



Medicinal Chemists: how can we reduce attrition?

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A Breakdown of Industry Attrition

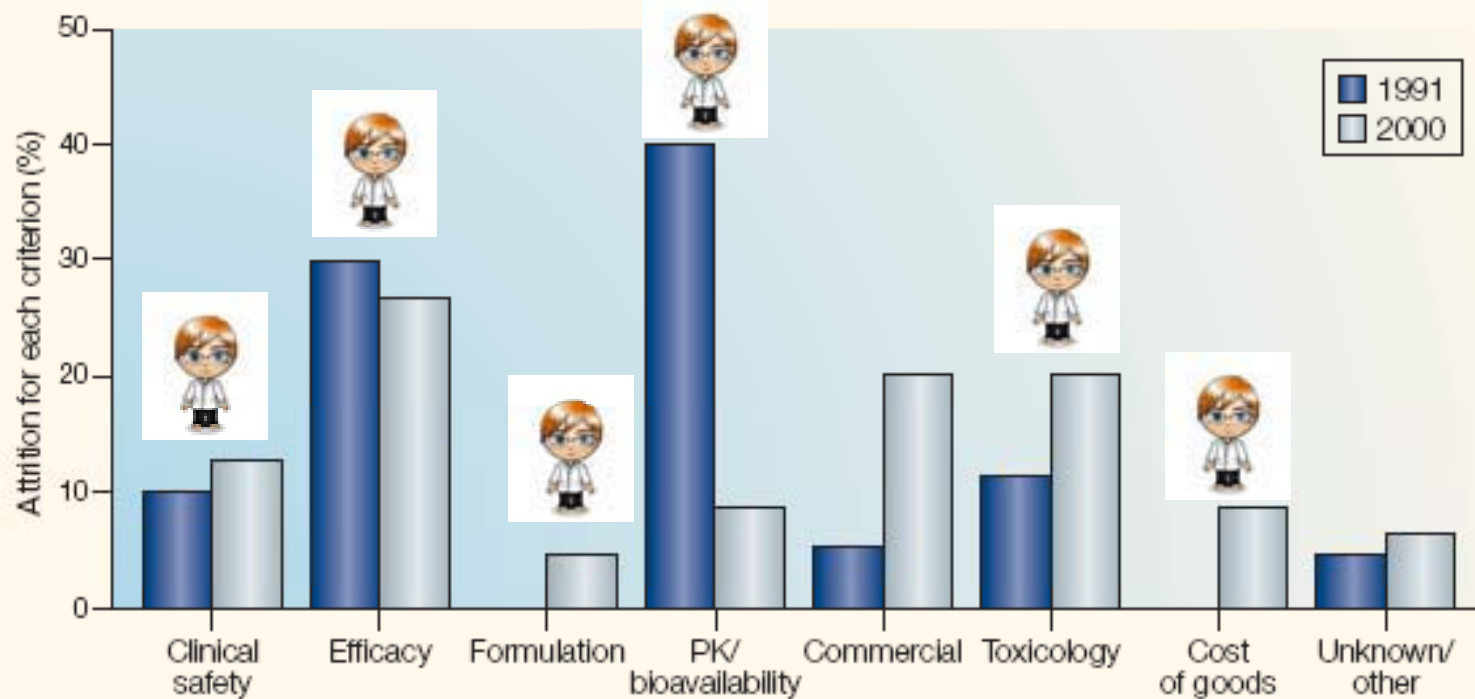


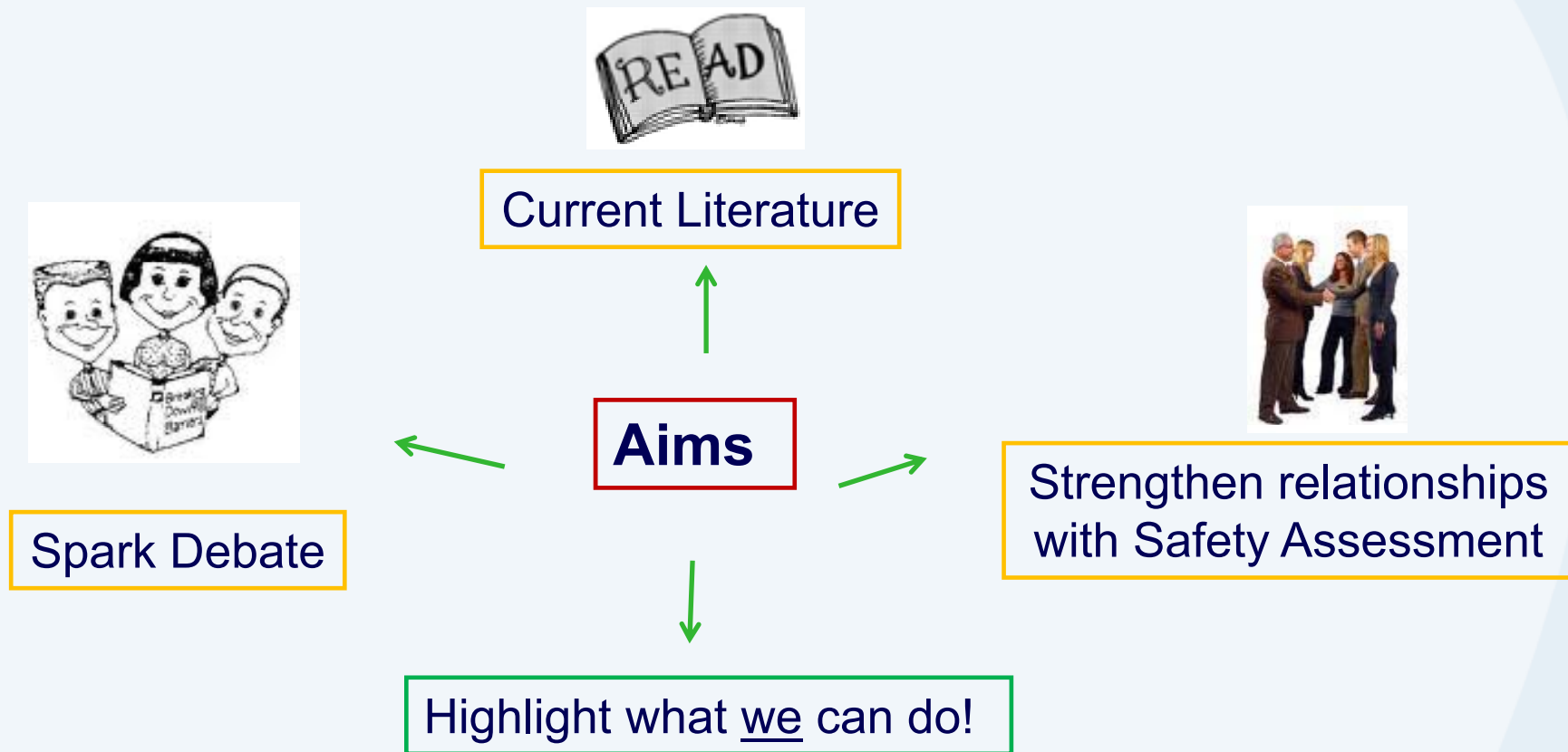
Figure 3 | Reasons for attrition (1991–2000).

Kola and Landis, Nature Rev Drug Disc, 3, 713 (2004)

- Where can Medicinal Chemists help?

A 'Local' Response

- May 2009 Simon Macdonald (department head), instigated this initiative and provided a simple remit, then left us to devise a means:



Departmental workshops – *but with a difference!*

- An experiment run with a small group of Medicinal Chemists within the Respiratory CEDD at GSK, Stevenage.



- Their objective: fresh evaluation of key ideas from the attrition literature and honest reflection on own compounds and culture.
- Main purpose was to define how we should improve ‘ourselves’

The Format of the Workshops

- 4 Interactive half day workshops involving 16-18 Chemists.
- Content defined by three lab based scientists;
 - To be fun, informal, pragmatic and inclusive.
- Rules:
 - Everyone expected to attend.
 - Everyone does the pre-reading and contributes.
- Regular break out sessions in groups of 3-5 from a cross-section of grades.
- Regular breaks + interactive quizzes with food/drink/prizes
 - which facilitated informal discussions.



