pharmacology

Physicochemical properties

Substructures

Whole molecule property (Typically)

In Silico approaches

Assays (Safety Assessment and DMPK)

Chemtox risk assessment

- *SMARTS matching*
- *QSAR models*
- *Similarity based methods*

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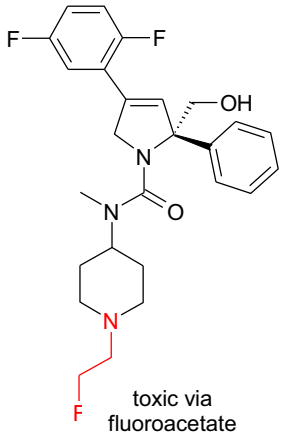
Structural Alerts

- Multitude of sub-structural alerts to be aware of
  - Reactive metabolites
  - Genotoxicity
  - Reactive structures
  - Toxic metabolites

IDEAL

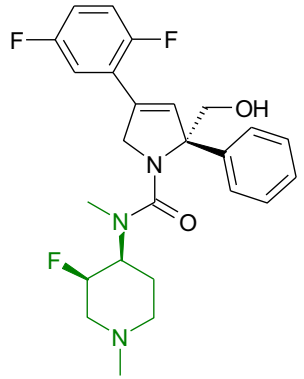
Integrate structural alerts into design tools

- Still appearing to cause problems for medicinal chemists
  - *Example: J. Med. Chem.* ***2008, 51, 4239–4252***



toxic via fluoroacetate generation

"we were surprised to find mortality within 12 h postdose in 2 of 3 rats in the 12 mg/kg group."



clinical candidate

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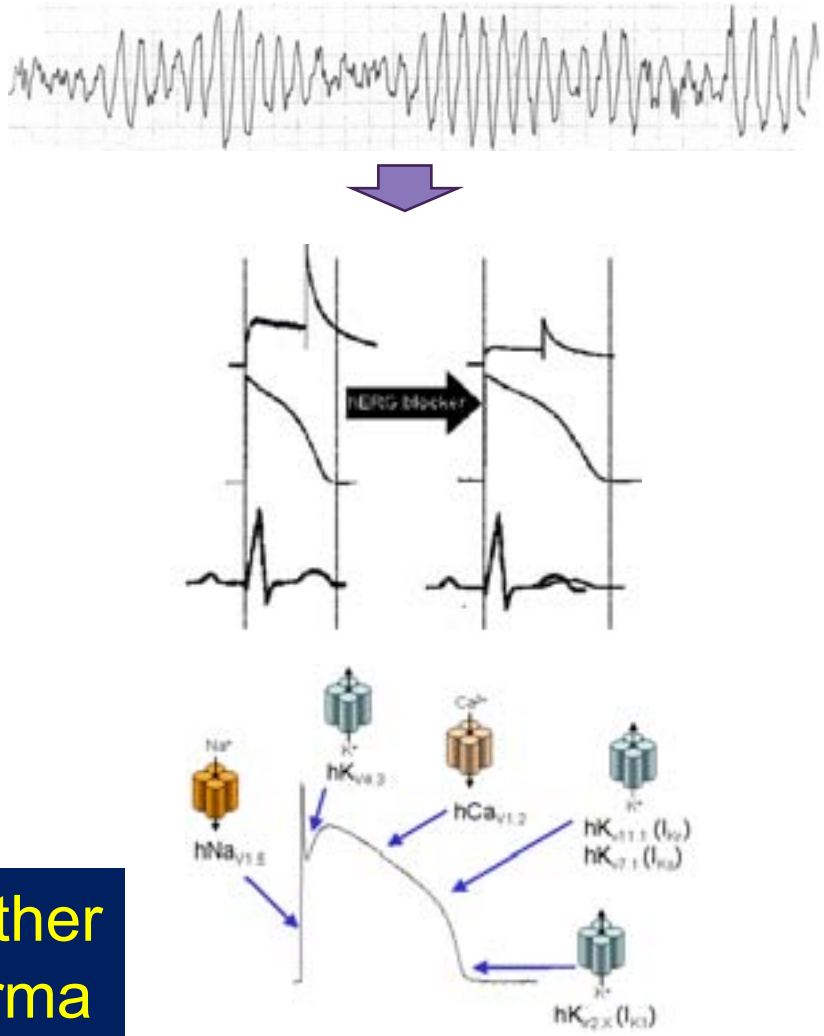
hERG: example of a mature target?

- Withdrawals in late 1990s for risk of Torsades de Pointes
  - E.g Terfenadine & Cisapride
- Identification of hERG as a leading cause of QTc prolongation
- ICH E14 guidelines in 2005 – introduced need for “thorough QT/QTc study”
- Significant investment in preclinical risk assessment and mitigation strategies



Routine assessment of hERG & other ion channels in AZ and other pharma

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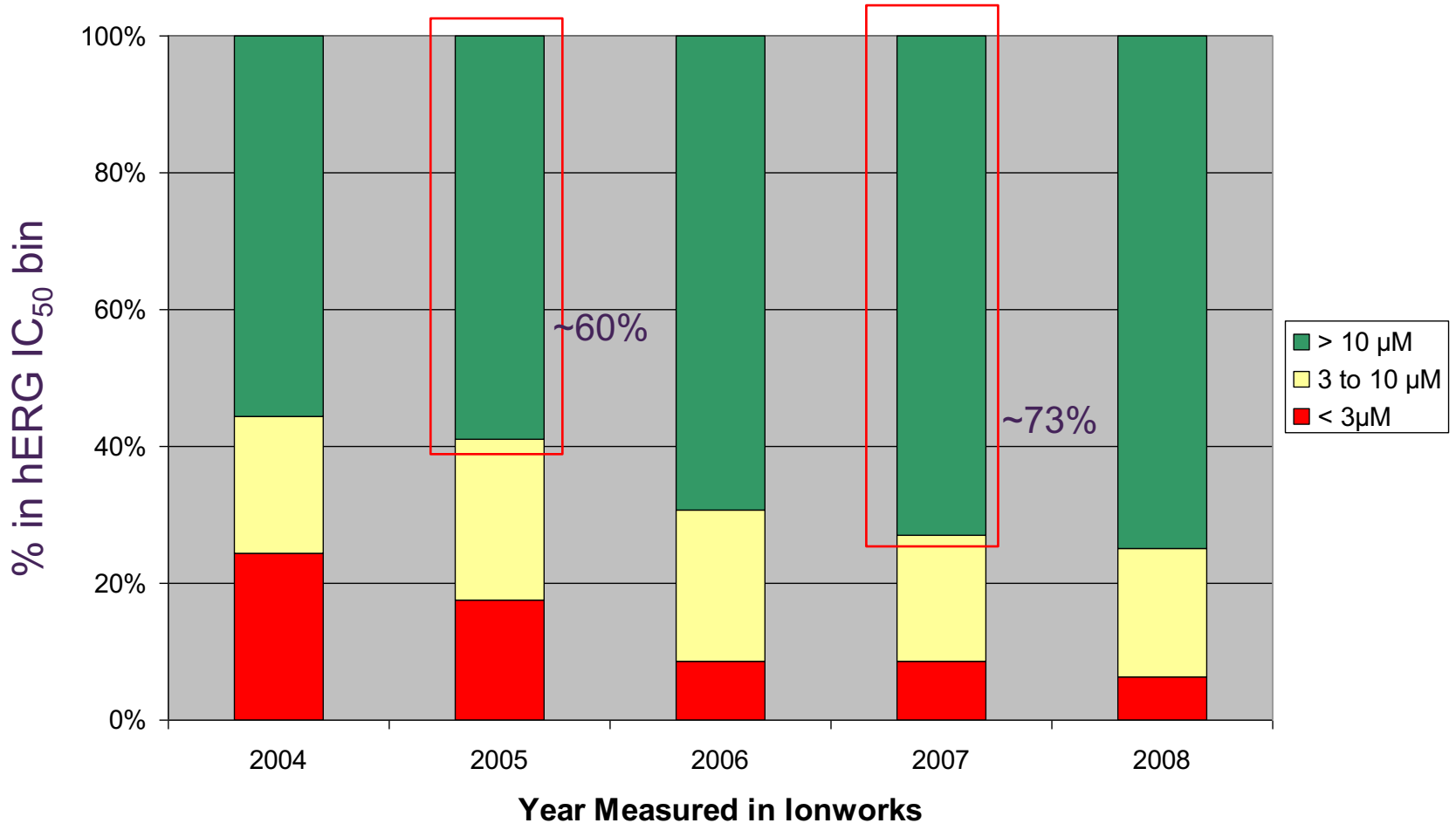
hERG: example of a mature target?

