# Polypharmacology – Foe or Friend?

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# Introduction

- Polypharmacology is the ability of a compound to interact with and affect multiple targets.
- Aspirin is a well known polypharmacological drug that has been used successfully.
- Due to nonselectivity which lead to drugs' adverse effects and toxicity, polypharmacology is discouraged by many researchers.
- However, this concept could be beneficial in intentionally designing multitarget drugs for the management of certain diseases by altering different pathways.

Jalencas, X.; Mestres, J. On the origins of drug polypharmacology. *Med. Chem. Commun.*, **2013**,4, 80-87

# What is the Purpose?

To prove that targeted polypharmacology holds opportunities for the discovery of better drugs

# In This Paper…

- Safety Panel Screening
  - Unintended *versus* Targeted Polypharmacology
- Promiscuity Predictions
  - Pharmacological Promiscuity Parameters
- Prevalence and Significance for Toxicity and Attrition
- Polypharmacological Drug Discovery
  - Efficacy and Safety Examples
  - Repurposing
  - Combinations of Drugs and Pharmacophores

# New Trends in Safety Panel Screening and Promiscuity Prediction

- Adverse drug reactions and preclinical toxicity account for 30% of all drug candidate terminations in clinical trials.
- Many ADRs come from a drug's unintended activity at an "antitarget".
- Animal toxicity studies do not reliably predict antitarget-related ADRs in humans due to species differences.
- Thus, safety panel screening has been developed by research organizations in which drug candidates are screened against panels of up to 180 safety-relevant targets.

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# Table 1. Frequently Encountered Antitargets

| antitarget | hit rate[a] (displacement assay) (%) | associated adverse effects |
|---|---|---|
| hERG channel | (see text) | arrhythmia |
| serotonin 5-$HT_{2B}$ receptor | 14 | agonists: valvulopathy, pulmonary hypertension |
| serotonin 5-$HT_{2A}$ receptor | 11 | agonists: cognition impairment, hallucination |
| $\alpha_{1A}$ adrenergic receptor | 10 | agonists: arrhythmia; antagonists: orthostatic hypotension |
| dopamine $D_2$ receptor | 9 | agonists: confusion, emesis; antagonists: orthostatic hypotension |
| histamine $H_1$ receptor | 6 | antagonists: weight gain, sedation, somnolence |
| $\alpha_{2A}$ adrenergic receptor | 6 | agonists: hypotension, sedation |
| dopamine $D_1$ receptor | 5 | antagonists: dyskinesia, tremor |
| $M_{1-5}$ muscarinic receptors | 5 | multiple cardiovascular and metabolic adverse effects, cognition impairment |
| $\mu$-opioid receptor | 3 | agonists: sedation, respiratory depression, abuse potential |

[a]Hit rate: percentage of druglike compounds, which bind to this target with an $IC_{50} < 1$ $\mu$M in the BioPrint data set.

# Early Safety Screening Criteria

- Assessing off-target activities should be earlier in the drug discovery process.
- Panels should contain only key antitargets and avoid a redundancy of targets.
- Targets with no clear links to ADRs should be omitted from the screening panel.
- Targets with low hit rates can be omitted.

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# Pharmacological Promiscuity Parameters

- Many molecular properties have shown to be vital in determining pharmacological promiscuity.
- Studies have shown that lipophilic compounds tend to be more promiscuous. (fig. 1)
- Basic compounds that are protonated at physiological pH are frequently promiscuous in safety screens.
- MW does not seem to be a useful predictor of promiscuity due to contradictory results.
- Compounds tend to be less promiscuous if they are of high complexity, of little flexibility, or decorated with many side chains.
- Specific structural fragments also play a role in predicting promiscuity. (chart 1)

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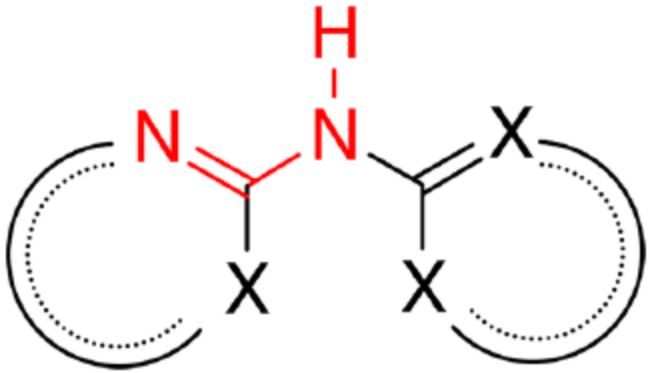
# Chart 1. The "Heteroaryl-NH-aryl" Motif Is Predictive of Kinase Activity




Compounds containing the bisarylaniline motif, heteroaryl-NH-aryl, often inhibit a wide variety of kinases.