Overview

- **Workshop 1: Drug-likeness**



- Review the literature
- Honest reflection on our programmes

- **Workshop 2: Toxicology and Predictive Tools**



- Invited speakers from toxicology groups, short presentations and discussions
- Drug or Fug

- **Workshop 3: Physical Properties and Controlling Exposure**



- The importance of physical properties
- Controlling exposure/dose

- **Workshop 4 : Bringing all the information together, future plans**

Workshop 1 : Drug-likeness

● Literature review

- In groups, discussed and summarised selected papers, identifying the main messages.*

● Ideal properties for a candidate molecule

- Voted on what **we** think the ideal properties are?
e.g. revealed variation in opinions for PSA
- What are the barriers which stop us achieving these?
- Truly interactive debate everyone contributed!

● Reviewed our own programme metrics

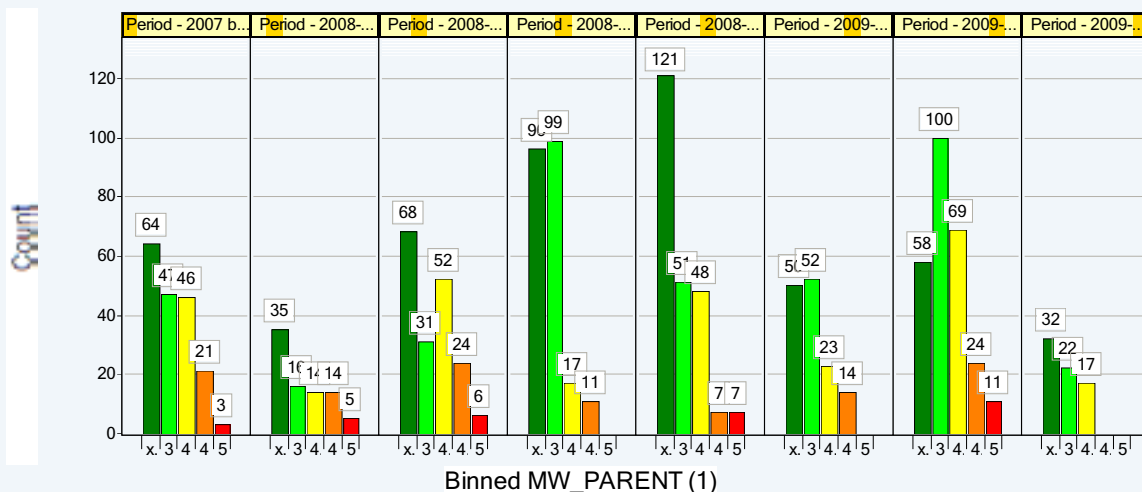
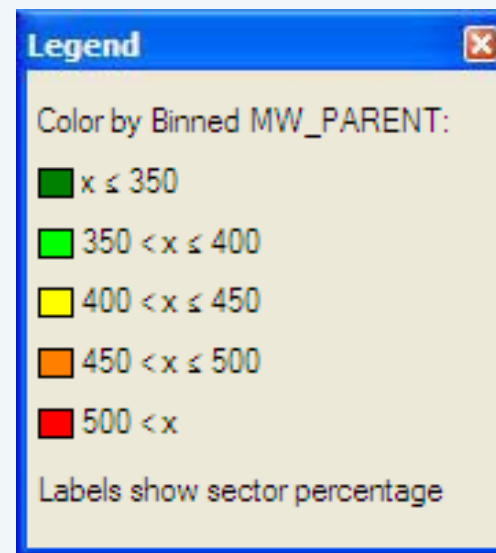
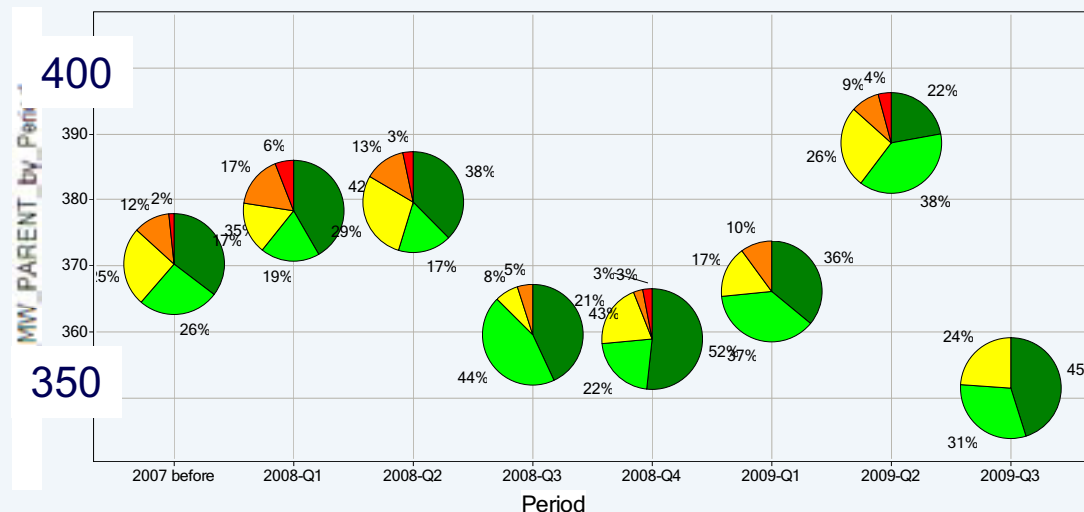
- Honest reflection on our current programmes