Less cardiac arrythmia liability over time



Strategies to avoid well understood, many projects can avoid through early focus – evidence of improved compound design?

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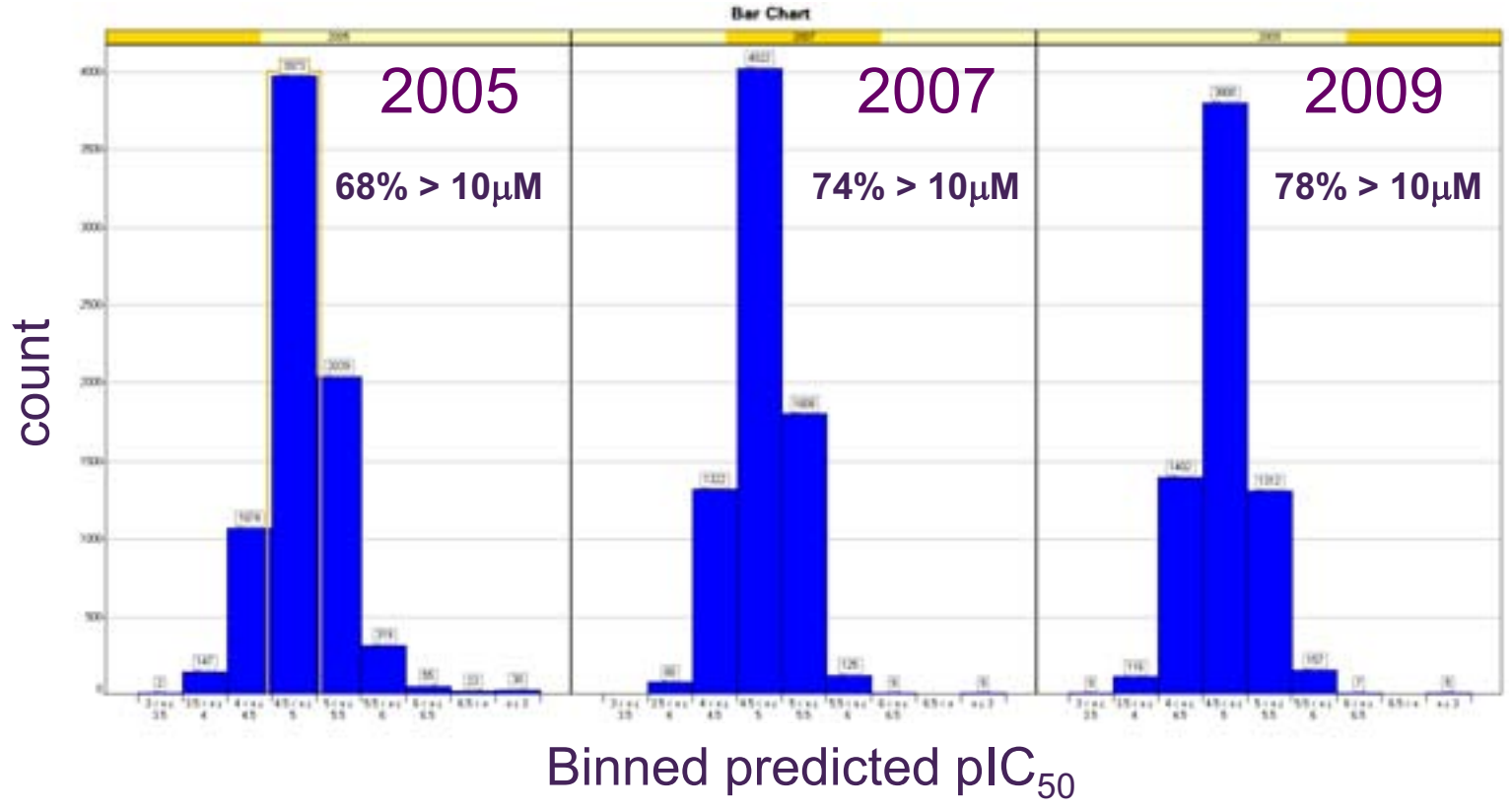
Are we improving design against hERG?

- Global QSAR Model:
  - Comparison of hERG predictions for 1st 10k compounds by year



~30% fewer compounds with predicted hERG activity < 10μM since 2005

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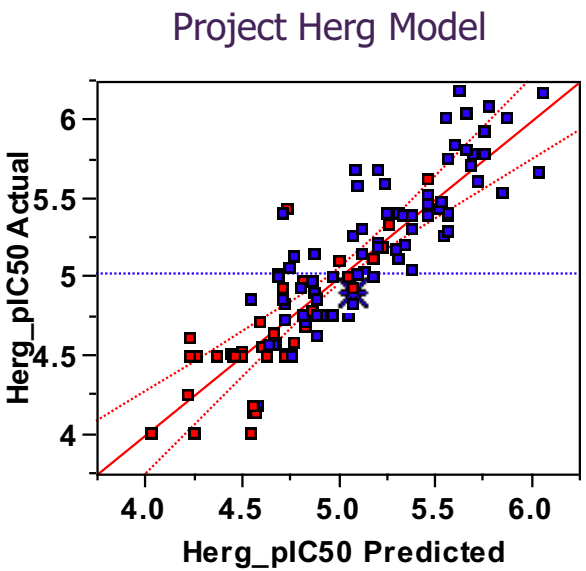
Working with hERG in Projects

- Project hERG Model
  - Sub-structure corrections
  - Interpretable with respect to SAR
  - Lipophilicity Model for ClogD
- Better performance than global Models for some projects



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Molecular Matched Pairs

Probability for given transformation X to Y

+ive
-ive
neutral

But context may be important

$R^1 - X$ 

$R^2 - X$ 

↓

$R^n - X$ 

WizePairZ: A Novel Algorithm to Identify, Encode, and Exploit Matched Molecular Pairs with Unspecified Cores in Medicinal Chemistry
Daniel J. Warner, Edward J. Griffen and Stephen A. St-Gallay
Journal of Chemical Information and Modeling
2010 50 (8), 1350-1357

