Prioritizing Therapeutics for Lung Cancer: An Integrative Meta-analysis of Cancer Gene Signatures and Chemogenomic Data

Fortney et al.
Presented by Erkin Otles

Approach

Identify drugs that reverse gene expression signature of a disease

Issues analyzing signatures:

Inconsistency across studies

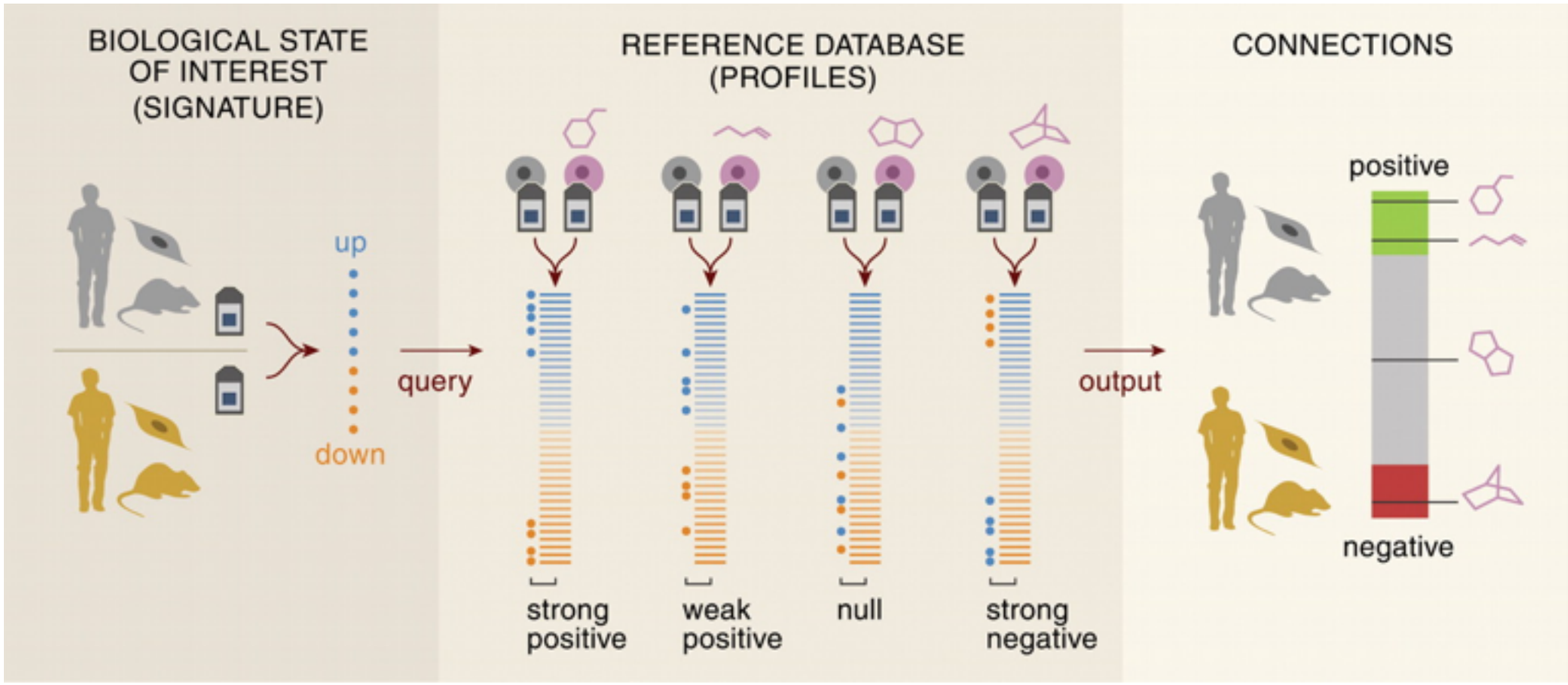
Different study designs?