* Leeson, P. D.; Springthorpe, B. *Nature Reviews Drug Discovery*, **2007**, 6, 881-890
Keserü, G. M.; Makara, G. M. *Nature Reviews Drug Discovery*, **2009**, 8, 203-212

Programme Metrics

- Data was *Independently* generated on each of our departmental programmes
 - MWt, clogP, CHI log D and LE vs time.



- Non-defensive reflection on data in teams and discussion around current chemistry.

Workshop 2 : Toxicology

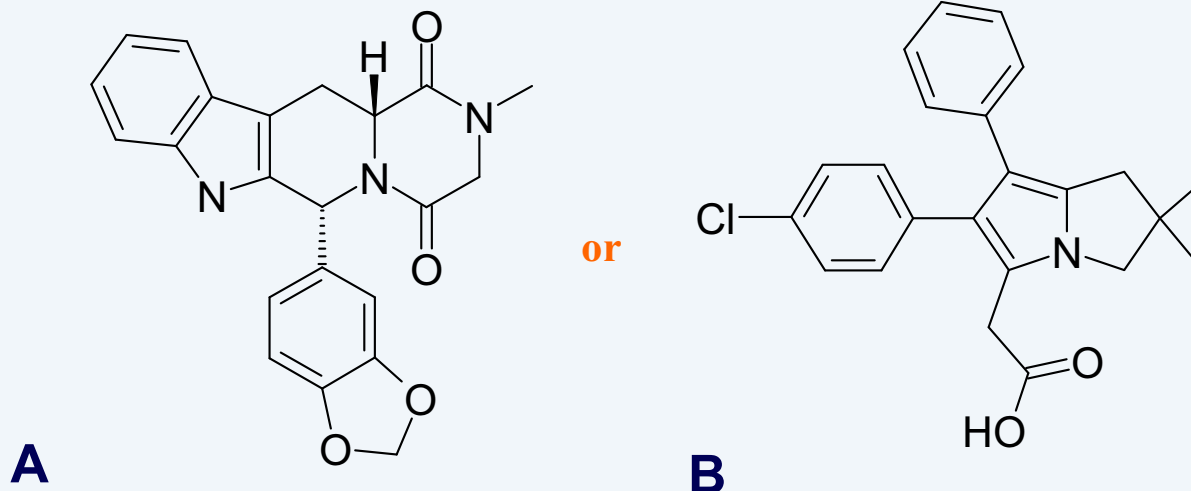
- **Asked Safety Assessment colleagues to run this workshop and suggest pre-reading.***

How can we improve our predictions?



