Systematic Exploration of Dual-Acting Modulators from a Combined Medicinal Chemistry and Biology Perspective

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(AstraZeneca R&D, UK and Sweden)

A. Manos-Turvey,
Wipf Group Current Literature
February 23rd, 2013

Drug Discovery and Development

- The cost of drug discovery continues to rise.
  - New drugs cost more than US$1 billion to get to the end point.

Estimates of the components of drug development costs from studies providing all components and assumptions.

	Hansen and Chien [1]	DiMasi [5]	DiMasi et al. [8]	Adams and Brantner [13]	Paul et al. [3]
Cash	1963-1975	1970-1982	1983-1994	1989-2002	1995-2010
Pre-clinical	$46.0	$111.0	$149.8	$164.6	$284.4
Clinical	$46.0	$81.5	$349.0	$383.7	$599.2
Total	$92.0	$192.5	$498.8	$548.3	$883.6
Capitalized					
Pre-clinical	$89.0	$263.7	$414.6	$471.5	$834.0
Clinical	$73.0	$127.5	$578.0	$602.7	$965.6
Total	$161.0	$391.2	$992.6	$1074.3	$1799.6
Assumptions					
Success rate	12.0%	23.0%	21.5%	24.0%	11.7%
Cost of capital	8.0%	9.0%	11.0%	11.0%	11.0%

Notes: Figures converted to year 2009 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis).

- Many drugs fail upon entering Clinical Trials.
  - How to reduce costs while increasing drug output?

S. Morgan *et al.*, *Health Policy*, **2011**, *100*, 4-17

An Efficacy Perspective: Network Pharmacology

- Current medicinal chemistry has focused upon single targets BUT targets and pathways are rarely singular entities.
- Many compounds have off target effects, which can impact upon the efficacy and toxicity of compounds.
- Working on a single target is often insufficient to stem disease progression.
  - For example, Hsp90 inhibitors for cancer treatment, downstream effects of inducing production of Hsp70.

A.L. Hopkins, *Nat. Chem. Biol.*, **2008**, *4*, 682-690

An Expanding World of Chem- and Bio-Informatics!

- PubChem
  - public repository of screening data.
- Chembl
  - manually curated biomedical literature activity data.
- BioPrint
  - commercial database of screening data of a set of compounds against a panel of targets.
- Drugbank
  - public database, combining drug data and target information.
- GoStar
  - example of a commercial database with activities extracted from journals and patents.

Polypharmacology

- DrugBank suggests a compound will average activity against 1.7 proteins.
  - Focuses on main target of drugs.
- If you consider further literature reports and predicted bioactivity:
  - a single compound can be active 2.7 moving up to 6.3 proteins!

J. Mestres *et al.*, *Nat. Biotech.*, **2008**, *26*, 983-984

Aim: Enabling Specific Disease Area Analysis

- List of Targets associated with a disease area
  - inhibitor, blocker, agonist, antagonist, positive/negative allosteric modulator.
- 5 general Medicinal Chemistry Workflows (**MCW**) for chemical feasibility investigation
- 2 Biology Workflows (**BW**) for mechanistic evaluation of opportunities
  1. Evidence of previous investigations of target pairs (**text mining**)
  2. Create an interaction map with targets, their bioprocesses and pathways (**bioprocess mapping**)
- Selection of a promising target pair combination
  - start a drug discovery project for a dual-acting modulator

Application to Gastrointestinal Disease

- Extract activity data from GoStar and BioPrint
  - Three different activity cut-offs analysed: 10 µM, **1 µM** and 100 nM.
  - 20 receptors were identified, 18 were used in the analysis.