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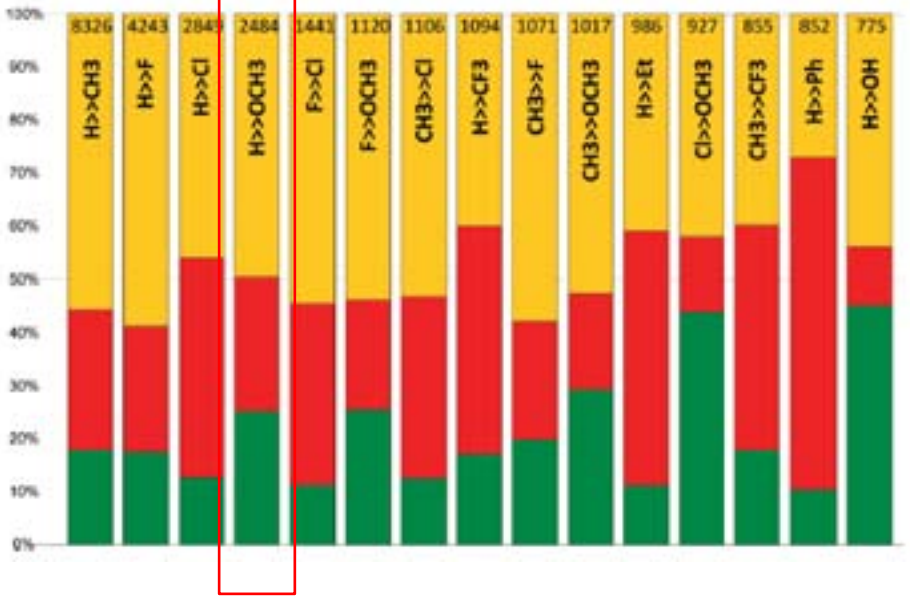
Matched Molecular Pairs & hERG

J. Chem. Inf. Model. **2010,** *50,* 1872
GSK and Univ. Sheffield



H>>OCH_3

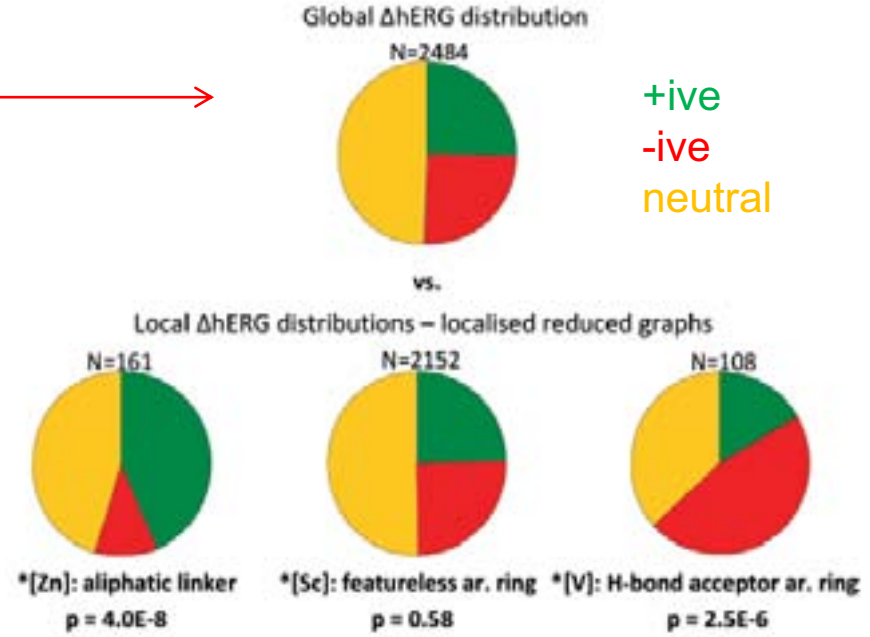


Figure 3. Global and local ΔP distributions for the H → OCH_3 transformation in the hERG data set. Colors as in Figure 2. Different trends are observed, depending on whether the reduced graph node of the attachment point is an aliphatic linker [Zn], a hydrophobic aromatic ring [Sc], or a polar aromatic ring [V]. *P* values signify the statistical significance of this observation. The number of examples for each case is shown above the respective pie chart.

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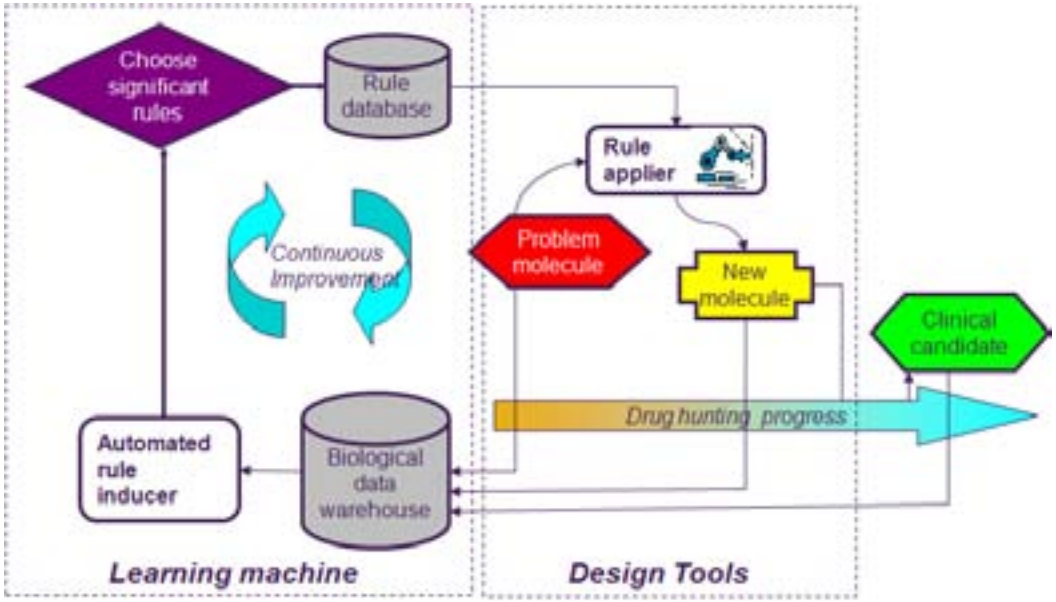
Molecular Matched Pairs

$$R - X \xrightarrow{\triangle P} R - Y$$

Probability for given transformation X to Y

+ive
-ive
neutral



But context may be important

$R^1 - X$

$R^2 - X$

$R^n - X$

Ref: Griffen, E. Future Medicinal Chemistry **1**:405-408 (2009)

WizePairZ: A Novel Algorithm to Identify, Encode, and Exploit Matched Molecular Pairs with Unspecified Cores in Medicinal Chemistry
Daniel J. Warner, Edward J. Griffen and Stephen A. St-Gallay
Journal of Chemical Information and Modeling
2010 50 (8), 1350-1357