Signature Source: CMap

Connectivity Map

Catalogue of responses to treatments

>1,000 small molecules



CMap

The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease
Lamb 2006

Traditional Approaches

Collapse disease signatures into meta-signature

Query CMap based on meta-signature

Meta-signature may be good, but CMap is noisy

Target lists are sensitive

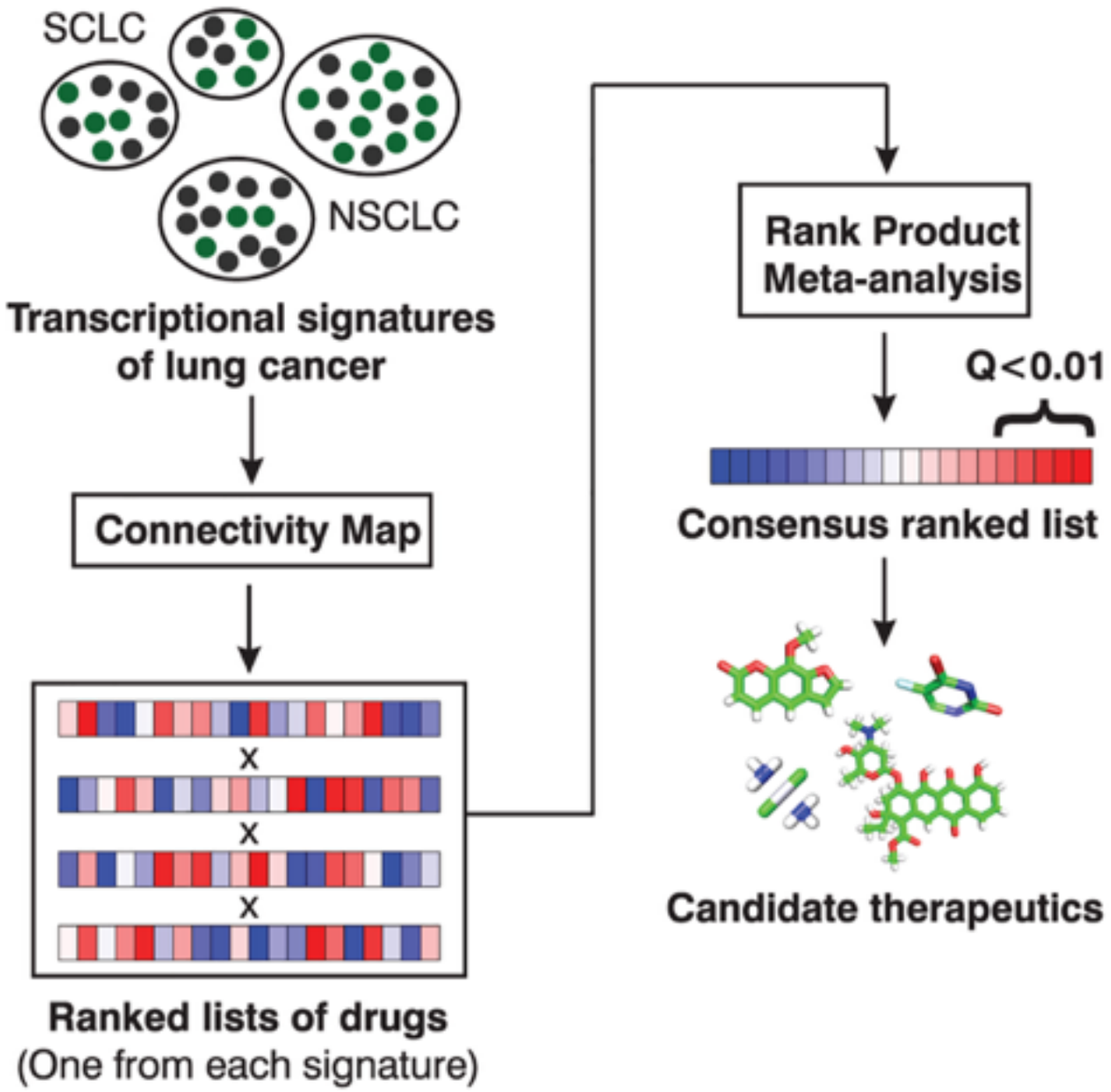
CMapBatch

For each cancer (disease) sample:

Calculate mean connectivity scores for all small molecules

Use mean connectivity score to create ranked lists of drugs

Look across signatures to find consistently highly ranked drugs (Rank Product!)