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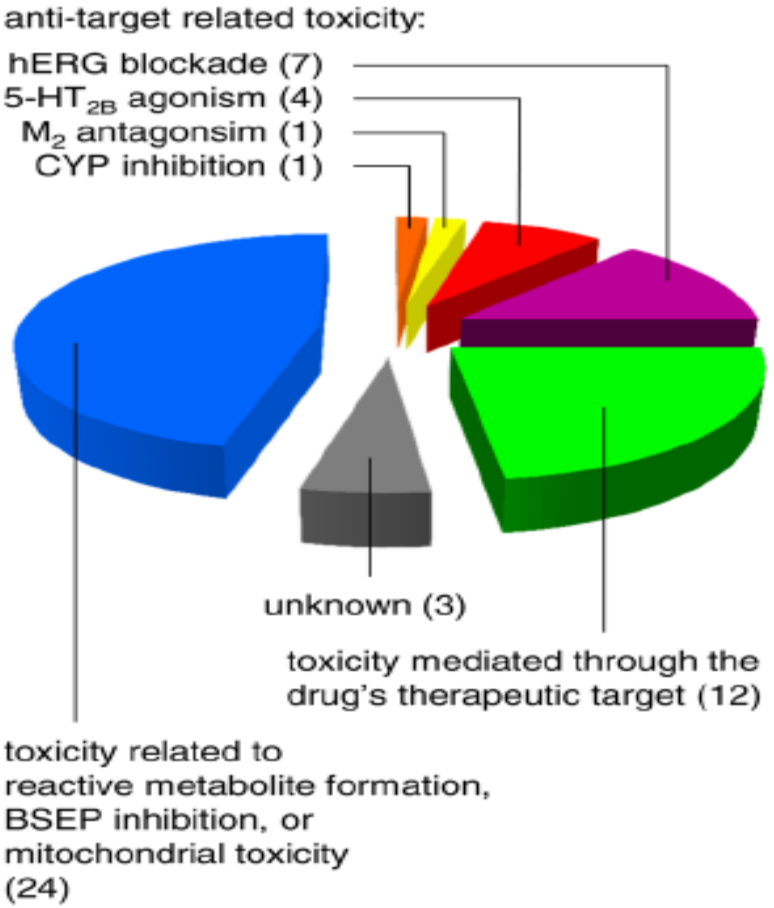
# Promiscuity Prevalence and Toxicity

- Significant percentage of compounds in large databases bind to more than one target.
- The actual prevalence of promiscuity is likely higher than 33–52%.
- Only a quarter of drug withdrawals can be traced back to unintended pharmacological activities.
- However, off-target activities must not be disregarded as an important cause of toxicity.




