Polypharmacology

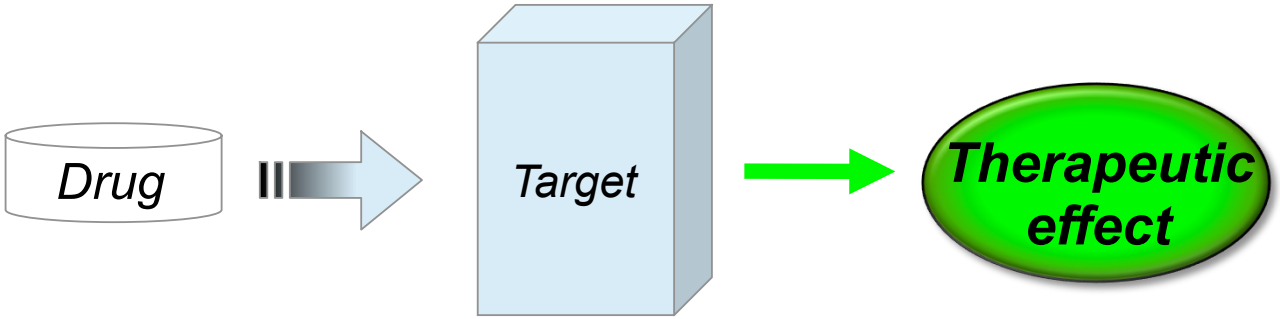
Giulio Rastelli
Molecular Modelling and Drug Design Lab
www.mmddlab.unimore.it

Dipartimento di Scienze della Vita
Università di Modena e Reggio Emilia
giulio.rastelli@unimore.it

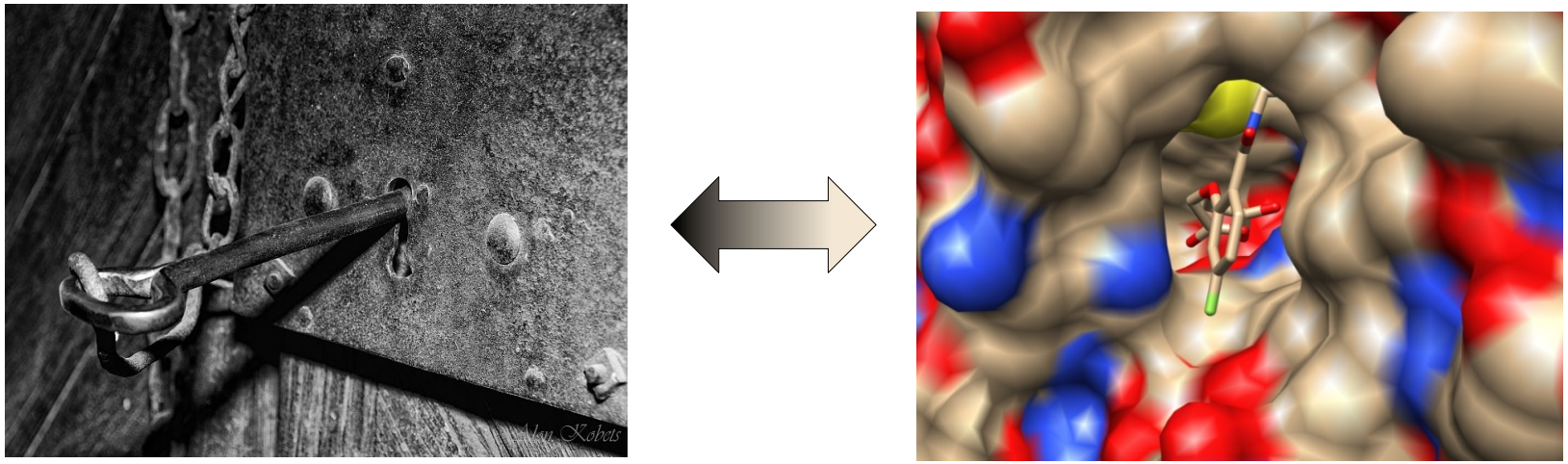
Magic Bullets in Targeted Drug Discovery