- Two analyses possible:
  1. 'normal' – all possibilities

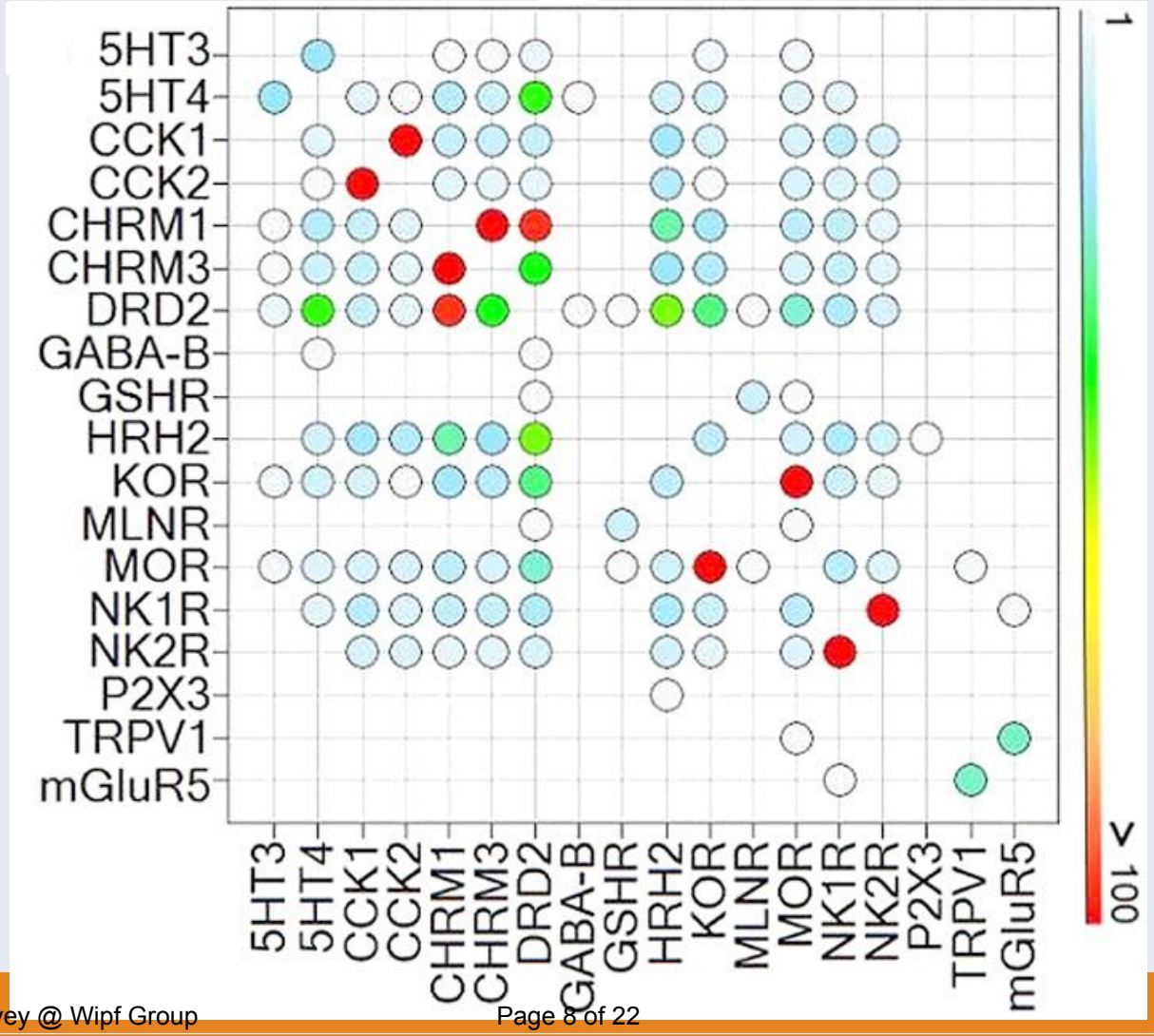
     OR

  2. "strict" – excludes patents without explicit activity data
     - eg. Threshold of 10 µM: 'normal' filter retrieves 217 650 vs. 'strict' which finds 105 576 different compounds.