CMap, CMapBatch, Batch Map Batch!

RankProduct

Drum Roll Please…

RankProduct - Breitling 2004

For an experiment examining n genes in k replicates, one might argue that the probability for a certain gene to be at the top of each list (rank 1) is exactly

$1/n^k$

if the lists were entirely random.

RankProduct - Breitling 2004

More generally, for each gene g in k replicates i, each examining n_i genes, one can calculate the corresponding combined probability as a rank product

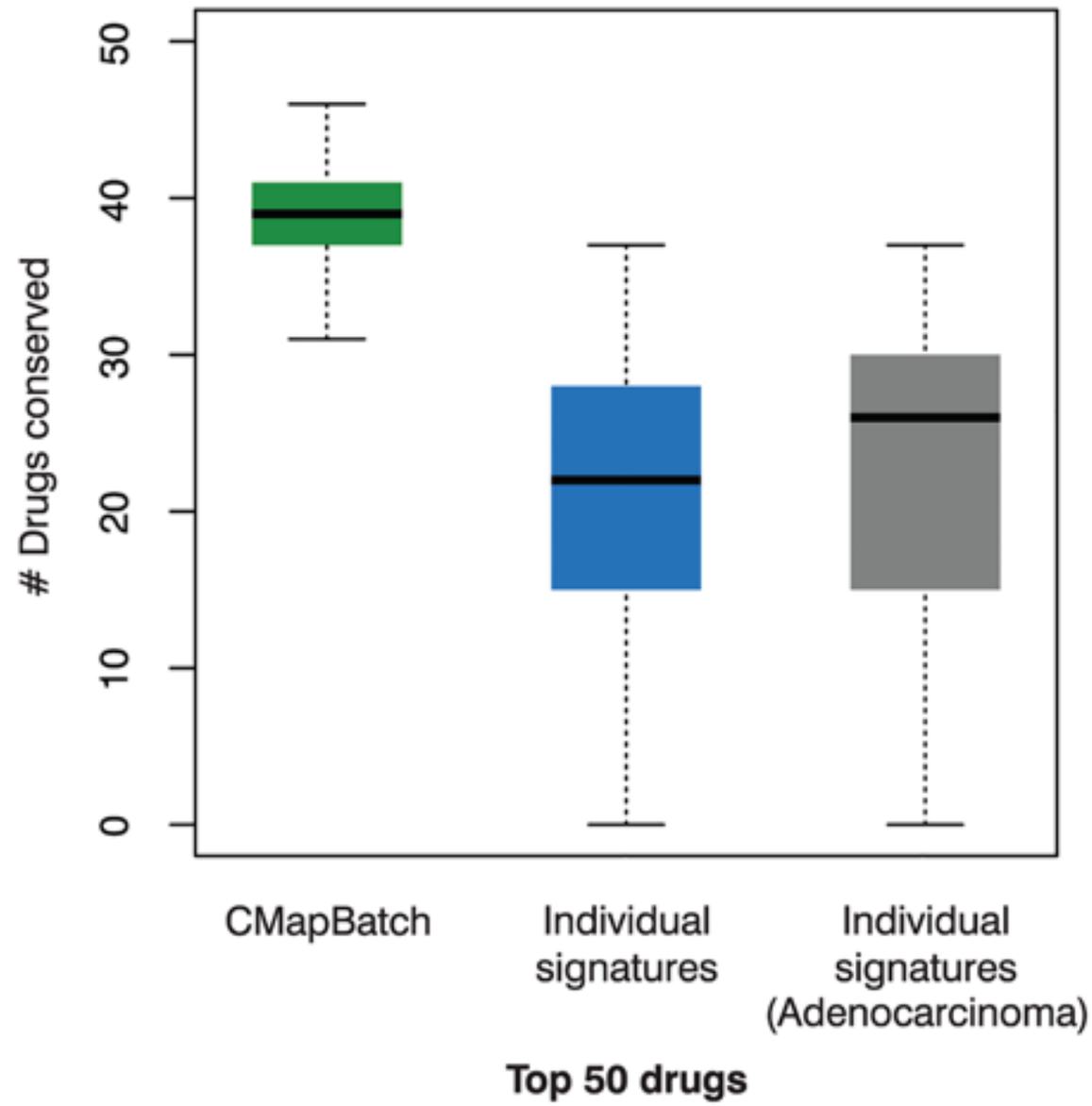
$$RP = \pi_{i \text{ in } k} (r_i/n_i)$$