One drug – One target principle

Design of drugs able to **selectively** interact with the therapeutic target



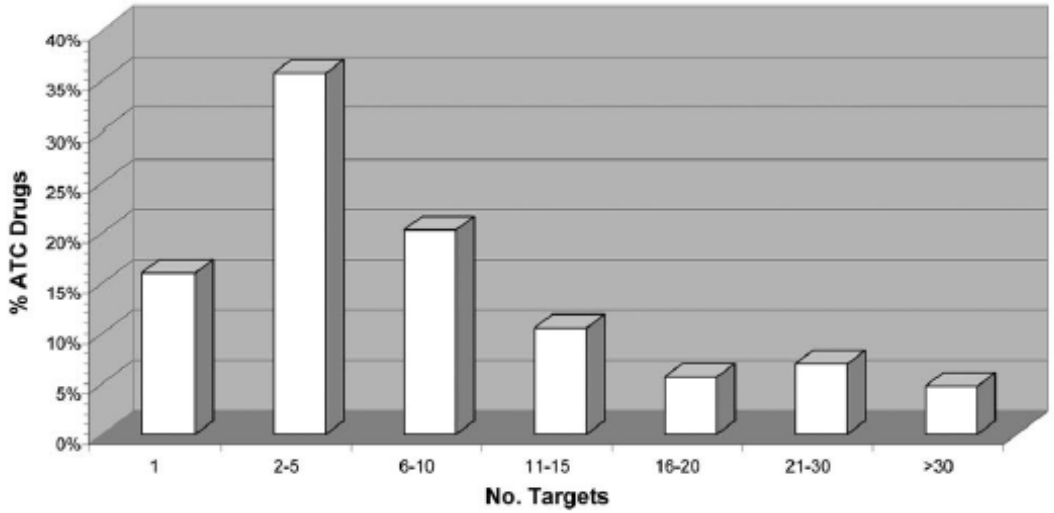
Direct cause-effect relationship



Target/compound profiling

Selective drugs are more the exception rather than the rule.

Most therapeutically effective molecules tend to interact with multiple proteins



Our perception of **drug selectivity** has been for years strongly biased by our limited knowledge of a drug's **complete target profile**.

Jalencas et al *MedChemComm* 2013, 4, 80

Polypharmacology

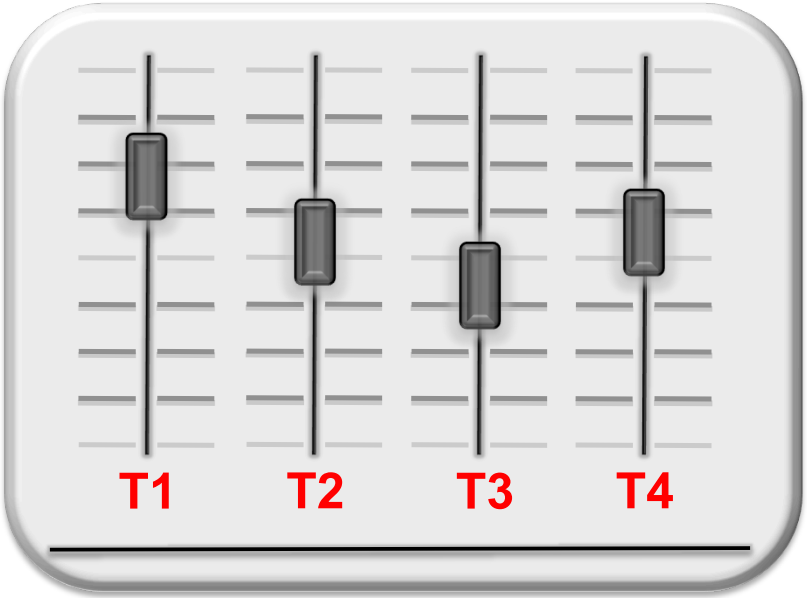
Molecules with high affinity and selectivity for ONE target