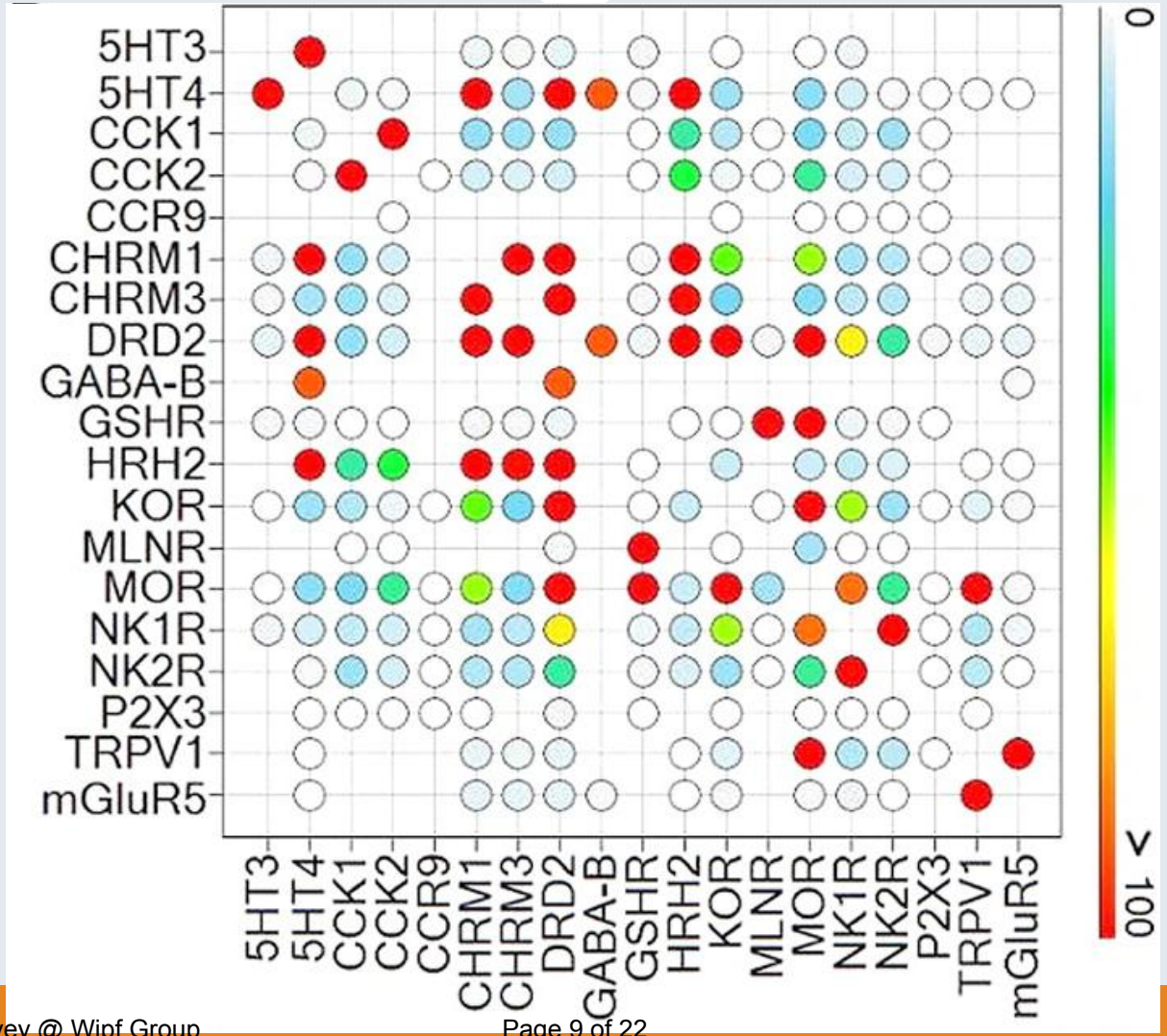
https://gostardb.com/gostar/

http://www.cerep.fr/cerep/users/pages/productsservices/bioprintservices.asp

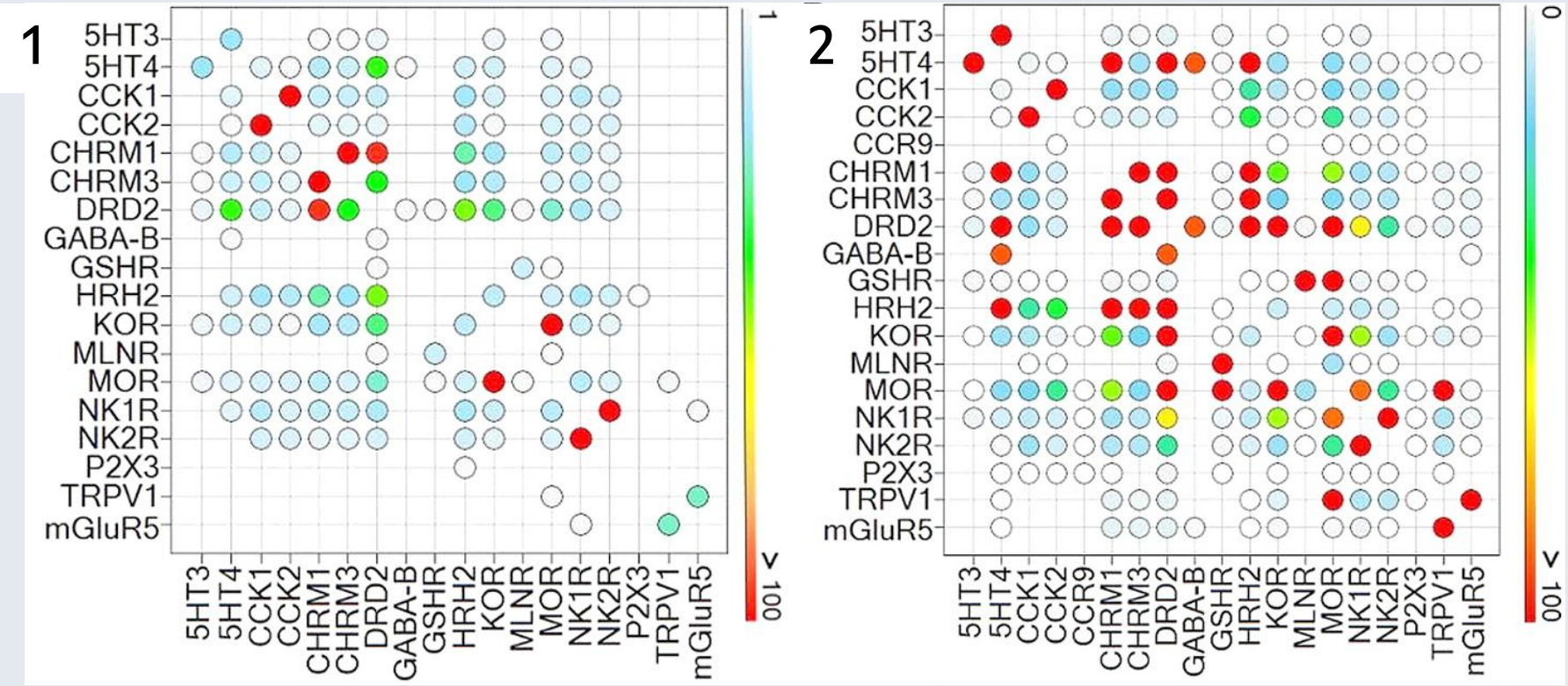