If $n_i = n$ for all replicates

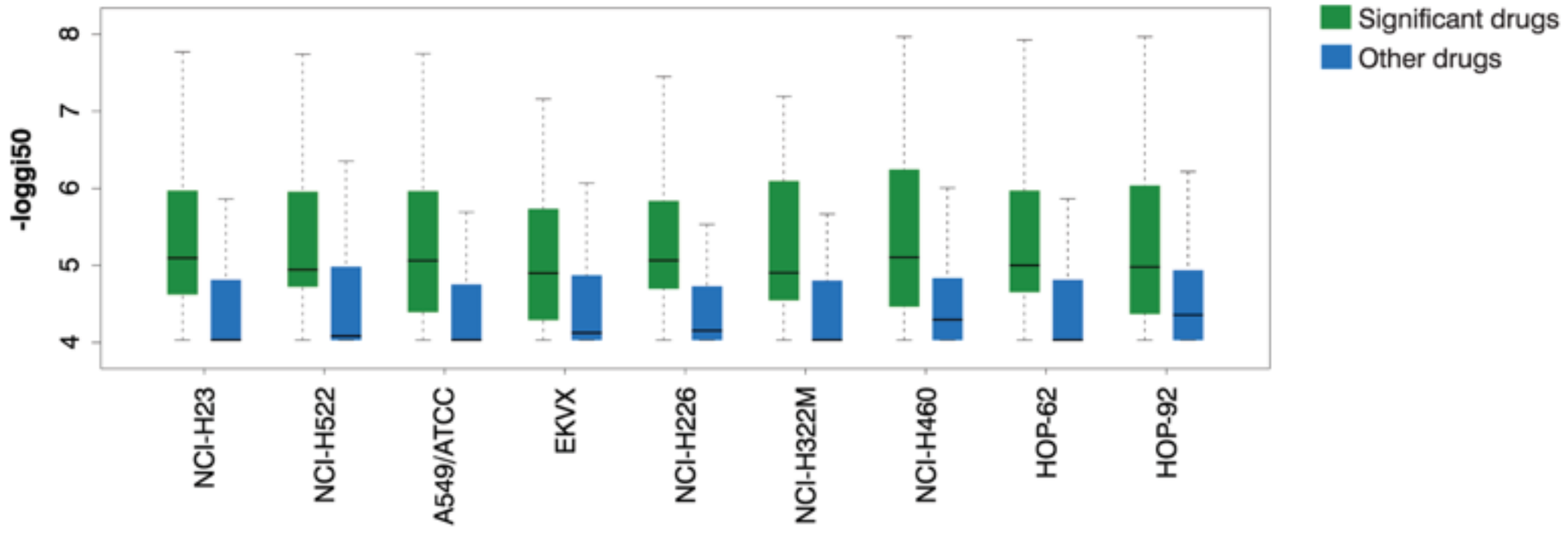
$$RP = (\pi_{i \text{ in } k} r_i)^{1/k}$$