Molecules able to interact with MULTIPLE targets

POLYPHARMACOLOGY

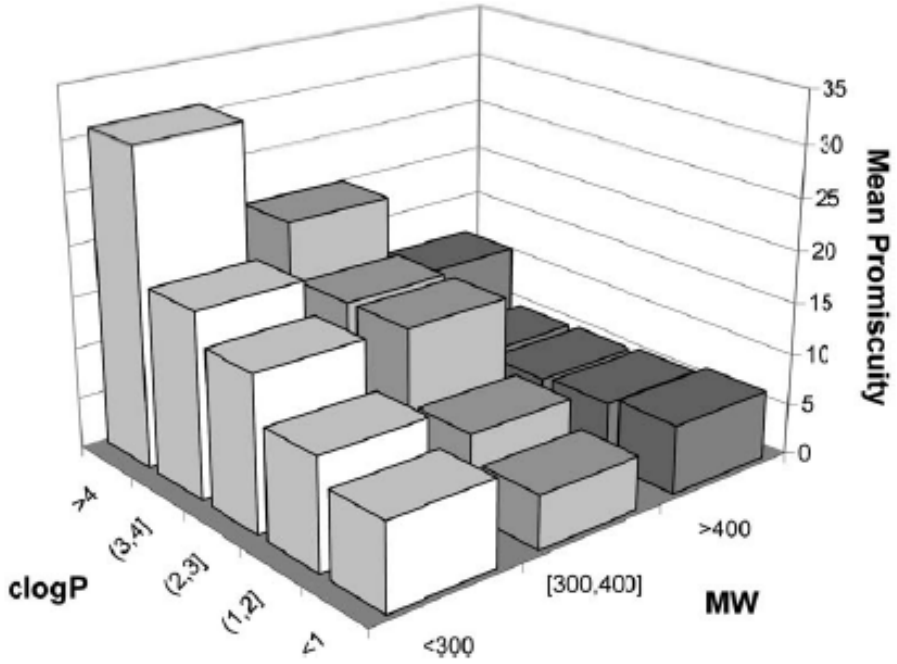
MULTI-TARGET DRUG DISCOVERY

- ❑ **Which target combinations?**
- ❑ **What level of activity?**
- ❑ **How can we design them?**



Chemical sources of polypharmacology

- Increasing **molecular complexity** will tend to limit drug polypharmacology
- Inverse correlation between **MW** and polypharmacology
- Most promiscuous drugs tend to be **highly hydrophobic** (logP ≥ 3)



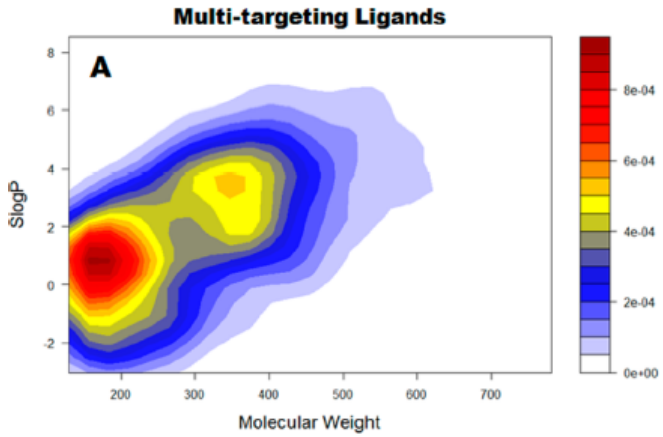
Set of 802 drugs with activity annotations

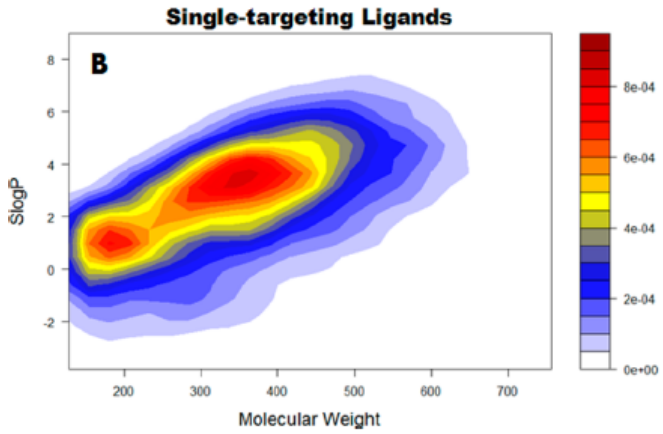
Jalencas and Mestres, *MedChemComm* 2013,4,80