- **8 Safety Assessment colleagues attended, topics covered;**
 - Genetic toxicology
 - hERG / cardiotox & *in silico* modelling
 - Hepatotox / cell health
 - Phospholipidosis
 - *In silico* prediction models
- **Forwarded specific questions from Chemists beforehand: discussed in detail within the workshop.**
- **Drug or Fug Quiz**

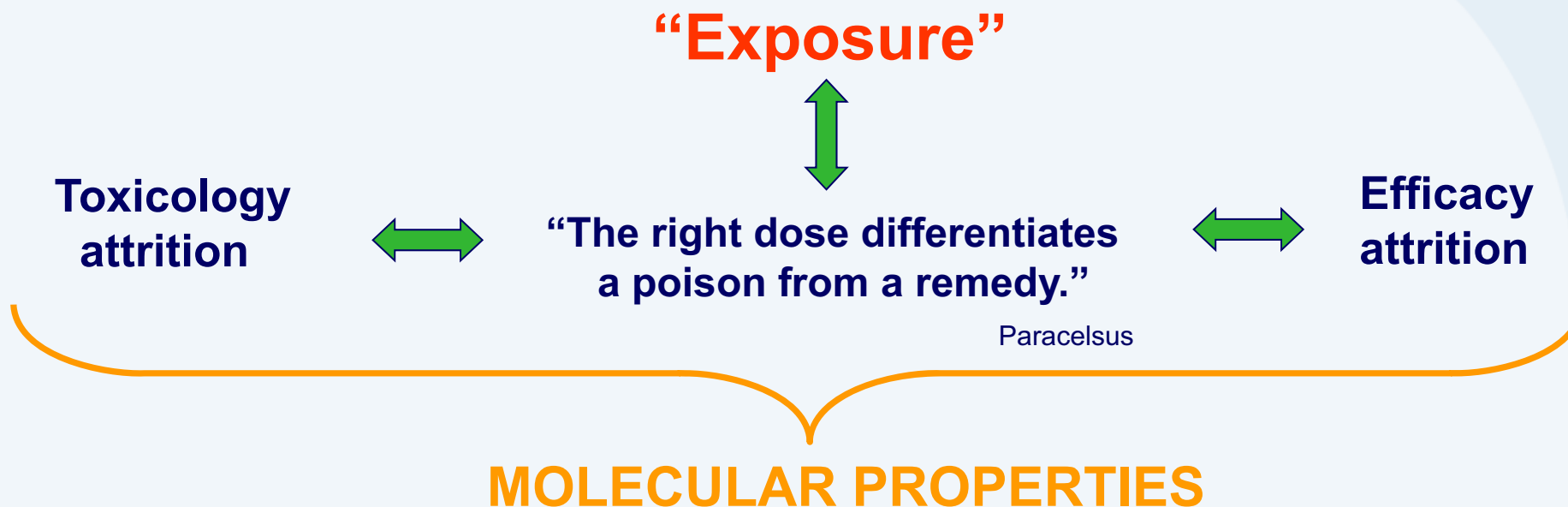
Can you tell a Drug or a Fug?



- Which is the drug and which is the Phase 3 'failure' (Fug)?
- Voted alongside our SA colleagues on a range of structures
 - very varied opinions, highlighting some "secret rules of drug-likeness"!
- Sparked some deep debate.
 - Should we be far more imaginative in our structural motifs /chemistry?
 - Can we reliably predict likelihood of tox. from structure?

