Key Considerations in Compound Collection Composition and Quality Seeding Success in Hit Follow Up

Kristian Birchall
Centre for Therapeutics Discovery, Stevenage

- Deliver potential therapeutics in areas of unmet medical need

**Academic Research**
- Novel Potential Targets

**De-Risking**
- Selective, Potent Lead Compounds or Antibodies

**Industry Partners**
- Clinical Candidates

- Chemistry, Biology and Biotherapeutics groups
- >100K Compound Collection

**Diversity Sets**
- Pre-2010 42K
- 2010 29K
- 2016 34K

**Target-Focussed Sets**
- Ion Channel 5K
- Kinase 9K
- PPI 14K

**Other Collections**
- Nat Prods 3K
- Known Drugs 1K
- Fragments 2K
The Perception of Quality

- Quality ≈ progressability
  - Many factors affect the prospects of a hit
    - Stability, solubility, toxicity, synthetic tractability

- Improving over time
  - Rule of 5 -> PFI, QED
  - Reactive groups -> PAINS

...chemists can spot the uglies

- Beauty is in the eye of the beholder...
  Exceptions will always occur – usually for good reason – such things do not have a place in a generic HTS collection
Diversity Set 2016 - Introduction

- 42K compounds dating back to 2006 expiring
  - Stocks run low, samples may degrade over time
  - Quality lower compared to recently available compounds

- Aim to purchase a similar number to replace these
  - Must be high quality, diverse and complementary to remainder of MRCT collection

- Emphasis on **quality**
  - Limit resource wasted on false positives and *non-progressable* compounds from HTS
  - Computational methods required (chemical space is vast) but use with care – can’t remove all junk, and can actually add some!

*Have every compound independently approved by two Chemists*
Diversity Set 2016 - Overall Workflow

Gather Commercial Compounds

Remove Similar to Remaining MRCT Collection

Remove Property Extrema

Check Purchase Feasibility

Standardise and Merge

Refined Substructure and Property Filters

Initial Substructure Flag Filtering

Cluster and Selection for Chemist Triage

Triage and Purchase

Numbers:
- 10M
- 6.4M
- 6.0M
- 2.2M
- 1.8M
- 1.2M
- 275K
Clustering and Selection for Triage

From remaining 1.2M select most attractive and diverse representatives and present these to facilitate manual triage

- i.e. manageable numbers of chemically meaningful groups

Clustering

- Must strike right balance between *density* and *diversity*
  - How to cluster and select representatives?

- 4-12 representatives per cluster is desirable
  - Scaffolds typically have up to 3 points of variation with 2-4 fundamentally different types of group at each position
  - More encouraging to follow up, less prone to missing patches of activity

Compounds in Chemical Space
Clustering and Selection for Triage

- **Clustering method**
  - Fingerprint-based approaches are fast, but error prone...
  - Maximum common substructure (MCS) approaches are much more intuitive, but far too slow...
  - Solution is to perform rough fingerprint-based clustering first, then more sophisticated MCS procedure to ensure meaningful clusters
    - 30K cpds removed at fingerprint stage since in clusters sized <4
    - 16K clusters rejected at MCS stage for failing to contain a significant common substructure

- **Selection of cluster representatives**
  - Based on pharmacophore feature counts
    - Keep the smallest, most attractive example for each combination of features
  - Up to 12 representatives selected per cluster
    - 11K clusters rejected since their limited pharmacophoric diversity meant that fewer than 4 representatives could be selected
Chemists Triage

- 275K molecules contained in 39K clusters sized 4-12 available for triage by Chemists
- Web-based tool developed to allow simple rapid triage
  - Clusters of compounds presented in grids aligned by their MCS
  - 100 clusters per subset, allocated randomly to each chemist
  - Single click to reject individual molecules or entire clusters
  - *Each cpd viewed by 2 chemists – keeping only those passed by both*
- Clear objectives set out
  - Give your own opinion bearing in mind we are looking for *hits*, not *drugs*, we want to *avoid non-progressable compounds* – minor liabilities can be tolerated – *multiple/inescapable liabilities should be avoided*
    - “Is the compound worthy of a chance to be a screening hit – one that you would be willing to work on”
1) Click link in email  
2) Choose subset  
3) Triage by clicking

Pilot study carried out - 3 chemists triaging 6 subsets each

- Agreed pass verdict 70% (stdev 7%)
- ~30 min per subset
Chemist Triage Result Summary

- 14 chemists volunteered, study ran for 3 weeks – most completed in 2
- Each processed 13 subsets of 100 clusters (4-12 per cluster)
- 140,792 examined
  - 70,396 unique molecules with 2 votes on each to give verdict
- 43,705 pass verdict (62% cf. 70% pilot)
  - 5,506 fail verdict (7.8% cf. 7.3% pilot)
  - 21,185 mixed verdict (30% cf. 22% pilot)

Green-Red is high-low agreement with other user
How do the Different Suppliers Fare

Not all suppliers are equal
Not all libraries are equal

<table>
<thead>
<tr>
<th>supplier</th>
<th>library</th>
<th>initial size</th>
<th>post-filters</th>
<th>passed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>489,936</td>
<td>90,987</td>
<td>19%</td>
</tr>
<tr>
<td>A</td>
<td>2</td>
<td>506,216</td>
<td>314,442</td>
<td>62%</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>1,214,156</td>
<td>162,639</td>
<td>13%</td>
</tr>
</tbody>
</table>

Triage pass rates tell a similar story – computational filtering evened things up, removing most but not all junk!