Drug Withdrawal Reasons

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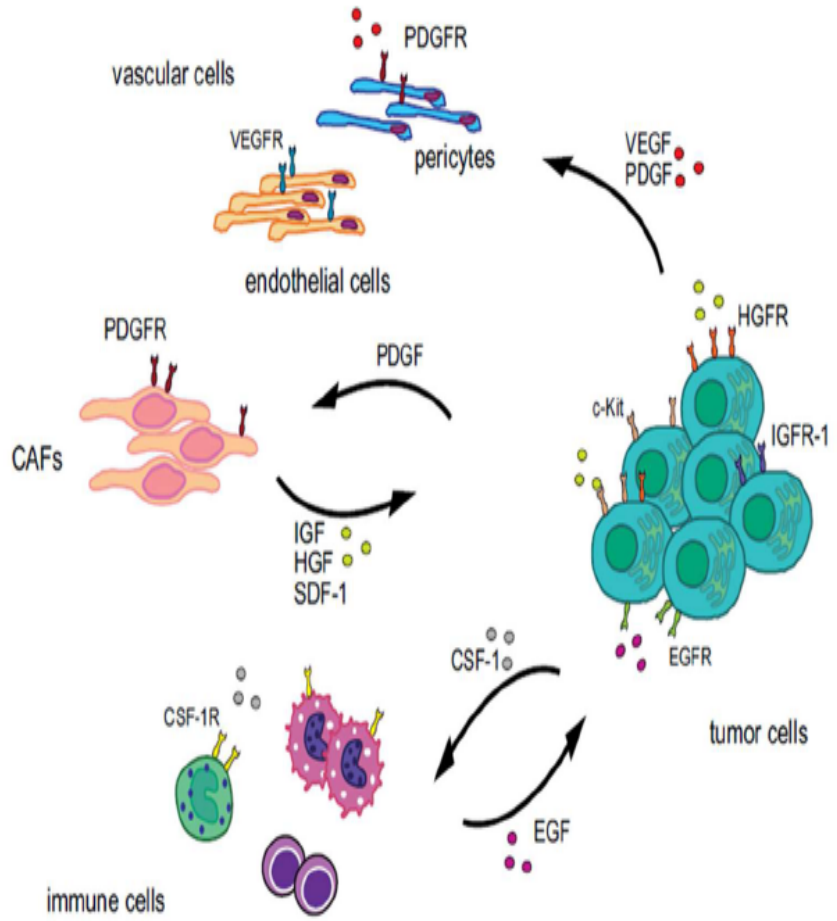
# Polypharmacological Drug Discovery: Examples

- Multikinase anticancer drugs disrupt several signaling processes.
- Sunitinib blocks the receptor kinases of many growth factors associated with cancer.

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## Table 2. Recently Approved Multi-Kinase Inhibitors as Anticancer Drugs

| drug | first approval | targets | FDA approval for (status April 2013) |
|---|---|---|---|
| sorafenib | 2005 | B-Raf, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, Fms-like tyrosine kinase 3 (Flt-3), RET | liver cancer<br>kidney cancer |
| sunitinib | 2006 | VEGFR, PDFGR, c-Kit, Flt-3, RET, colony stimulating factor 1 receptor (CSF-1R) | kidney cancer<br>gastrointestinal stromal tumors (GIST)<br>pancreatic neuroendocrine tumors |
| dasatinib | 2006 | BCR/ABL, Src, c-Kit, ephrin receptors | chronic cyelogenous leukemia (Philadelphia chromosome positive) |
| lapatinib | 2007 | ErbB1, ErbB2, epidermal growth factor receptor (EGFR) | hormone-positive and human epidermal growth factor receptor 2 (HER2) positive advanced breast cancer |
| pazopanib | 2009 | VEGFR, PDGFR, c-Kit | advanced renal cell carcinoma<br>advanced soft tissue sarcoma |
| vandetanib | 2011 | EGFR, VEGFR, RET, BRK, TIE2, Src, ephrin receptors | unresectable, locally advanced, or metastatic medullary thyroid cancer. |
| crizotinib | 2011 | ALK, Ros-1, hepatocyte growth factor receptor (HGFR) | locally advanced or metastatic nonsmall cell lung cancer (anaplastic lymphoma kinase-positive) |
| axitinib | 2012 | VEGFR, PDGFR, c-Kit | advanced renal cell carcinoma after failure of prior systemic therapy |
| bosutinib | 2012 | BCR/ABL, Src | chronic myelogenous leukemia (Philadelphia chromosome positive) |
| regorafenib | 2012 | VEGFR, PDGFR, fibroblast growth factor receptor (FGFR), TIE-2, B-Raf, c-Kit, RET | advanced gastrointestinal stromal tumors (GIST)<br>previously treated metastatic colorectal cancer |
| cabozantinib | 2012 | RET, MET, VEGFR, c-Kit, Flt-3 | progressive, metastatic medullary thyroid cancer |
| ponatinib | 2012 | BCR/ABL, c-Kit, RET, Flt-3 | chronic, accelerated or blast-phase chronic myeloid leukemia |

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# Opportunities for Repurposing and for the Discovery of New Drugs

- "Drug repurposing" or "repositioning" refers to the use of an old drug for a new indication.
- Polypharmacological drugs can be repurposed based on their "off-target" activities.
- Thalidomide is an example of repurposing.
- Polypharmacology-based repurposing also led to the discovery of several important drug classes in the early years of drug discovery. (e.g. Antihistamine)