Workshop 3 : Physical Properties

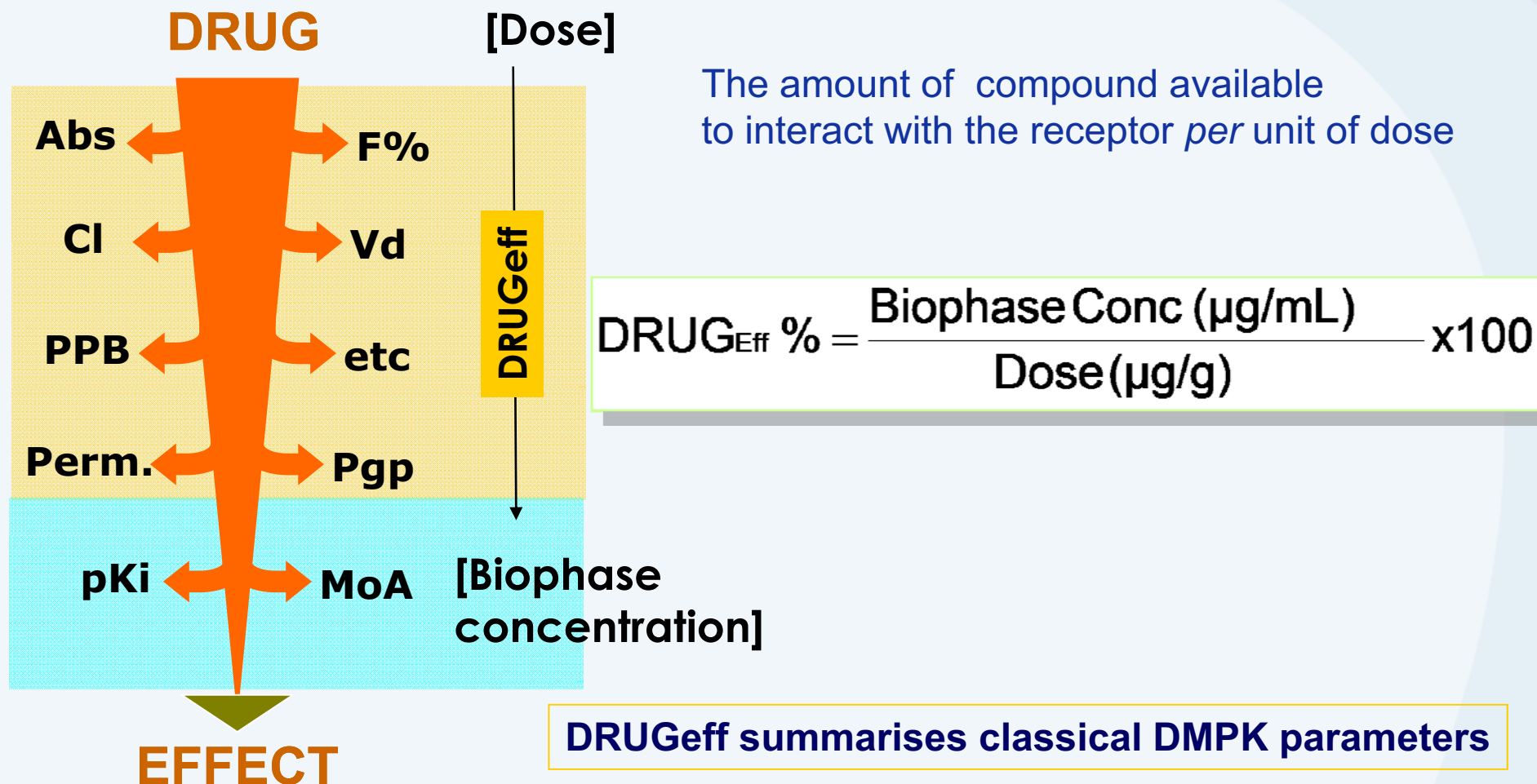
- Impact of physical properties on molecular properties



- Quizzes; how good are we at estimating properties from structures?

Strategies for improving PPB, permeability, DMPK, solubility, etc.

Drug Efficiency



Braggio, S.; Montanari, D.; Rossi, T.; Ratti, E.; *Expert Opin. Drug Discovery*, **2010**, 7, 609-618
 D. Montanari, E. Chiarparin, R. Longhi, K. Valko, M. P. Gleeson, T. Rossi and S. Braggio,
 submitted to *Drug Discovery Today*, **2011**

Workshop 4 – Pulling it all together

- Defined individual and programme team learnings and actions.