MCW 1: Compounds Active on 2 Targets in 1 Publication



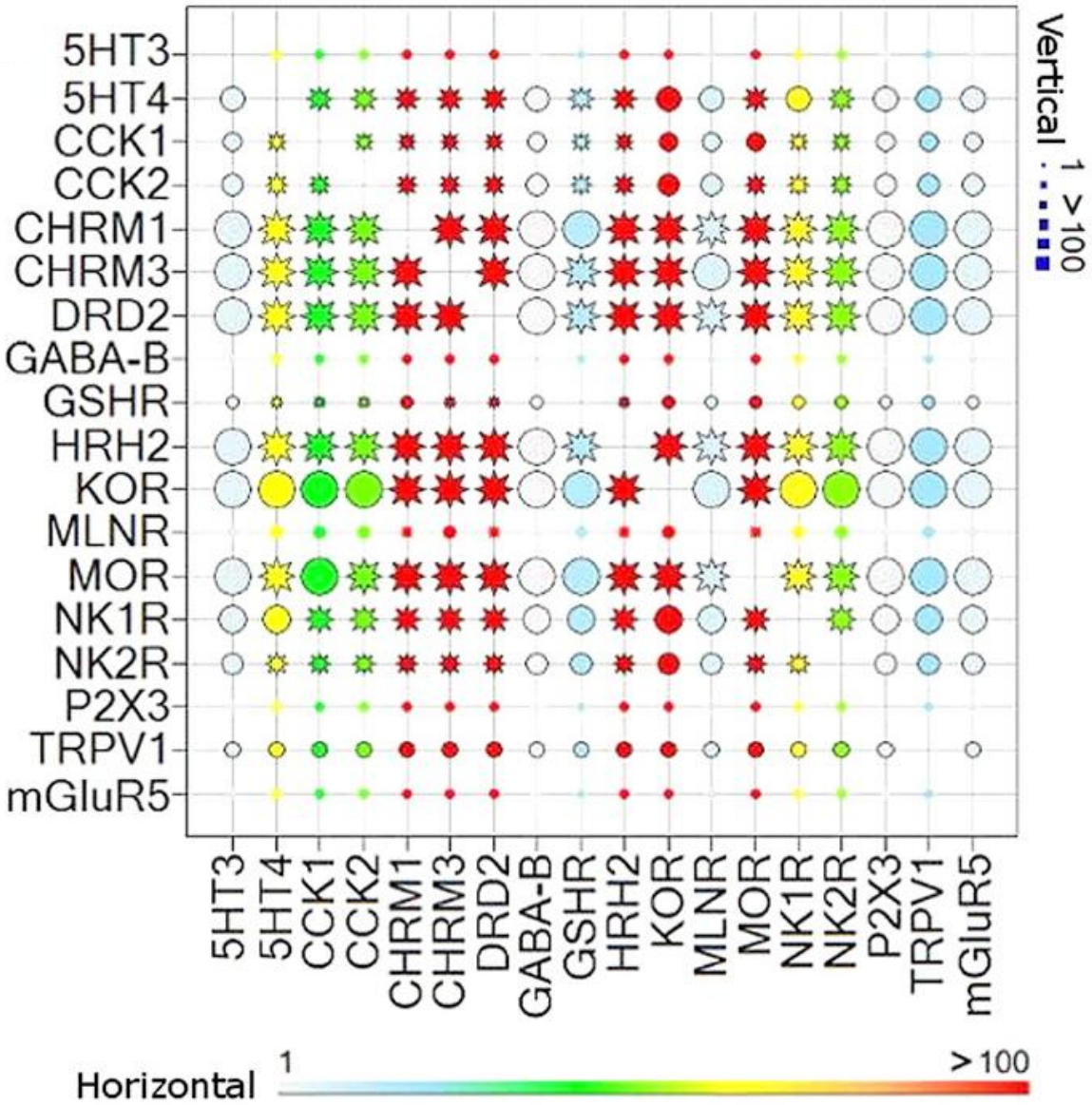
MCW 2: Active on 2 Targets in Unrelated Publications AND Molecules With Similar Structures