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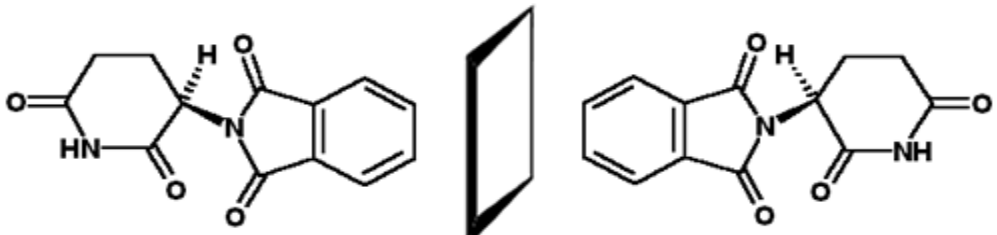
# Repurposing: Examples




R-Thalidomide
(sleep-inducing)

S-Thalidomide
(teratogenic)

- **Indication:** morning sickness
- **ADR:** birth defects

>

- **Indication:** treatment of erythema nodosum leprosum

>

- **Indication:** multiple myeloma

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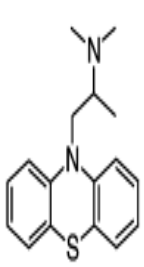
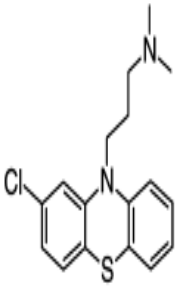
# Repurposing: Examples

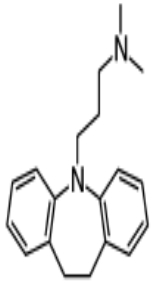
- Promethazine was the starting point to develop antipsychotic drugs which led eventually to the discovery of tricyclic antidepressants.
- Although the discovered drugs retained antihistamine activity, they showed an increase in potency toward their specific targets.



promethazine
~ 1949
antihistamine



chlorpromazine
1952
antipsychotic



imipramine
1955
antidepressant

| Receptor | Target for ... | $IC_{50}$ (radioligand binding, μM) | | |
|---|---|---|---|---|
| $H_1$ | allergy | 0.0054 | 0.012 | 0.027 |
| $D_2$ | schizophrenia | 0.1 | 0.021 | 0.41 |
| 5-$HT_{2A}$ | schizophrenia | 0.023 | 0.0034 | 0.22 |
| SERT | depression | 7.59 | 0.12 | 0.0035 |

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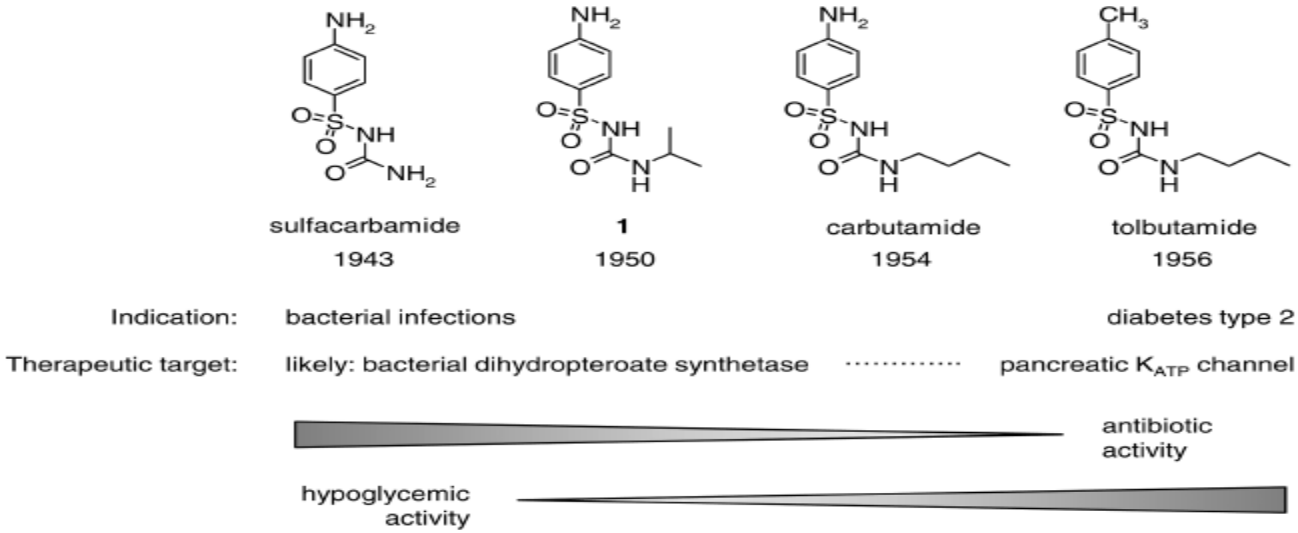
# Repurposing: Examples