- Example Actions;

- Phys. Chem. properties are calculated and stored centrally.
- Discipline to submit compounds to answer specific questions as sets.
- Use whole blood potency as an efficiency measure.
- The highest quality targets are synthesised.
- Maintain direct contact with Safety Assessment colleagues

Outcomes So Far.....

- Department communicates better.
- More focus on physical chemical properties.
- Regular discussion of attrition and what we can do!
- Top selling drugs always on display and debated.
- Much improved links with Safety Assessment.



Outputs include:

- “A Summary of Selected Working Hypotheses for Medicinal Chemists from the Literature” (DDT In Press.)
- “A Chemist’s Guide to Safety Assessment Assays”

Link to Njardarson top 200 drugs poster

<http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster>

Evolution of the Workshops



- All UK Chemists in the Respiratory CEDD have now attended attrition workshops.
- A second set ran to discuss how we should develop our Medicinal and Synthetic Chemistry skills.
- This workshop format has been used to share information from our Inhaled Sciences Group, with a broad range of scientists.

Profound Thanks and Recognition

Graham Inglis

Charlotte Mitchell

Simon Macdonald

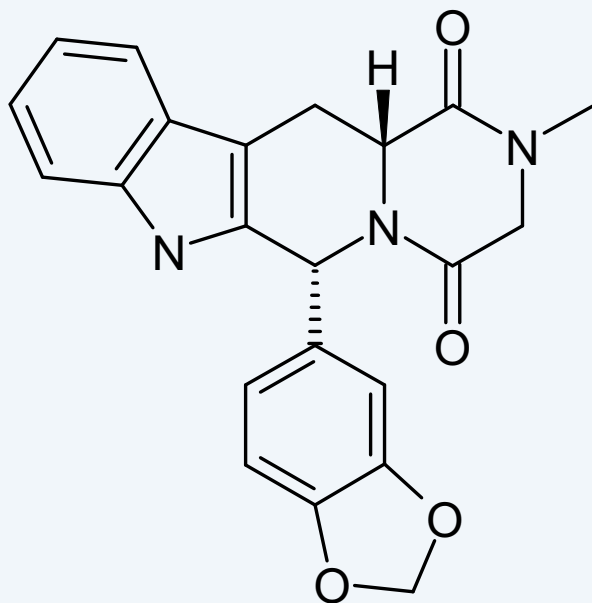
Safety Assessment colleagues:

- Colin Fish
- Maria Beaumont
- Paul Hastwell
- Jim Harvey
- Bronagh Heath
- Julie Holder
- Andy Nicholls
- Chris Luscombe (Computational and Structural Chemistry)

and most importantly of all.....the participants

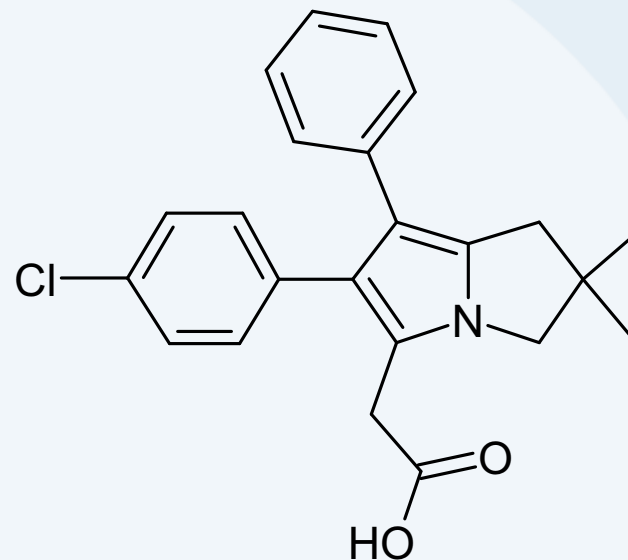
Back-ups

Drug or Fug



Tadalafil (Cialis)- DRUG

mw 389
clogP 2.6
psa 74.9
CMR 10.6



Licofelone - FUG

mw 379
clogP 5.6
psa 42.2
CMR 10.9