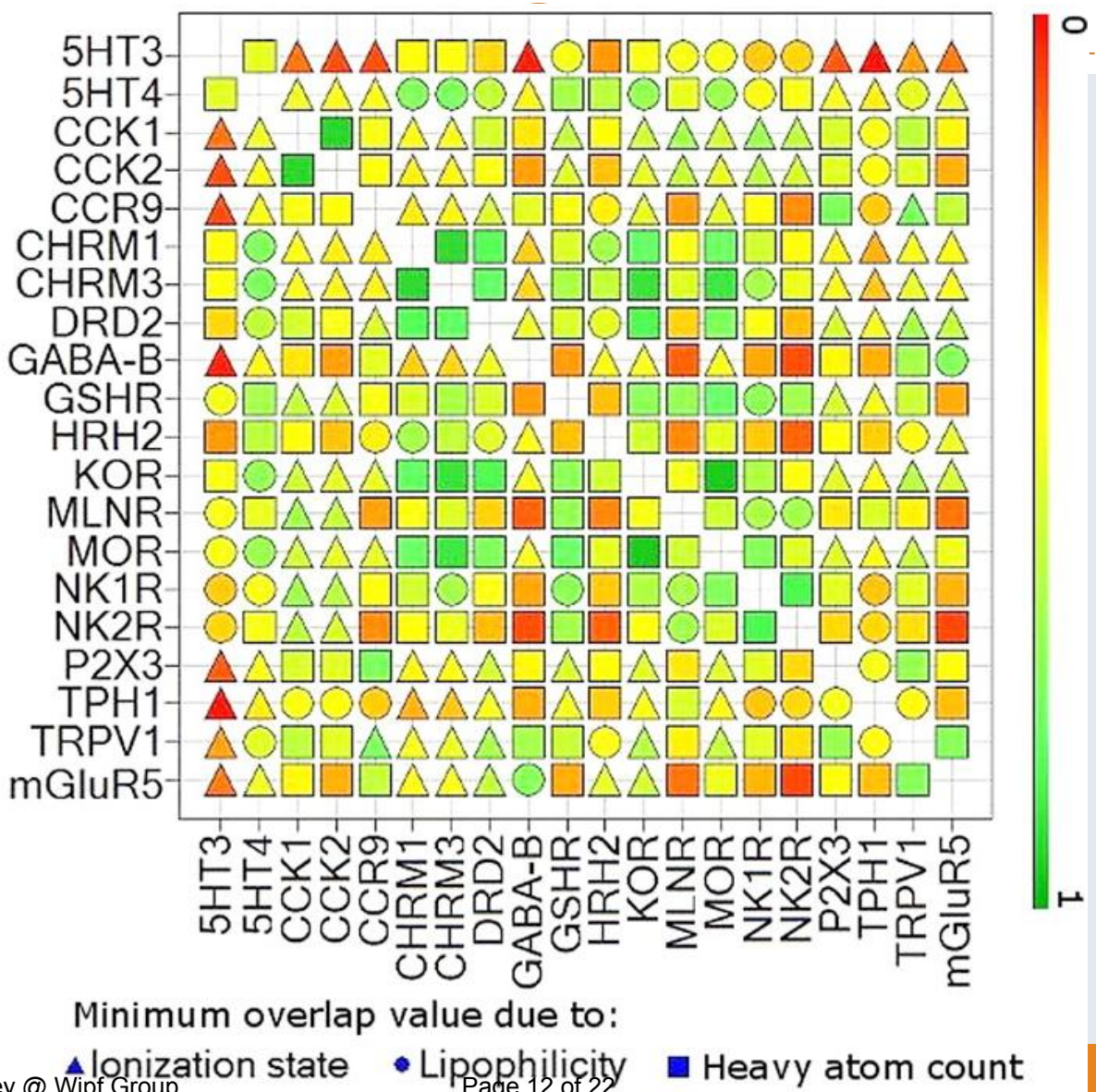
MCW 1 and 2


1
5HT3
5HT4
CCK1
CCK2
CHRM1
CHRM3
DRD2
GABA-B
GSHR
HRH2
KOR
MLNR
MOR
NK1R
NK2R
P2X3
TRPV1
mGluR5
1
> 100
2
5HT3
5HT4
CCK1
CCK2
CCR9
CHRM1
CHRM3
DRD2
GABA-B
GSHR
HRH2
KOR
MLNR
MOR
NK1R
NK2R
P2X3
TRPV1
mGluR5
0
> 100