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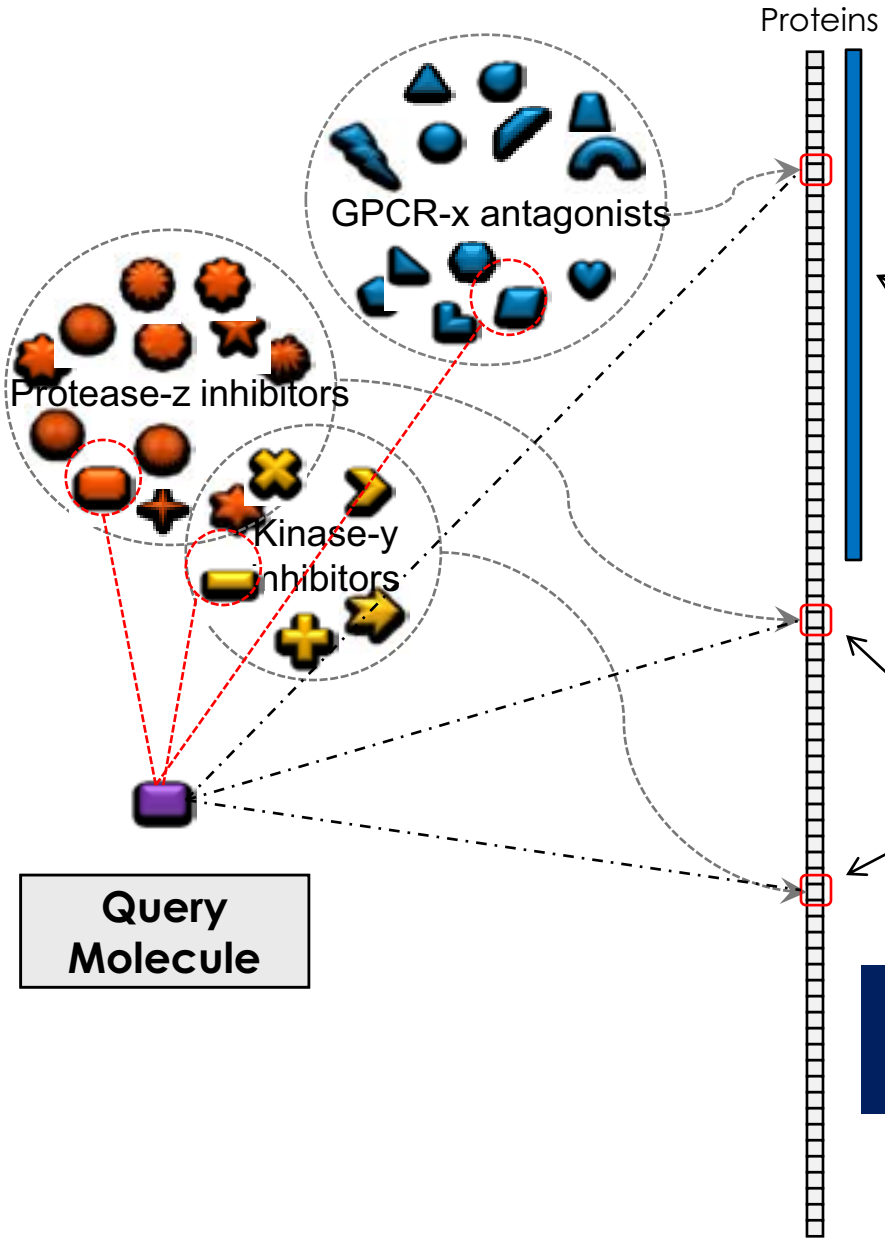
Predictive Secondary Pharmacology



- Vast number of ligand-protein interactions described in literature

Standard Target Panel

- Molecular structures & associated activity available and searchable in-silico

Additional screening targets

Inclusion of additional screening targets can lead to earlier risk assessment

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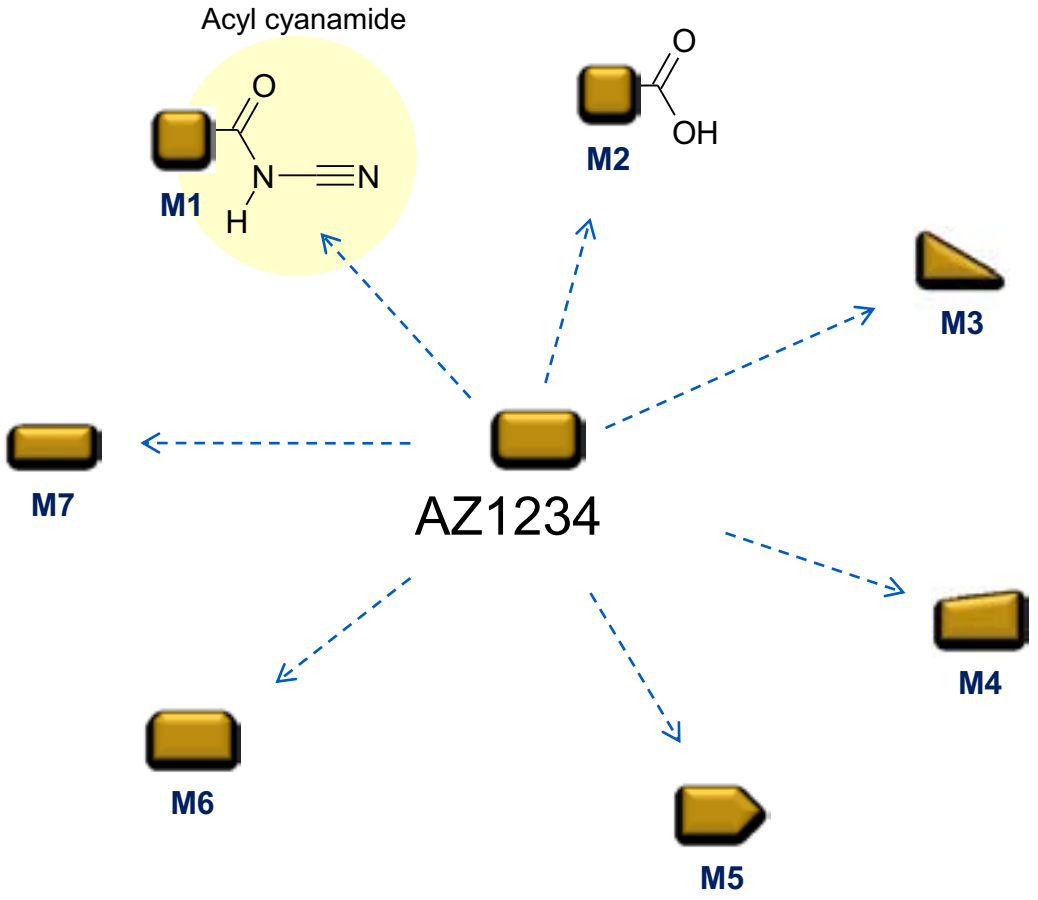
Use of PSP in problem solving

- AZ compound shown to cause cataracts in rats
- Circulating metabolites observed
- *Q. Could there be an association between metabolites and cataract formation?*

- Acylcyanamide substructure looks potentially reactive
  - Speculated protease inhibition?