Multi-target ligands and MW

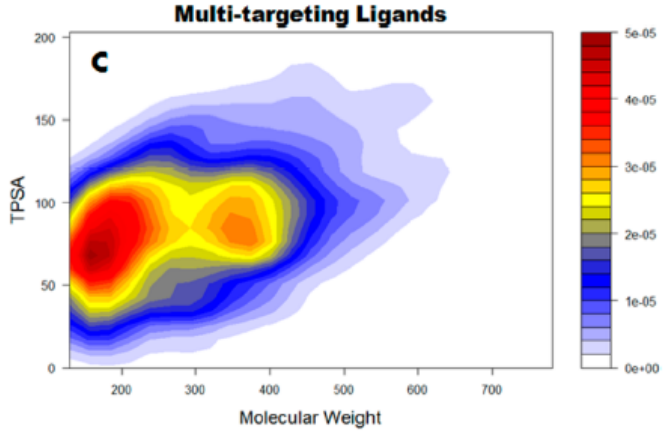
Analysis of ligands in the PDB

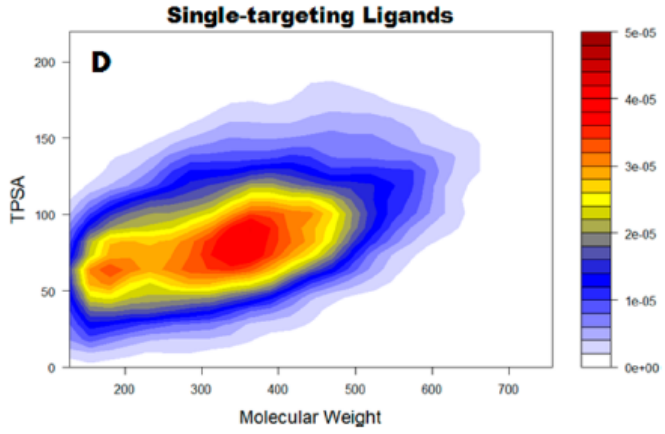
Multi-target ligands are on average **smaller** than single-target ligands





LogP



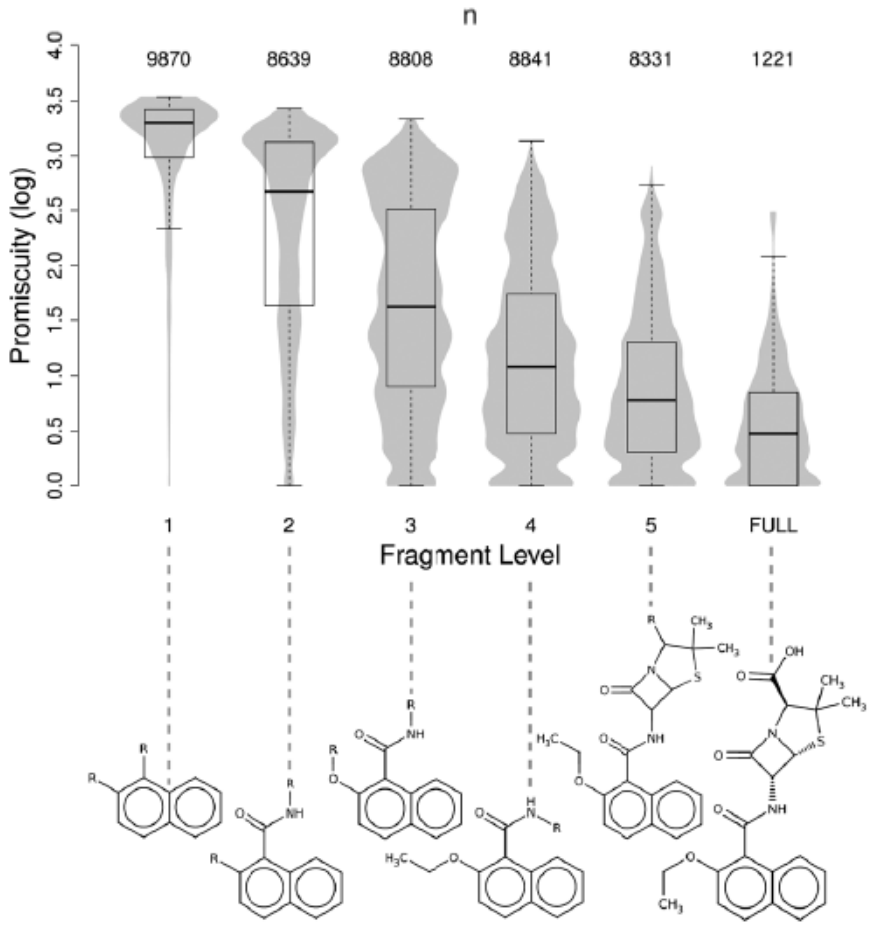


Polar Surface Area

Reddy et al, J. Chem. Inf. Model. 2014, 54, 2536.