- Sulfacarbamide was an important sulfonamide antibacterial after WWII but suffered from a short halflife.
- Loranil (1) was a follow-up compound with a longer half-life, but produced hypoglycemia.
- Carbutamide was then developed as an antibiotic and as a hypoglycemic drug for the treatment of Type-2 diabetes.
- Carbutamide was not approved in the U.S. It was therefore followed up by tolbutamide, an antidiabetic with no antibacterial activity.

# Combinations of Drugs and Pharmacophores

- Polypharmacological drug research has not been widely embraced.
- The combination of individual single-target drugs is an alternative to polypharmacological drug discovery.
- However, drug–drug interactions or poor compliance due to complex dosing regimens might be encountered.

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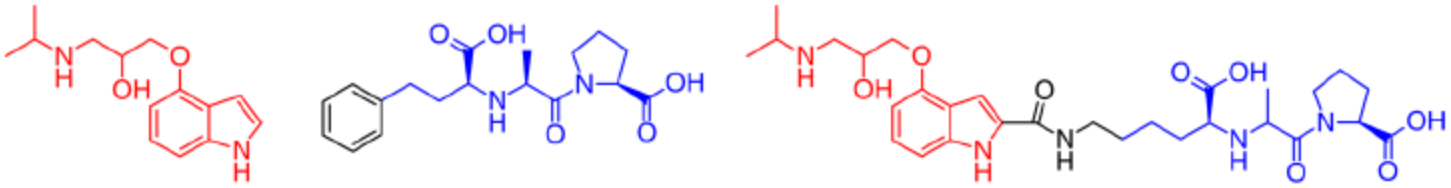
# Combinations of Drugs and Pharmacophores

- Polypharmacological leads can be designed by a combination of known pharmacophores into a single compound.

- However, this strategy leads often to a high MW and extreme lipophilicity with a little success.



pindolol
beta blocker
MW = 248

enalaprilat
ACE-inhibitor
MW = 348

**2** (BW-A575C)
dual beta blocker / ACE inhibitor
MW = 589

Example: The betablocker pindolol was connected to the angiotensin-converting enzyme (ACE) inhibitor enalaprilat to give the dual-target 2.

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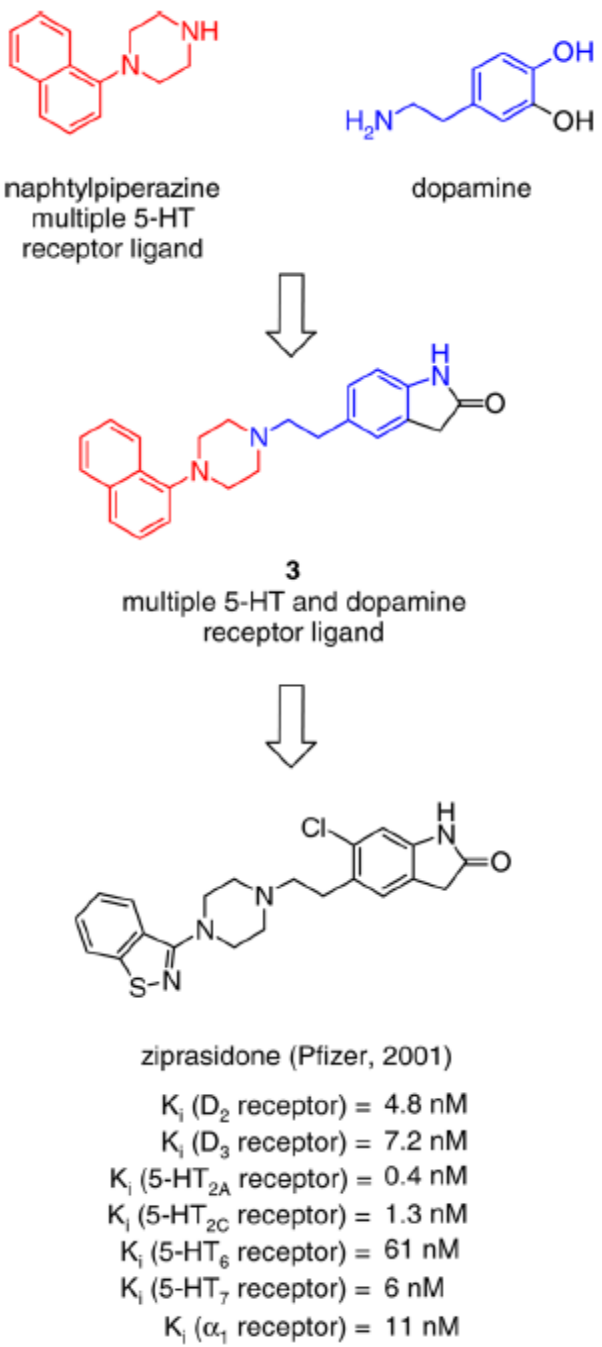
# Combinations of Drugs and Pharmacophores