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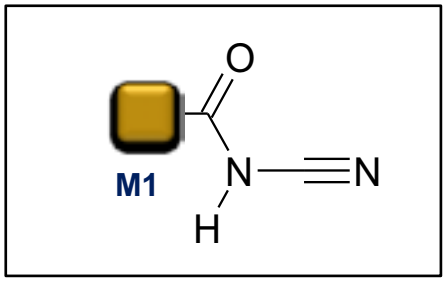
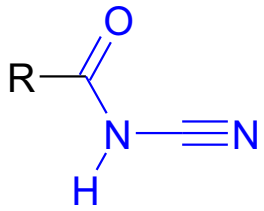
Use of PSP in problem solving



PSP search

- Conducted on acyl cyanamide substructure



Where R is any carbon containing group

Results (Selected examples)

WO 03/086325 A2
Cyanamides useful as reversible inhibitors of cysteine proteases
Cyanamide derivative as Cathepsin K, Cathepsin S, Cathepsin F, Cathepsin L and Cathepsin B inhibitor: Useful in the treatment of rheumatoid arthritis, multiple sclerosis, autoimmune diseases, osteoporosis, asthma, Alzheimer's disease, atherosclerosis and endometriosis

US 6878706 B1
Cyanamides useful as reversible inhibitors of cysteine proteases

US 20080267917 A1
N-functionalized amides as hepatitis c serine protease inhibitors

Conclusions

- Potential as cysteine and serine protease inhibitors highlighted
- All peptidomimetic inhibitors
- Structural & biological relevance uncertain

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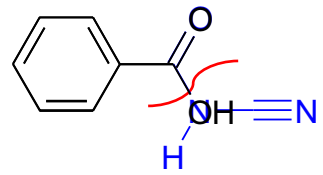
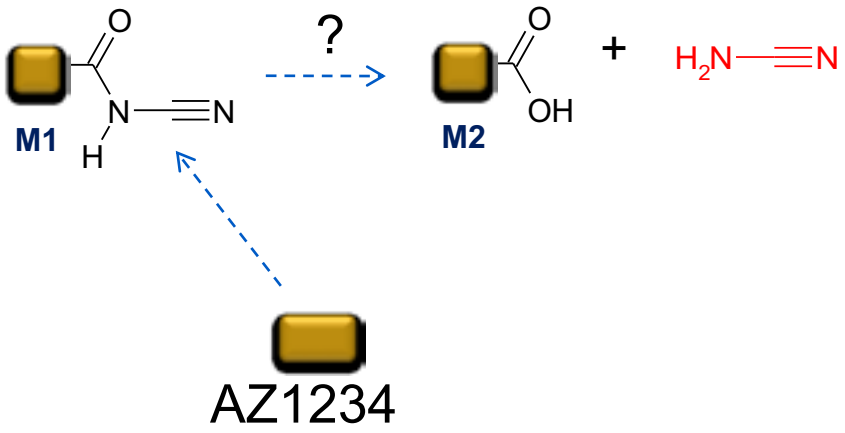
Use of PSP in problem solving

Results (cont'd)

J. Med. Chem. , 1986, 29 (10) 1922-1929
Acyl, n-protected alpha-aminoacyl, and peptidyl derivatives as prodrug forms of the alcohol deterrent agent cyanamide



benzoylcyanamide + cyanamide



- Benzoylcyanamide highlighted as closest analogue
- Benzoylcyanamide is a prodrug of cyanamide
- Cyanamide inhibits aldehyde dehydrogenase (ALDH) in-vivo in rats
  - Prodrug provides sustained activity compared with cyanamide (reduced acute effect)
- Cyanamide inhibition of ALDH implicated in formation of cataracts in rats lenses in-vitro
  - Journal of toxicology and environmental health. Part A (2009), 72(9), 577-84
- Formation of cyanamide consistent with AZ1234 metabolism

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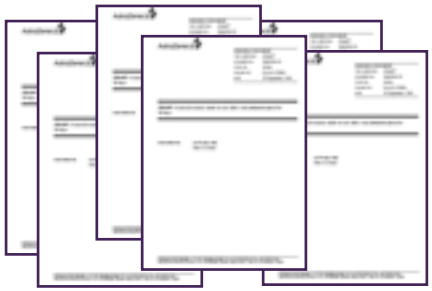
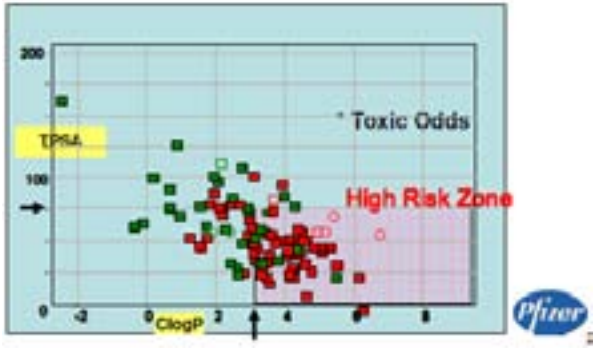
Availability of suitable data sets

- Limited in-vitro data sets of suitable size
- In-vivo safety data not organized for structure activity relationship determination



Reports

Structured data – observations aligned to exposure



Analysis

Data repurposing a significant but necessary challenge

Increasing desire for precompetitive data sharing

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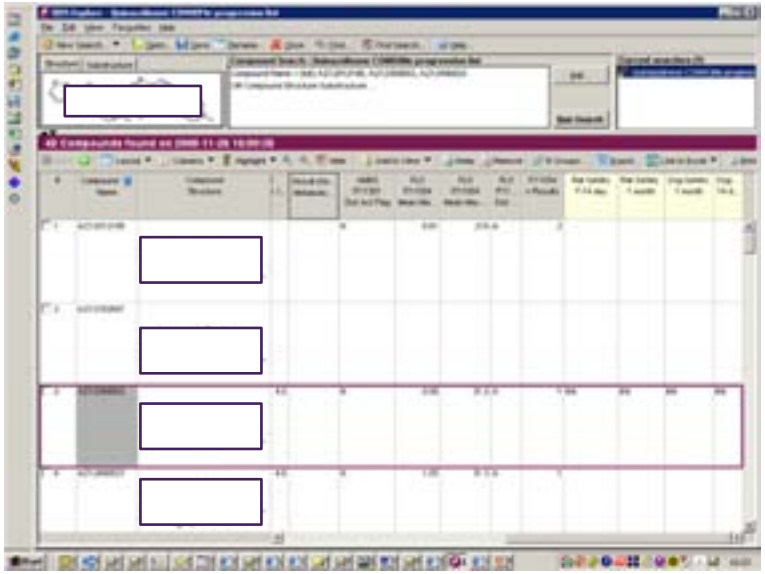
Availability of suitable data sets

- Biowisdom Collaboration



- Metadata from text mining available alongside biological & chemistry data
- Some challenging questions now readily searchable...
  - *Example*. Find compounds that have activity X that have a 1 month rat study