Using CMapBatch on Lung Cancer

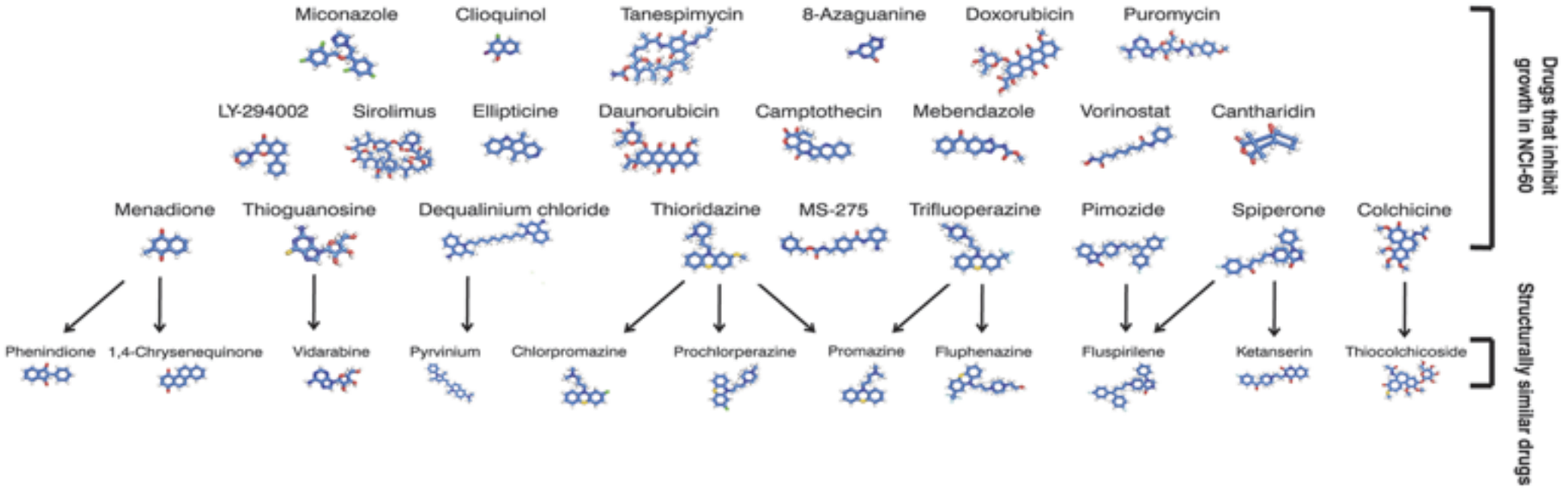
21 gene expression signatures from Oncomine and CDIP