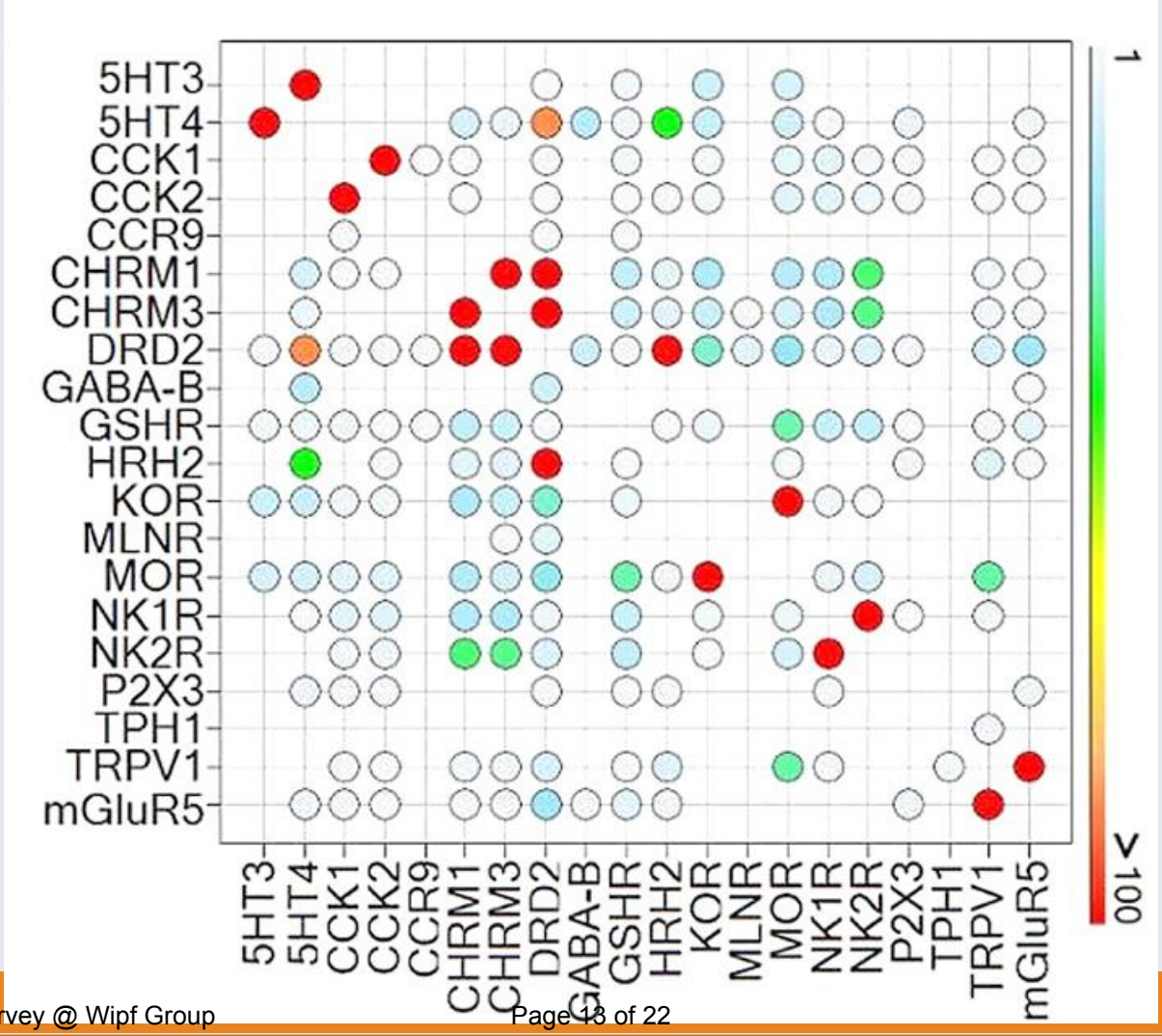
MCW 3: Validation of Target Combinations *in vivo*



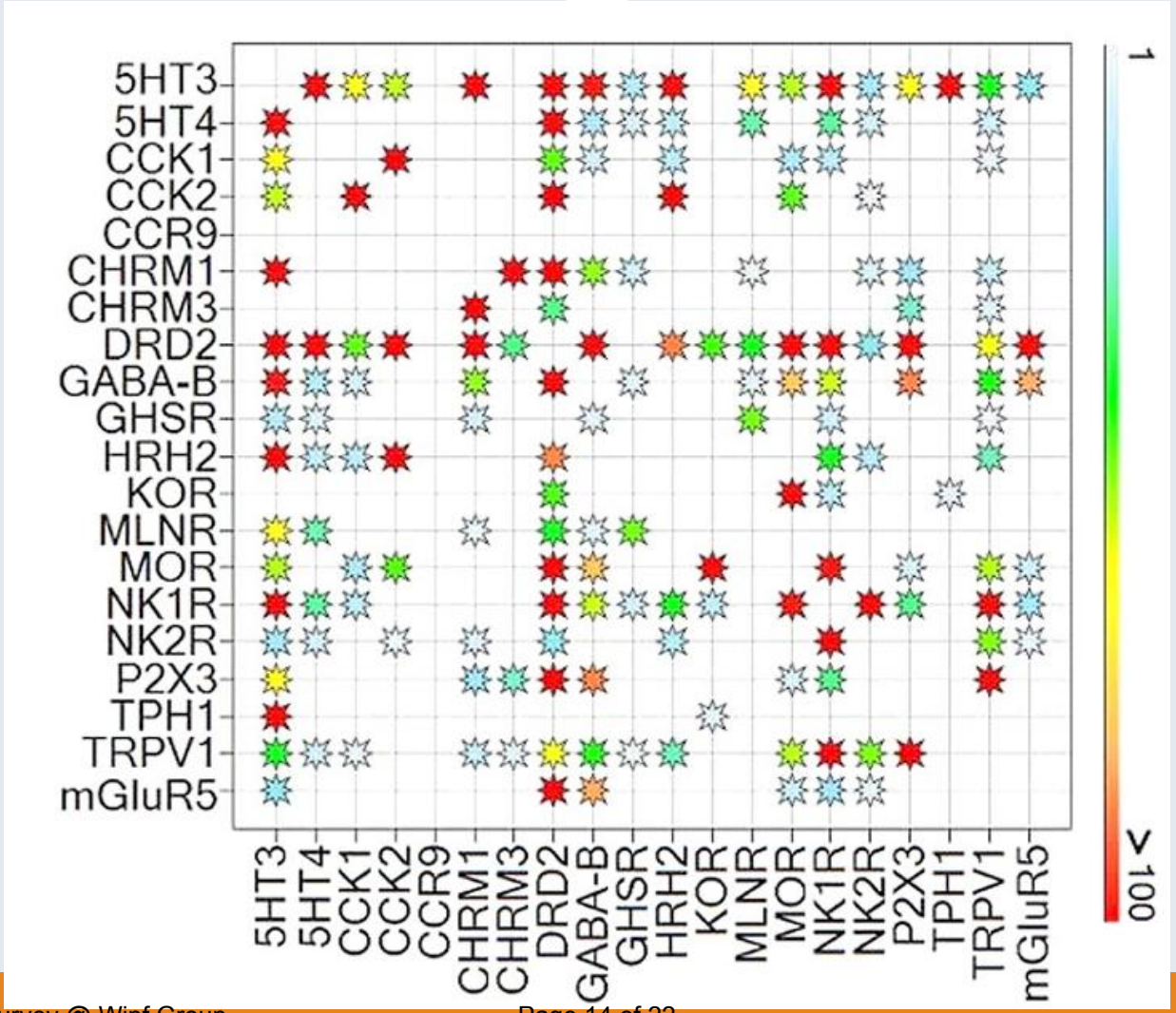
MCW 4: Similarity of Binding Cavities Between Receptors