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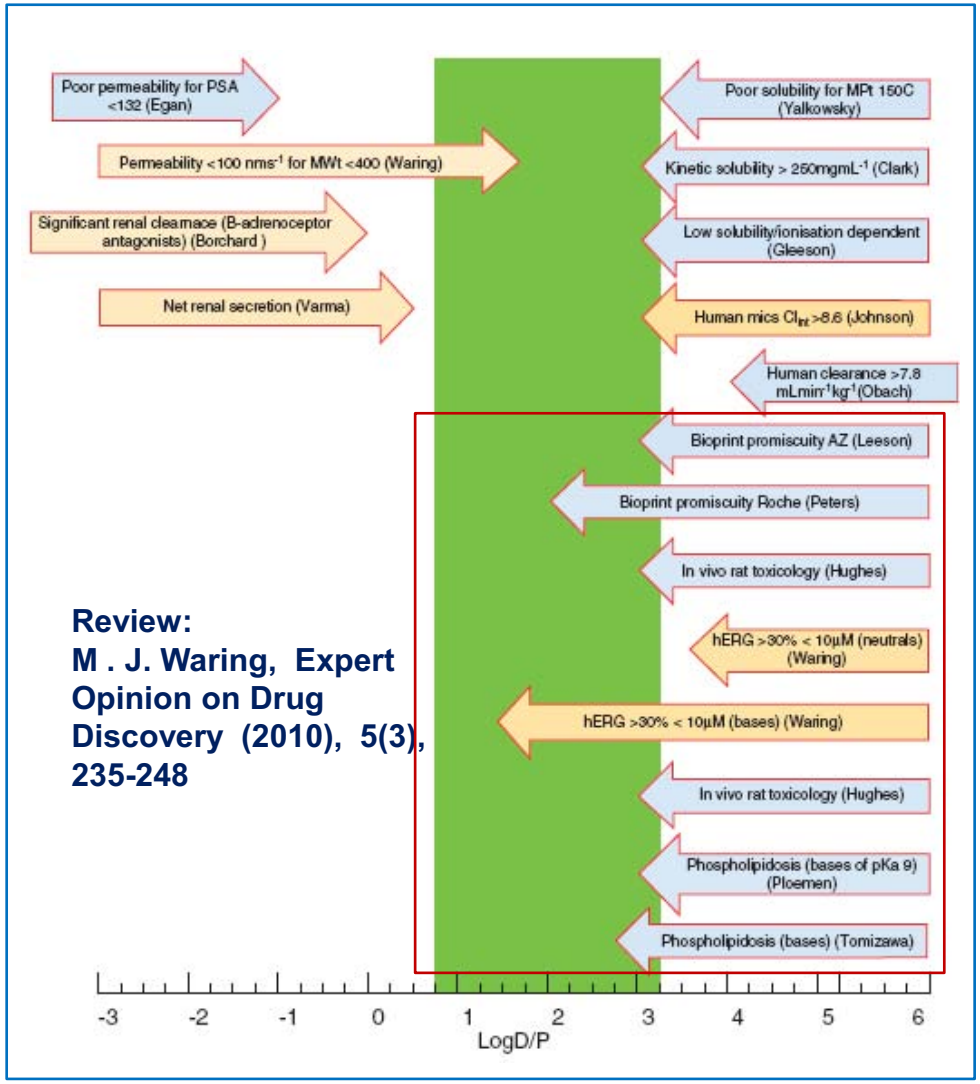
Physicochemical Properties and toxicity

- High lipophilicity associated with higher probability of poor outcomes against various relevant endpoints
- Pfizer ‘rule of 3/75’ based on in-vivo outcomes *Bioorg. Medchem. Lett*. **2008**, *18*, 4872
- Recent focus on minimizing lipophilicity contribution to potency in LG and LO



Review:
M . J. Waring, Expert Opinion on Drug Discovery (2010), 5(3), 235-248

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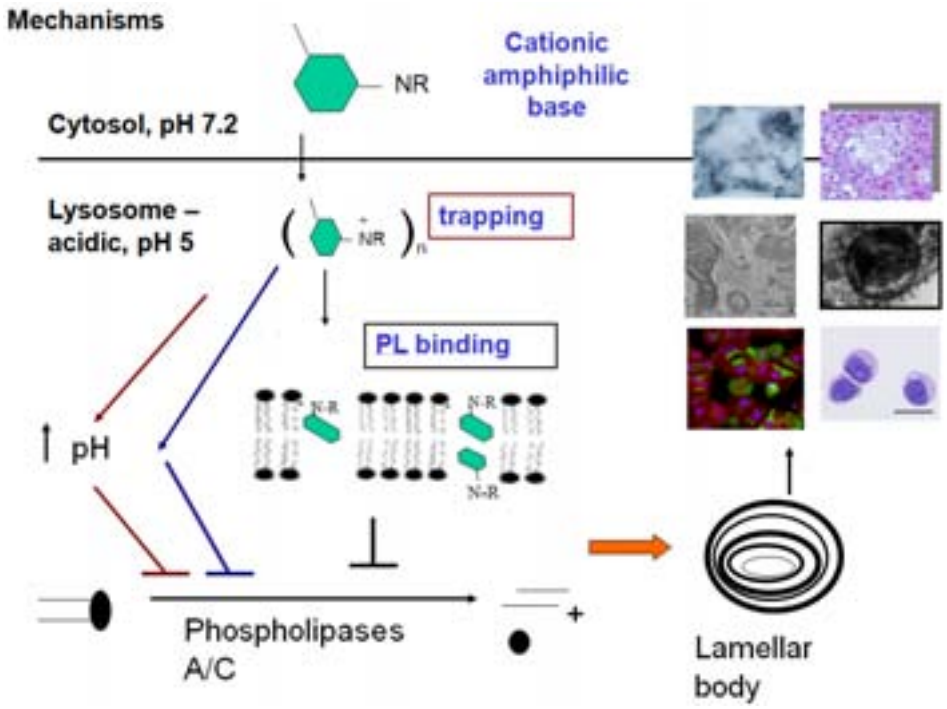
Phospholipidosis

- Generally considered an adaptive response
  - Some compounds display adverse effects pre-clinically & in humans



Predictive in-silico models and assays available

Are phospholipogenic compounds associated with more toxicities than non-phospholipogenic compounds?

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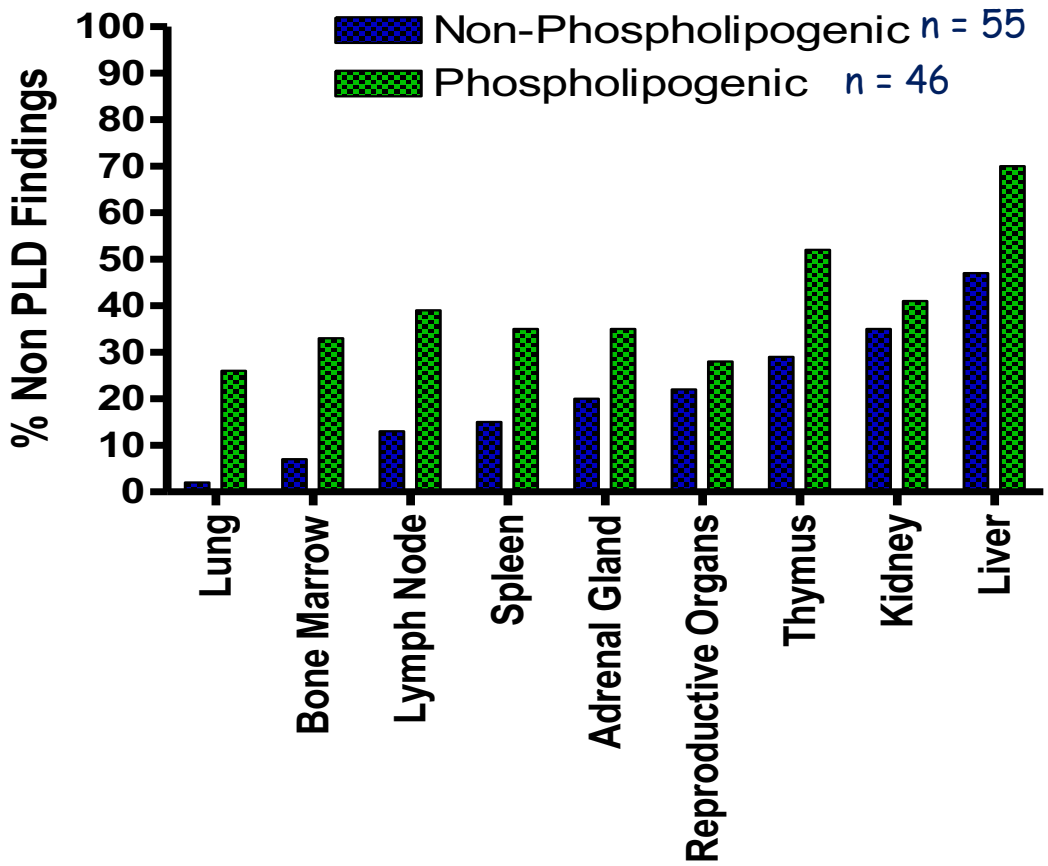
Phospholipidosis