Improved drug list stability

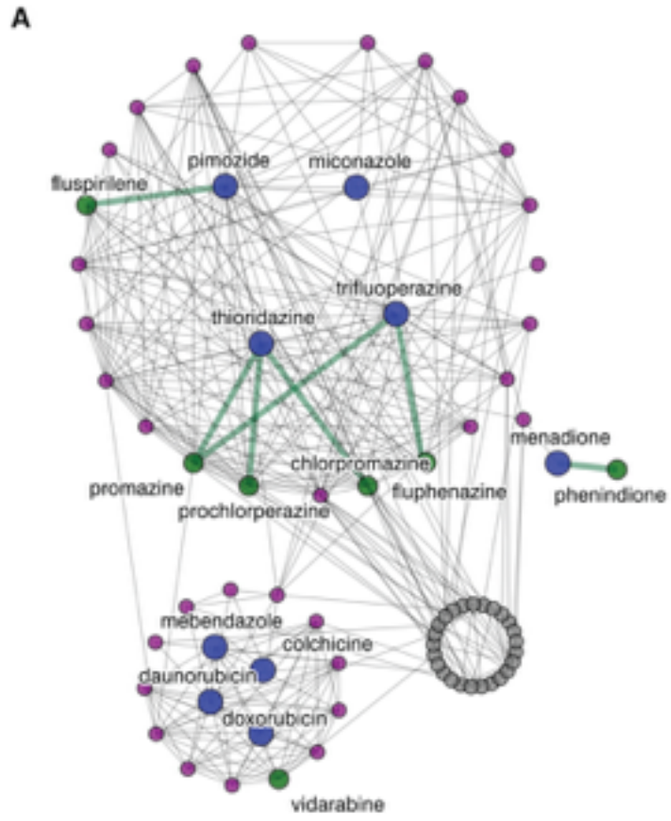


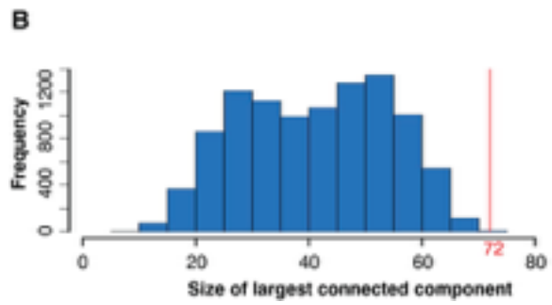
Candidate drugs inhibit growth better



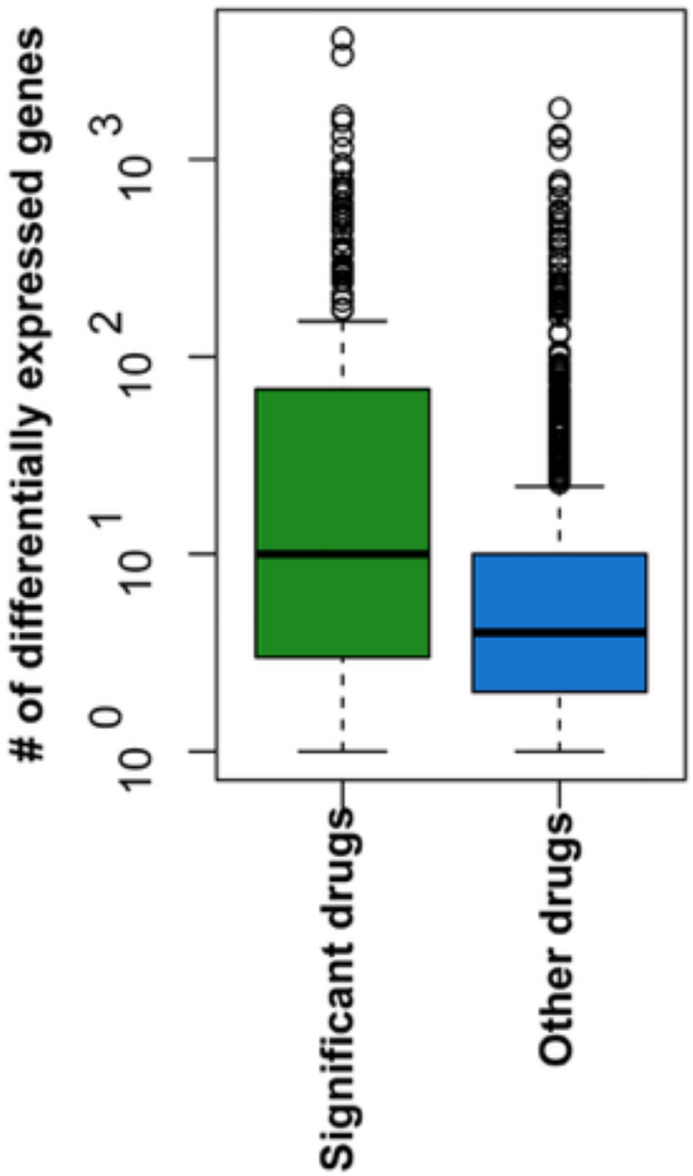
Prioritized drugs have similar structure

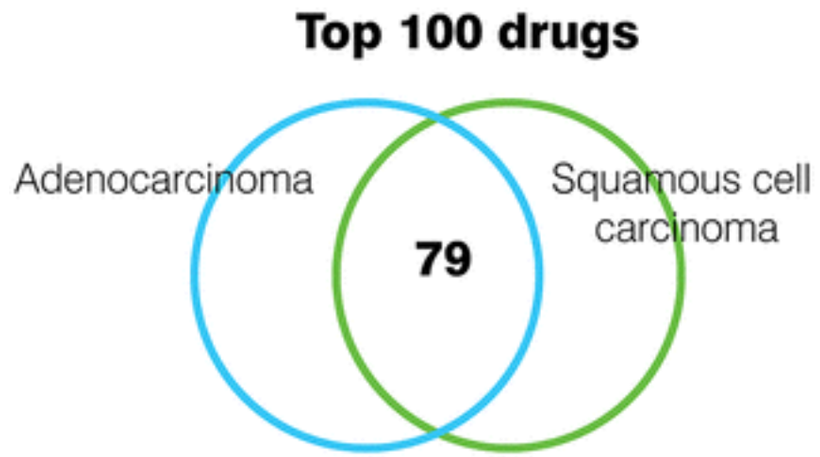
Is this due to CMapBatch picking broad acting agents?