- Similar pharmacophores, although, may overlap in a single molecule successfully.
- For example, naphtylpiperazine and dopamine were merged into (3).
- Further optimization resulted in ziprasidone, which was successfully developed as an antipsychotic.

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# SUMMARY

- Unintended polypharmacology must be avoided.
- Early screening of compounds against small panels of frequently hit antitargets is recommended.
- The opportunities of polypharmacological drug discovery are increasingly being appreciated.
- The gap between theoretical network concepts and practical discovery of polypharmacological drugs should be resolved.

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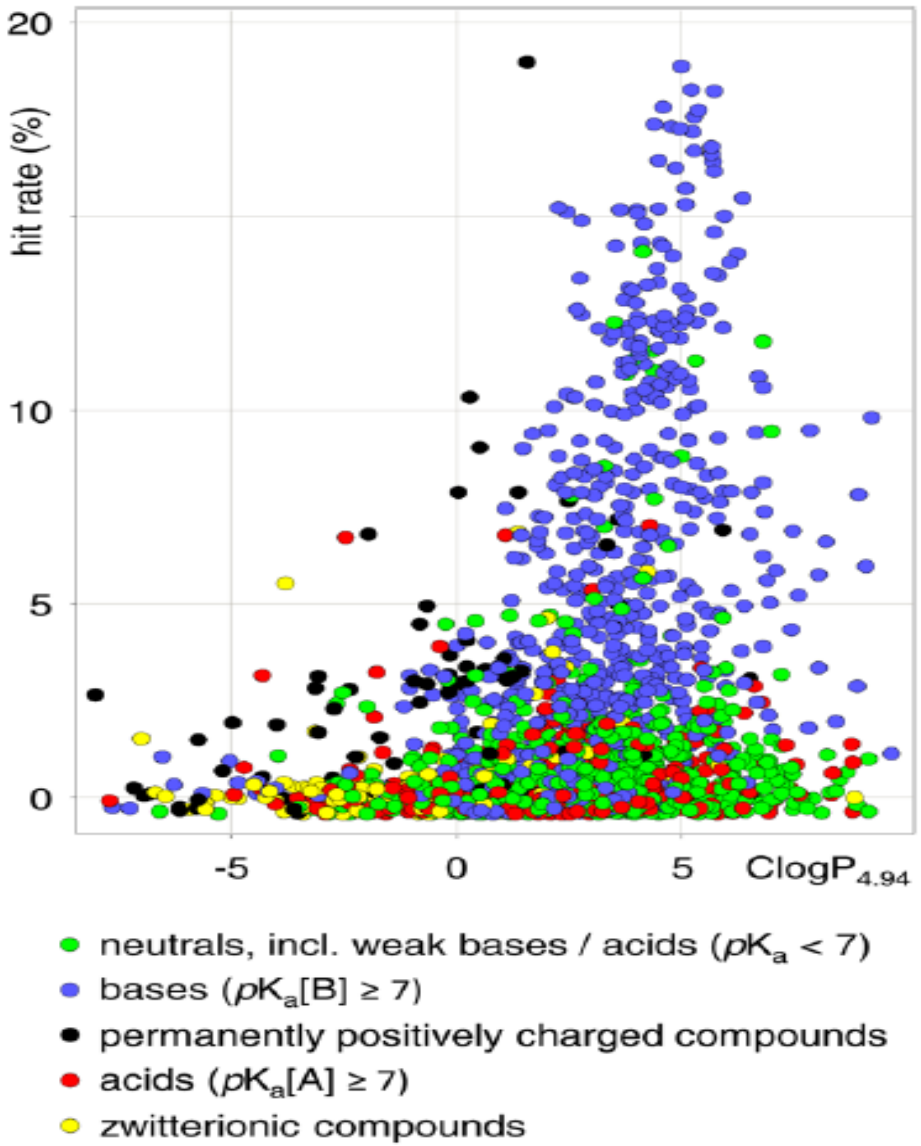
# Thank You