- Study Report text mining



Note: Exposures greater in non-phosphilipogenic set

Phospholipogenic compounds show more non-PLD related findings in all organs despite lower exposure

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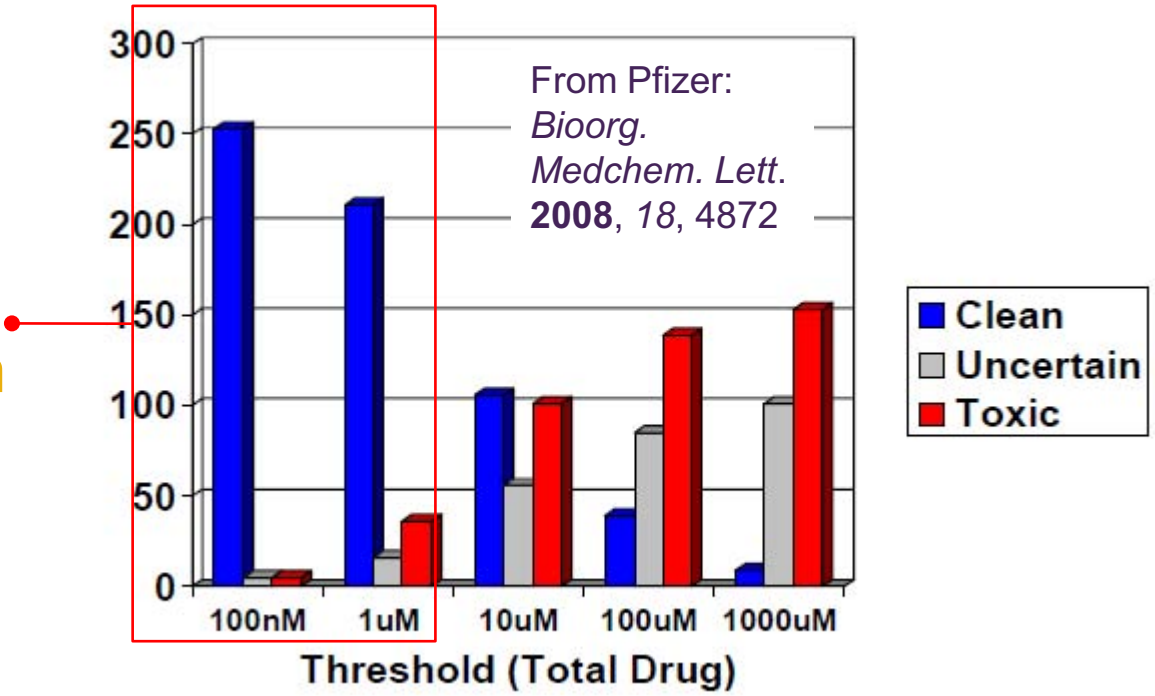
Importance of Dose and Exposure

'*All things are poison, and nothing is without poison; only the dose permits something not to be poisonous*' - Paracelsus – 1493-1541

- Exquisite potency and PK to work in this area
- Greater exploitation of biochemical efficiency?
  - Kinetics and PD



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The importance of binding kinetics and residence time

- A review of biochemical mechanisms of FDA approved NMEs 2001-2004 highlights
  - 80% utilize secondary mechanisms in addition to initial mass action binding
  - Slow dissociation & irreversible 25%
  - For reviews see
  - *Curr. Opin. Drug Disc. & Dev.* **2009**, *12*, 31
  - *Curr. Opin. Drug Disc. & Dev.* **2009**, *12*, 488

Table 2. Drugs with slow or irreversible dissociation rates.

Drug	Target	Dissociation ($t_{1/2}$)
Candesartan	Angiotensin II receptor 1	11.5 h
Tiotropium	Muscarinic m3 receptor	34.7 h
Desloratadine	Histamine H1 receptor	> 6 h
Maraviroc	CCR5	10.5 h
Lapatinib	EGF receptor	300 min
Buprenorphine	μ-opioid receptor	166 min
Olmesartan	Angiotensin II receptor 1	72 min
Amlodipine	L-type calcium channel	77 min
Aprepitant	Neurokinin 1 receptor	154 min
Oseltamivir	Viral neuraminidase	33-60 min
Darunavir	HIV-1 protease	> 240 h
Aspirin	Cyclooxygenase	Irreversible
Omeprazole	H^+K^+ ATPase	Irreversible
Lansoprazole	H^+K^+ ATPase	Irreversible
Clavulanate	β-lactamase	Irreversible
Sulbactam	β-lactamase	Irreversible
Tazobactam	β-lactamase	Irreversible
Selegiline	Monoamine oxidase	Irreversible
Tranylcypromine	Monoamine oxidase	Irreversible
Celecoxib	Cyclooxygenase 2	Irreversible
Finasteride	Steroid 5α-reductase	Mechanism-based
Formestane	Aromatase	Mechanism-based
Procarbazine	Guanine alkyltransferase	Irreversible
Orlistat	Pancreatic lipase	Irreversible
Vigabatrin	GABA transaminase	Irreversible

Data from Tummino and Copeland 2008 Table 2 [5] , Swinney 2008 Table II [7] and Swinney 2004 Table 1 [8].

Potential to minimize exposure through extended PD

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Summary

- Significant investment in Discovery Toxicology needed to improve safety related attrition rate
- Repurposing of data a significant but necessary challenge
- Precompetitive sharing of data sets should offer significant value in some areas
- In silico approaches are showing value in improving compound design & safety hazard identification
- Physicochemical property control important – mechanistic understanding is limited
- Earlier understanding of biochemical mechanisms and kinetics may offer pharmacodynamic opportunities

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Acknowledgements

- PLATO & PSP
  - Scott Boyer
  - Tobias Noeske
  - Ola Engvist
  - Mike Rolf
  - Catrin Hasselgren
- PLD
  - Paul Ciaccio
  - Jim Damewood
  - Linda Barone
  - James Fikes
- WizePairZ & Application
  - Dan Warner
  - Ed Griffen
  - Stephen St Gallay
- Data Repurposing
  - Biowisdom
  - Sherri Mattis
  - Dave Cook
- IDEAL
  - Andrew Poirrette
  - John Cumming

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Extras

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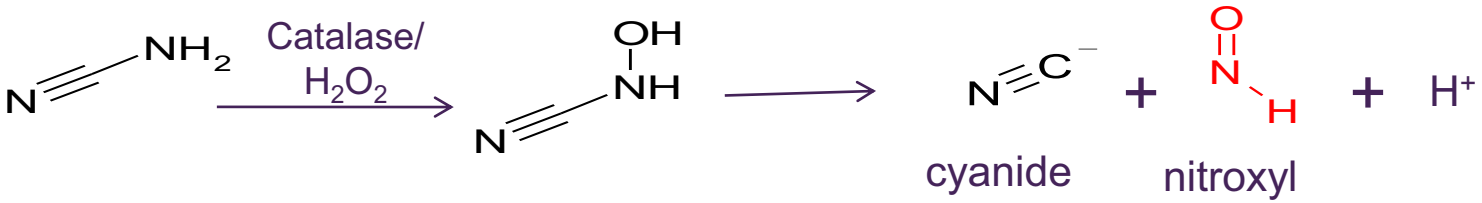
Use of PSP in problem solving

- Mechanism of cyanamide inhibition?