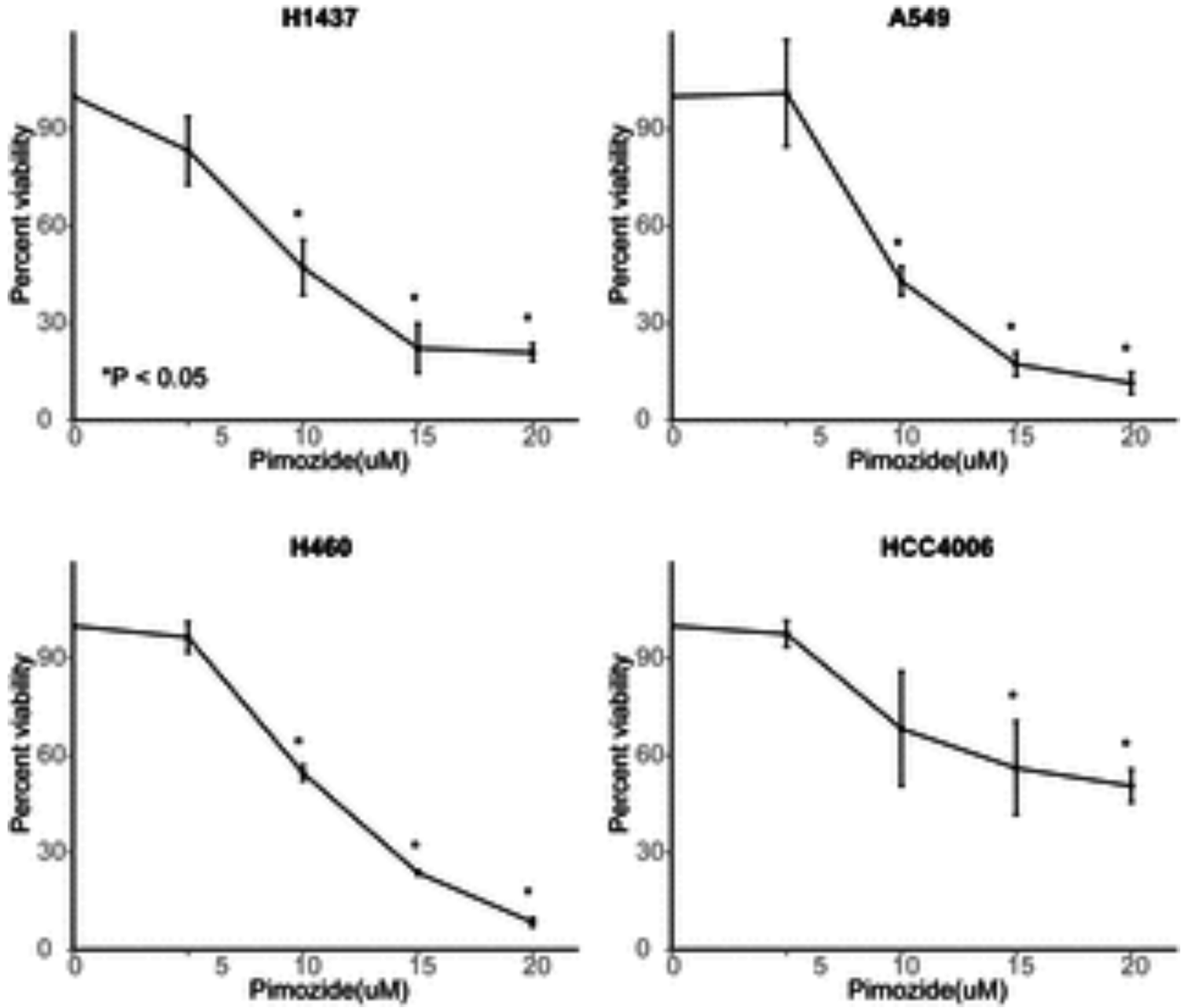
Significant drugs share protein targets





CMapBatch picks broad acting drugs

Is this a good thing?



Pimozide reduces viability of lung cancer