# Early Alerts of Potential Polypharmacology

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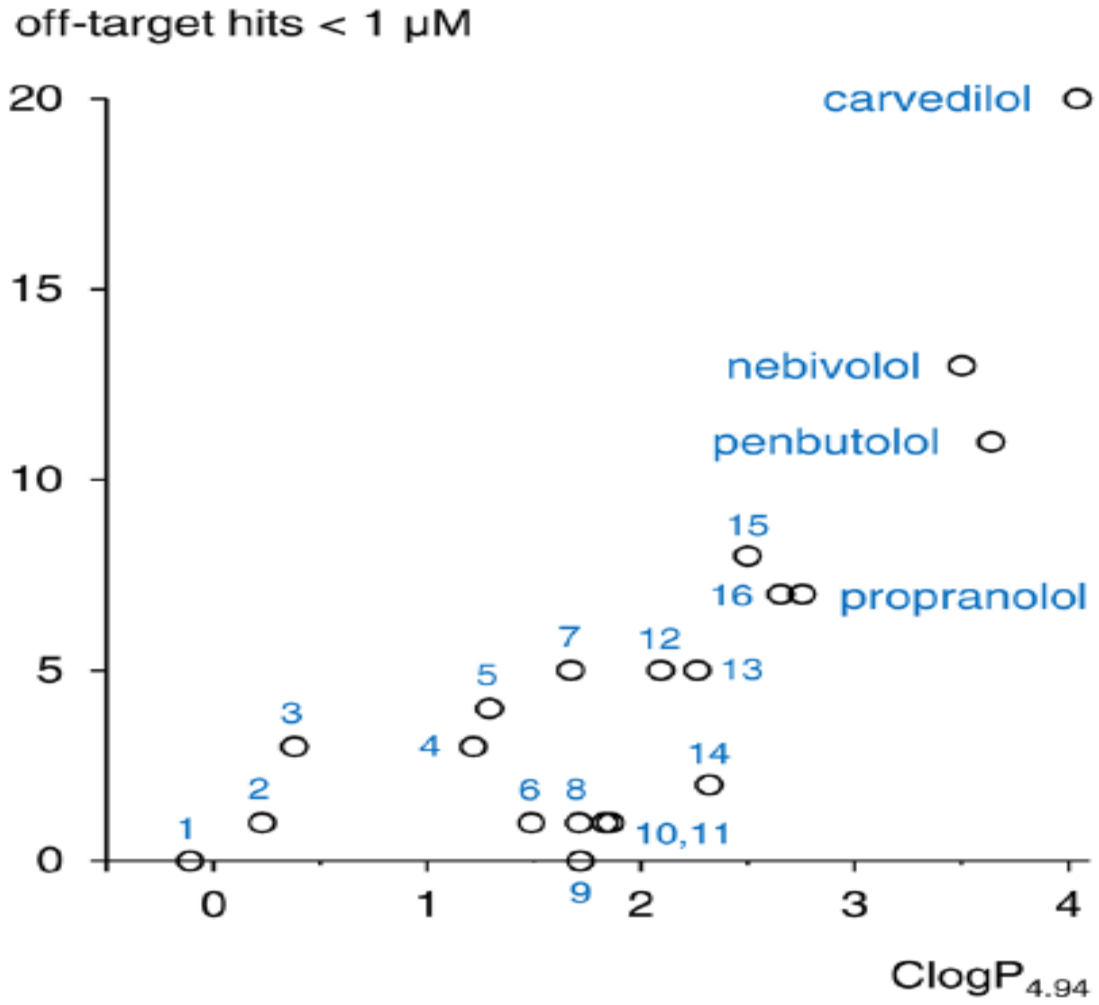
# Dependence of pharmacological promiscuity (off-target hits) on the lipophilicity of marketed beta-blockers. Lipophilic beta-blockers tend to be more promiscuous.

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