Chem. Res. Toxicol. 2005, 18, 790

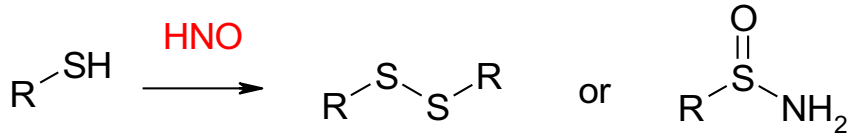
Nitroxyl generated from cyanamide



Molecular and cellular proteomics, 2009, 85, 887

Nitroxyl implicated in protein modification via cysteine

Disulfide or sulfinamide formation



Response likely dependent on cellular location scavenging mechanisms etc

Credible hypothesis generated, new structural alert?

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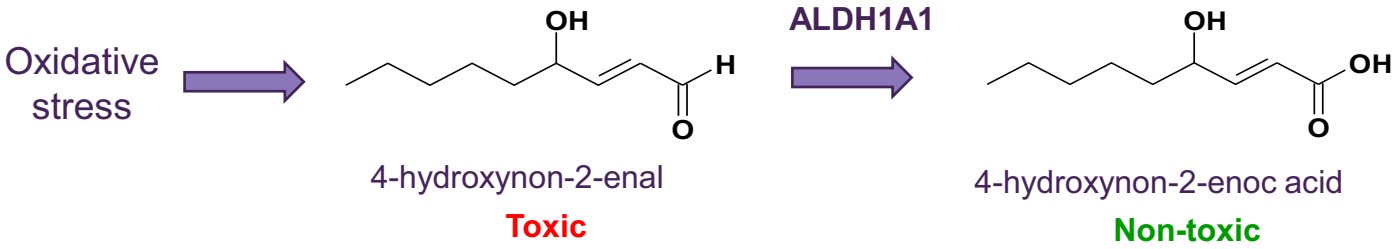
Use of PSP in problem solving

- Cyanamide inhibition of ALDH has been implicated in cataract formation in rats in-vitro

Journal of toxicology and environmental health. Part A (2009), 72(9), 577-84



- Toxic lipid derived aldehydes formed by oxidative stress
- 4-hydroxynon-2-enal (HNE) formation leads to lens damage
- Detoxified by ALDH1A1
- Inhibition of ALDH1A1 leads to increased toxicity

Credible hypothesis generated, new structural alert?

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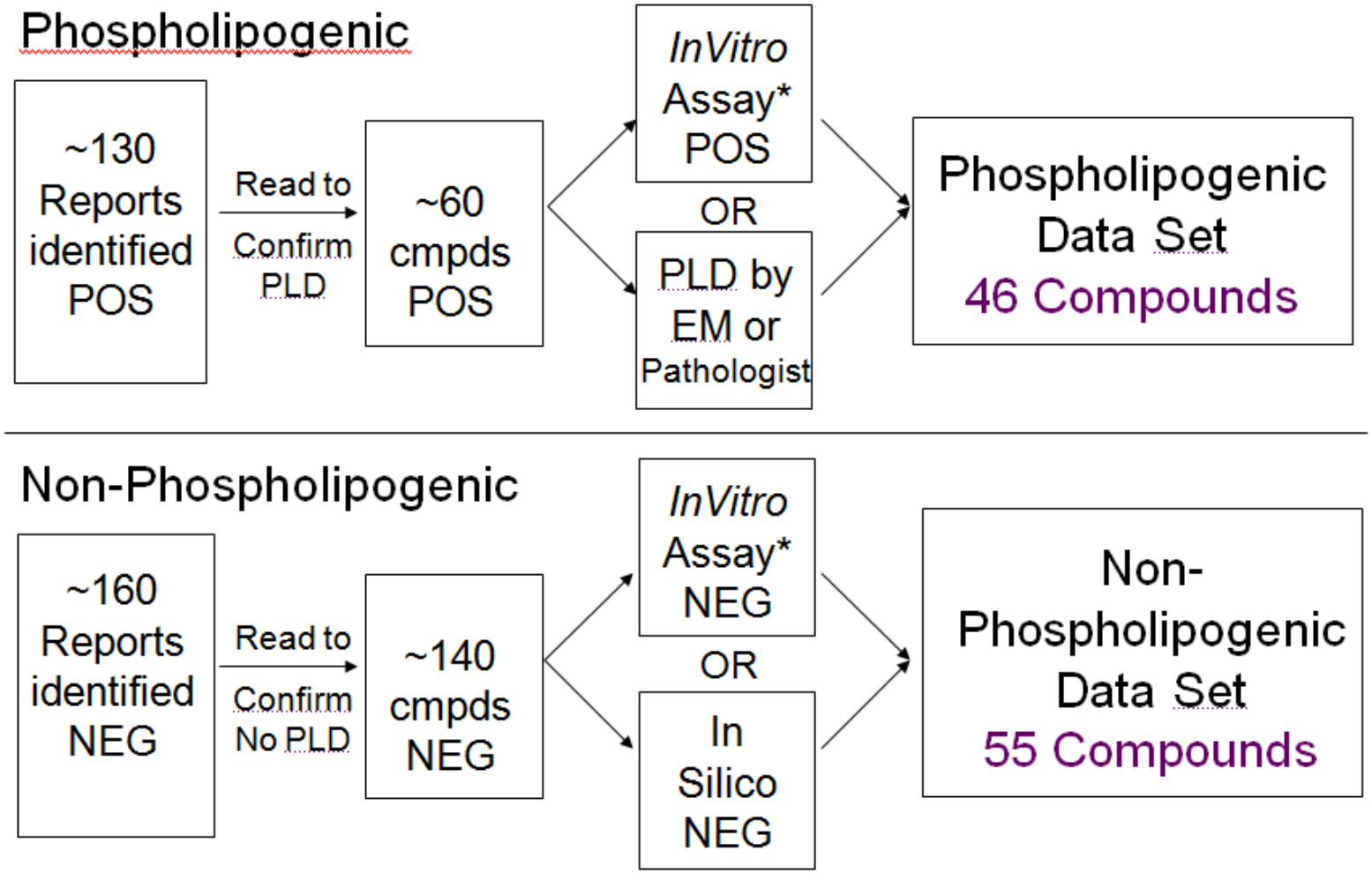
Phospholipidosis

- Study Report text mining



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