Medicinal Chemists: how can we reduce attrition?

Juliet Simpson, Charlotte Mitchell, Graham Inglis
A Breakdown of Industry Attrition

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:

Current Literature

Aims

Spark Debate

Strengthen relationships with Safety Assessment

Highlight what we can do!
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

• 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.
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 / cardiotoxic & in silico modelling
- Hepatotox / cell health
- Phospholipidosis
- \textit{In silico} prediction models

Forwarded specific questions from Chemists beforehand: discussed in detail within the workshop.

Drug or Fug Quiz

Greene, N.; Naven, R. Curr. Opin. Drug Discovery & Dev., 2009, 12, 90-97
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

"Exposure"

Toxicology attrition

"The right dose differentiates a poison from a remedy."

Paracelsus

Efficacy attrition

MOLECULAR PROPERTIES

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

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


Drug Efficiency

The amount of compound available to interact with the receptor per unit of dose

\[
\text{DRUGeff} \% = \frac{\text{Biophase Concentration (}\mu\text{g/mL})}{\text{Dose (}\mu\text{g/g})} \times 100
\]

DRUGeff summarises classical DMPK parameters

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
Tadalafil (Cialis) - DRUG
mw  389
clgP  2.6
psa  74.9
CMR  10.6

Licofelone - FUG
mw  379
clogP  5.6
psa  42.2
CMR  10.9