MCW 5: Number of Privileged Scaffolds *per* Target Pair

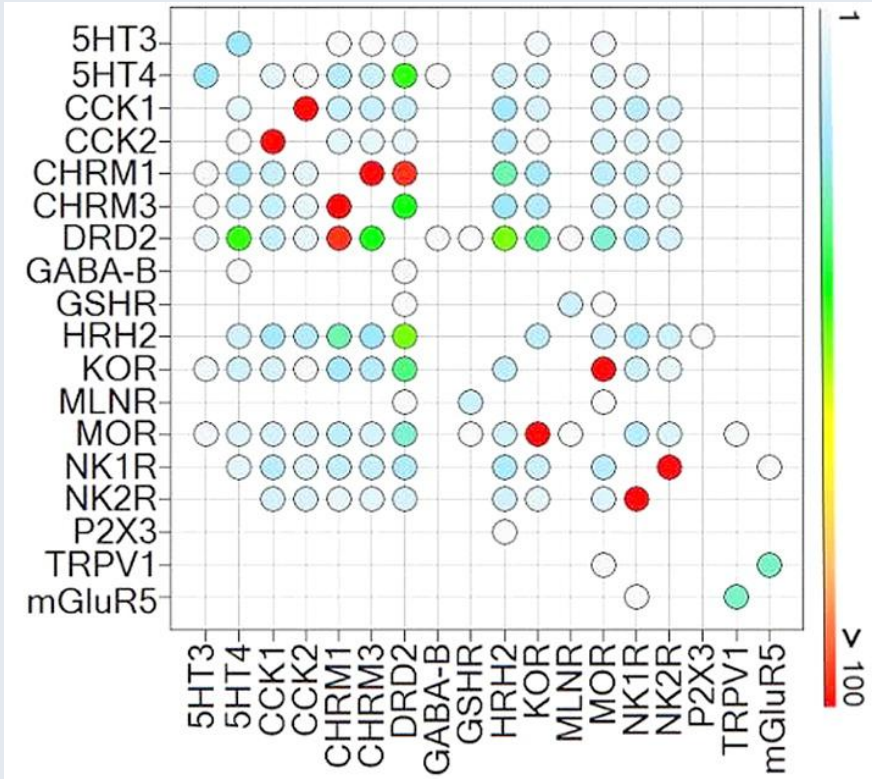


BW 1: Text Mining

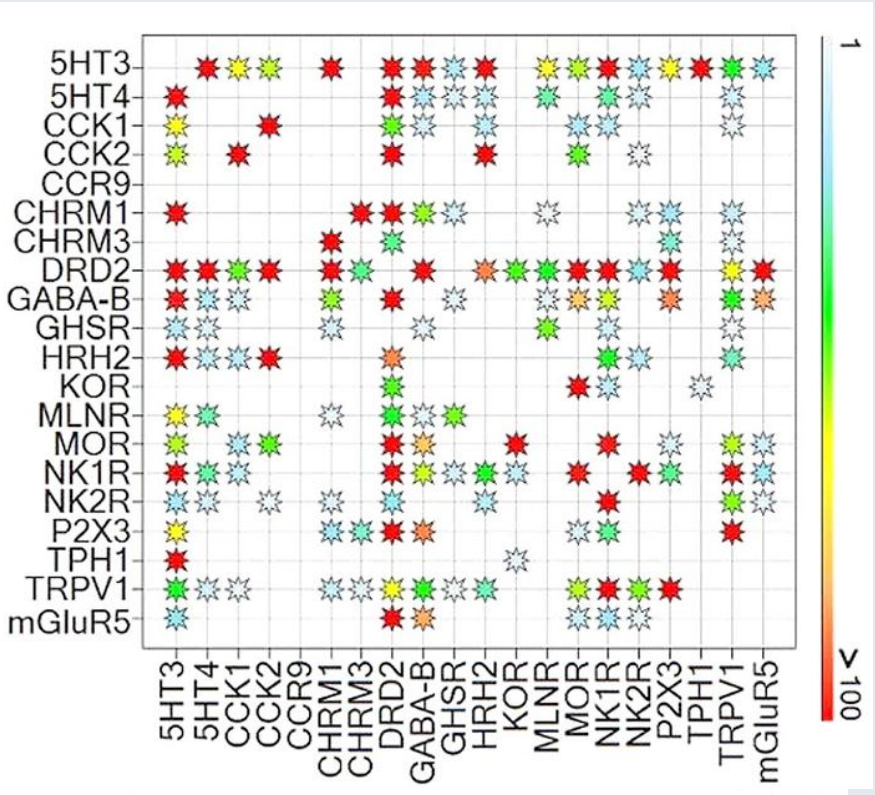


BW 1: Text Mining

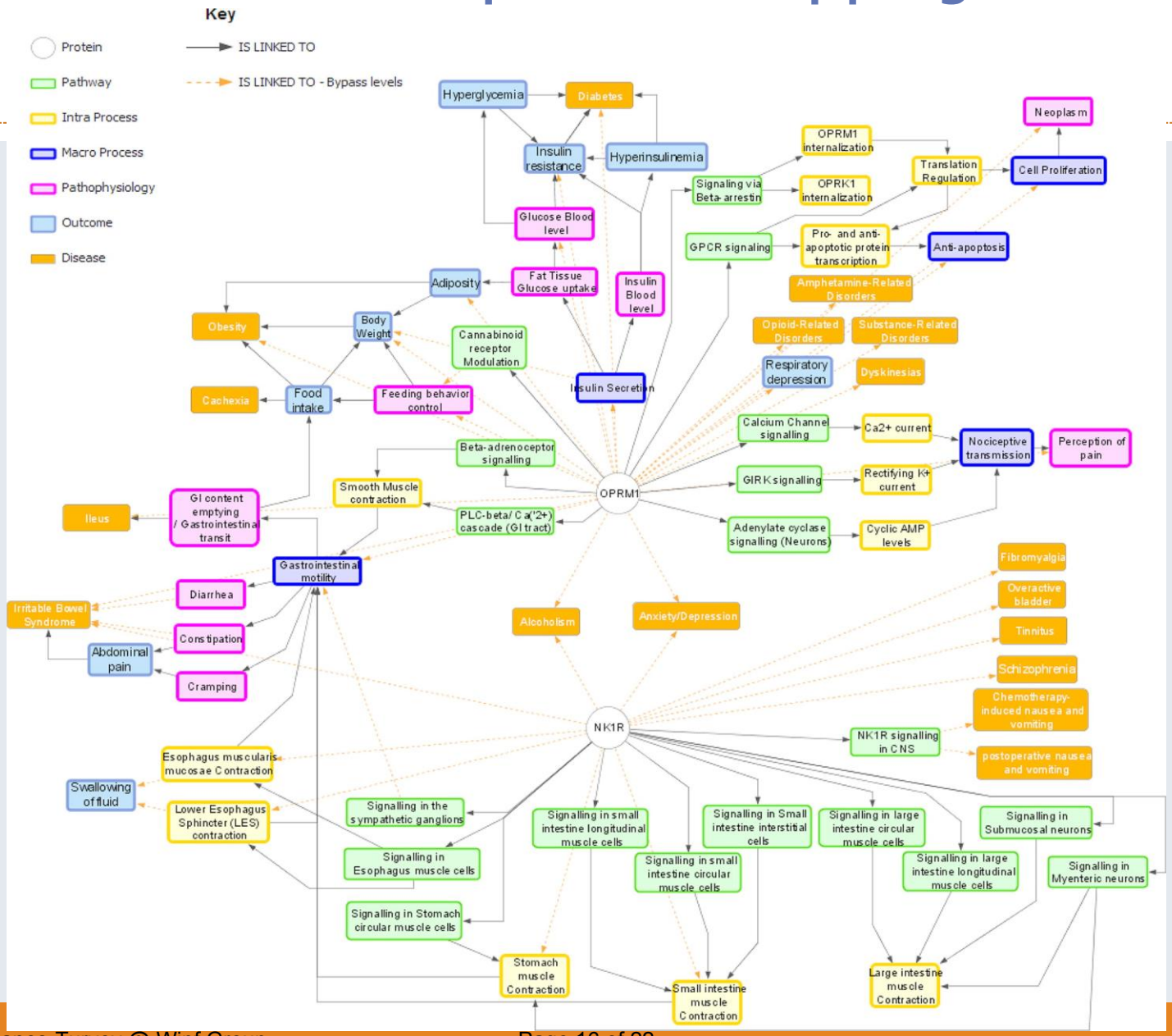
MCW1



BW1



BW 2: Bioprocess Mapping



BW 2 Utility

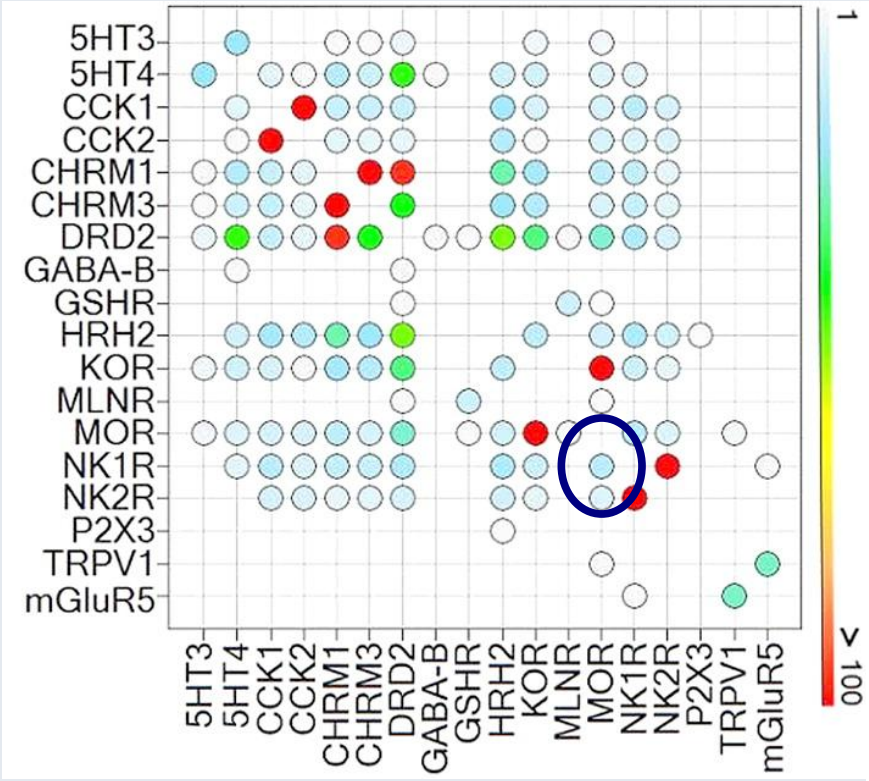
- The key factor is to provide a multi-level view to highlight similarities and differences between the two chosen receptors.
- Very labour intensive, major text mining and collaboration with biologists in the specific field is required.