Example prices if buying 5K in same format
Supplier A Lib 1 $3.90
Supplier A Lib 2 $8.40
Supplier B Lib 3 $6.00
...You get what you pay for
Effect on Property Distributions - FAIL
Effect on Property Distributions - **PASS**

- Higher QED
- More lead-like
- Less greasy

Higher QED

More lead-like

Less greasy

More shape
Effect on Cluster Size Distribution

- **Initial molecules** vs. **Post-triage molecules**
- **70% in clusters of 3-9 molecules**
- **Good to have more compounds in larger clusters initially**

Desirable distribution achieved post triage – far fewer large clusters, but very few singletons
Other Density/Diversity Checks

Near Neighbour Distributions

- No trivial analogues
- 40% have at least 5 reasonable analogues
- <10% have up to 10 related
- Nothing with too many analogues

Murcko scaffold

<table>
<thead>
<tr>
<th>diversity set</th>
<th>molecules</th>
<th>scaffolds</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>33,600</td>
<td>28,103</td>
</tr>
<tr>
<td>pre-2010</td>
<td>41,667</td>
<td>15,041</td>
</tr>
</tbody>
</table>

20% fewer molecules but 90% more scaffolds
Achievements and Lessons Learned

- Upfront medicinal chemist triage is feasible, worthwhile and insightful
  - Good verbal feedback
    - Simple format, about the right length
  - Purchased those with better chance of progression
    - Avoided 7% with two independent rejections and a further 30% with dubious quality
  - Top reasons for rejection
    - Combination, location and frequency of structural features
    - Too complex/simple/unbalanced
    - Nicer alternatives available
Pre-Computation to Ease Hitlist Follow Up

What’s active, what’s inactive and what else didn’t we buy
Target Focused Sets - Using Experimental Data to Guide Compound Selection and Aid Follow Up
MRCT Kinase Focused Set Composition

- Commercial template subset
  - Structure and ligand-based pharmacophores identify scaffolds likely to bind at hinge, providing higher hit rates*

- Annotated subsets
  - Known kinase inhibitors – both published and from MRCT projects
    - Many kinases are similar – ‘off-target’ activities recorded during selectivity profiling can provide starting points for future kinase projects
    - Pro-active profiling to get head-start hits – continuing development
  - Crystal ligands (>2K in PDB)
    - Confident binding mode prediction is key to successful follow up - know which direction to expand and what sorts of groups to go for, even if don’t intend to pursue the crystal series can attempt crossover
    - Docking and homology modelling reliability is improved when using crystals where the ligand shares similarity to your ligand of interest** - due to induced fit effects

* Harris 2011 14 (6) 521-531
** Tuccinardi 2010 50 (8) 1432-41
Other Experiences in Using Focused Sets

Commercial Ion Channel Focused Sets

- Often built by taking known ion channel inhibitors and using similarity/pharmacophore methods to identify which other of their compounds are ion-channel-inhibitor-like
- Care required to avoid off-target liabilities such as hERG
  - Some compounds on offer are very similar to those with known hERG inhibition!

- Predictive ability limited by availability of data
  - For novel chemotypes where data does not exist, why not get some data upfront...
Using Experimental Data to Guide Selection

- Sample compounds from commercial ion channel library to check for hERG inhibition
  - ~20K filtered to ~8K based on properties etc.
    - Selected 300 representing 89 clusters
  - 24/300 (8%) had at least 50% inhibition at 10uM

Adding charge and aromatic causes hERG inhibition

- Selection of follow up 1.7K taking into account similarity to newly identified hERG inhibitor motifs
  - Part computational, part manual – similarity & inspect cluster

Scaffold liability
- LogP 1.5-3.5 (non-basic)
- All >40% inh.

Specific structural change
Index Set - 12K capturing diversity across MRCT collection

- Ideal for pilot or LTS, with focus on fast follow-up
  - Selection based on properties, diversity, coverage and representativeness
  - Selection restricted to ‘in-stock’ commercial compounds for reliable suppliers
- Greater level of annotation to steer hit triage
  - One of most frequently and diversely screened – few true frequent hitters emerge

Fragment set

- 2K in various subsets
  - Source/Type: 3D fragment consortium, metal binding, fluorinated, building blocks
  - Format/Technology: NMR, SPR, X-ray, 96 vs 384-well, concentration
- Desirability criteria shifted
  - Diversity still important but has different scale at fragment level
  - Number and diversity of type of growth vectors is critical
Make sure the screening collection is fit for purpose – choose carefully upfront to boost chances of finding a hit and avoid problems in follow up

• Quality is key for generic HTS collections
  – Chemical space is vast - avoid problem areas unless there’s a good reason not to and take care in how you perform the diversity selection
  – Composite property measures and substructure flags very useful – manually inspect
  – No substitute for medicinal chemist expertise – triage feasible

• Exploit existing data in target-focused subsets
  – Pharmacophore bias enables higher hit rates
  – Annotated sets allow us to learn from previous experience, providing alternative advanced starting points and flagging liabilities

• Other collections can provide more efficient hit to lead
  – Smaller index set has broader application and allows fast follow up if representative
  – Fragment screening success heavily dependent on growth potential
Thank you for Your Attention
Questions & Comments

Andy Merritt, Chido Mpamhanga, Claire Wallace, David Tickle, Denise Harding, Ed McIver, Joanne Osborne, Jon Large, Kevin Gillen, Martin Ambler, Stephen Lewis, Simon Osborne, Tim Chapman