Example of Utility: NK1 and MOR

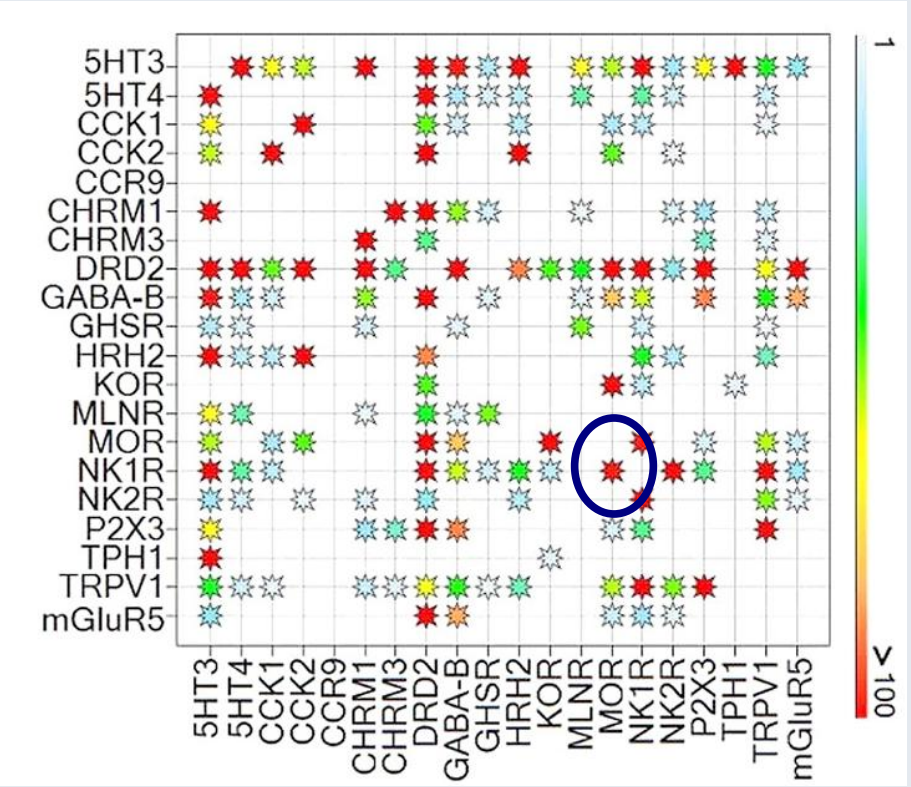
- Neurokinin type 1 (NK1) and opioid receptor μ1 (MOR).
- Opioids are analgesics particularly.
- Pain management drugs are in high demand but difficult to pinpoint,
  - neuropathic pain requires consideration of tolerance, physical dependence and CNS penetration
- NK1 binds substance P, a peptide involved with intestinal motility.
  - These pathways appear to be linked: MORs and NK1 receptors are co-expressed in the CNS
  - Chronic opioid treatment results in substance P release and up-regulation of NK1

NK1 and MOR

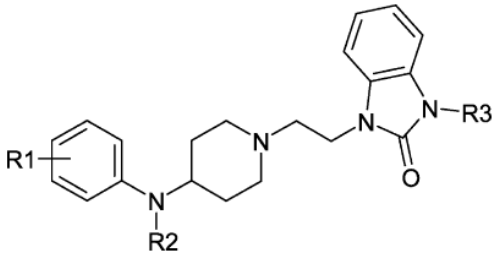
MCW1

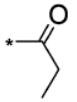
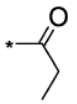
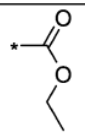
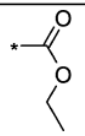


BW1



NK1 and MOR



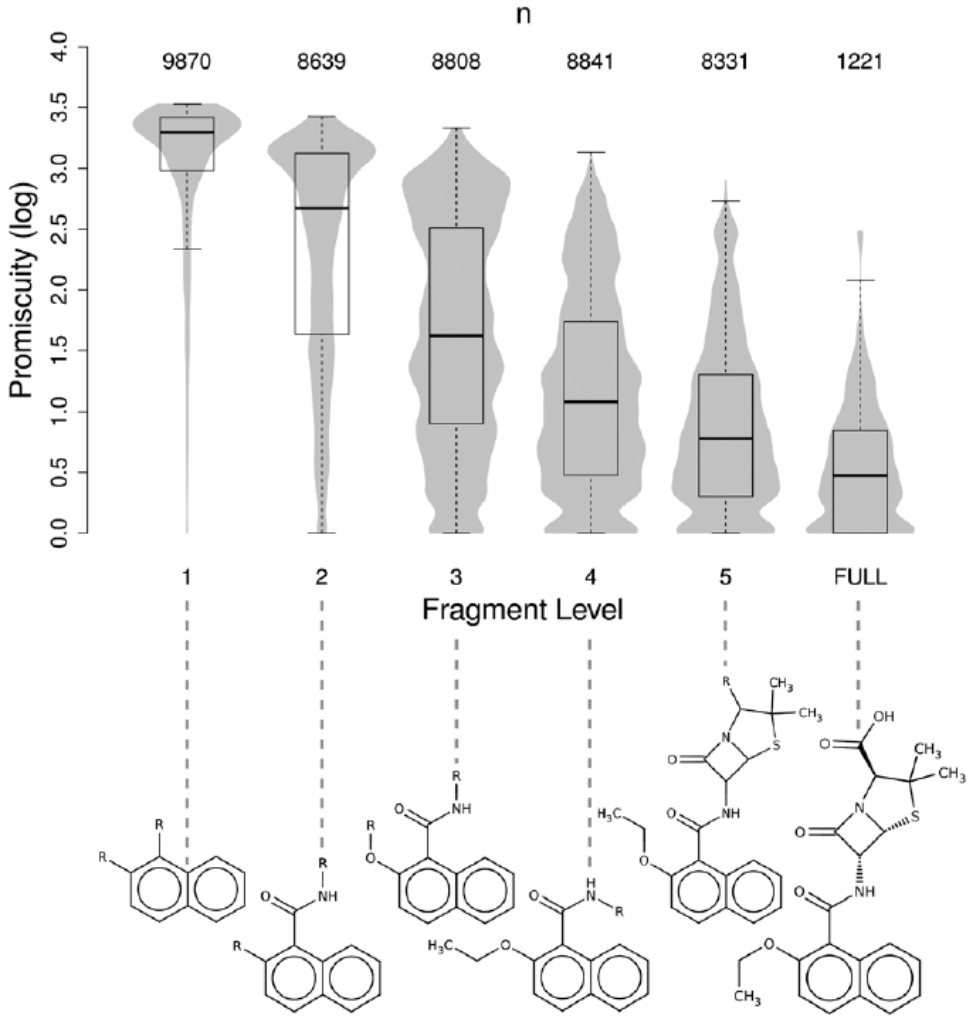
R1	R2	R3	NK1 Receptor K_i (nM)	MOR K_i (nM)
3-Cl			2.8	37
2,5-diCl			220	19
3,4-diCl			1	540
H			120	3

G. Rémond *et al.*, *Eur. J. Med. Chem.*, **1997**, *32*, 843-868

Conclusions

- Through comprehensive analysis of existing medicinal chemistry and biological data, the authors have created a way to design dual-acting modulators, avoiding poor physicochemical properties.
- Could aid in targeted fragment screening (especially looking at MCW5)
- Removal of large dual-modulators
  - These molecules are often too large to be orally available.
- Hope to find new orally available drug candidates.

Polypharmacology



X. Jalencas and J. Mestres, *Med. Chem. Comm.*, **2013**, *4*, 80-87