Chemical sources of polypharmacology

- **Many drugs described by only a limited number of scaffolds**
- **"Privileged" structural motifs** may enhance the ability of small molecules to bind multiple targets
- **Fragment-based drug design**
- **Frequent "hitters"**
- **Target promiscuity value**

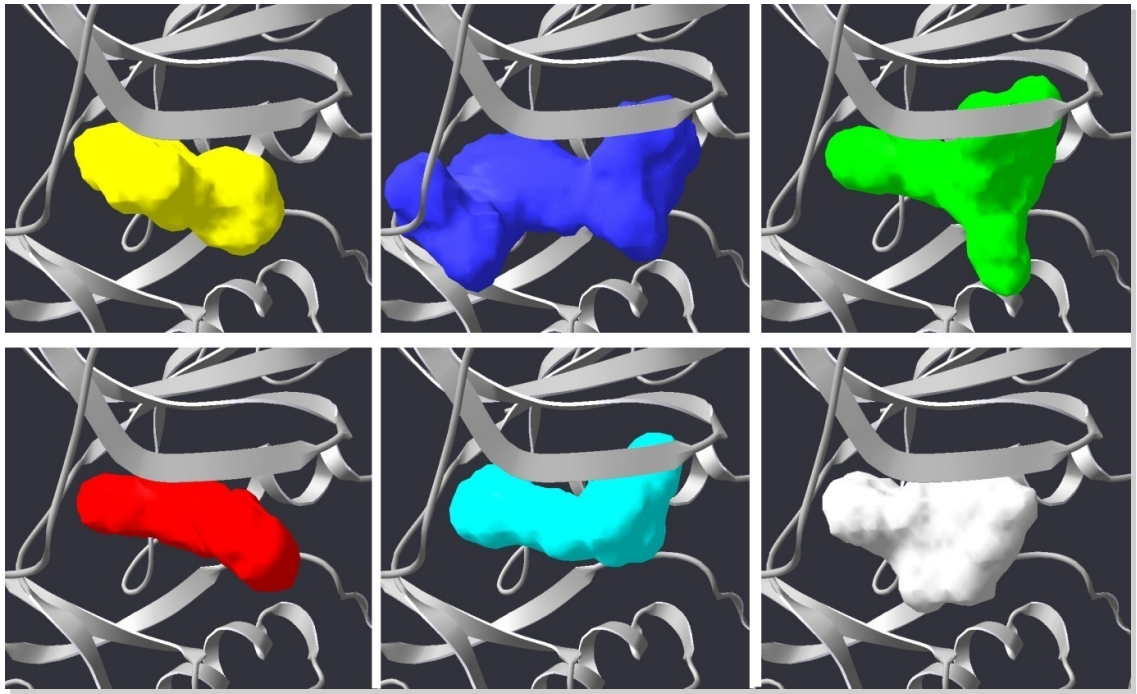


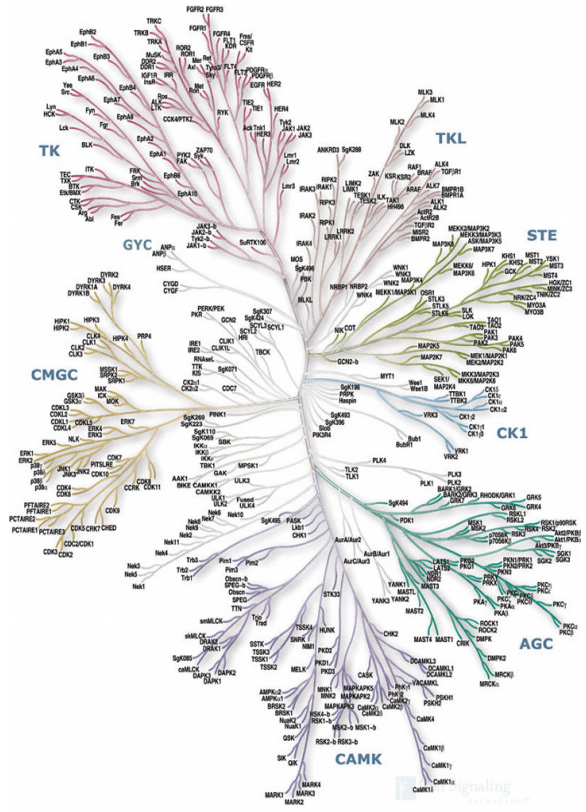
*By **fragmenting** a set of > 350.000 compounds with annotated known activities into fragments of different "**levels**", a target promiscuity value is assigned by counting the # of targets for which molecules that contained these fragments had affinity >10 μM*

Biological sources of polypharmacology

- **Sequence identity (target phylogeny) and/or binding site similarity are major causes of drug polypharmacology.**

- **Major examples of this are protein kinases, GPCRs, nuclear receptors, cytochrome P450s.**





Polypharmacology in GPCRs

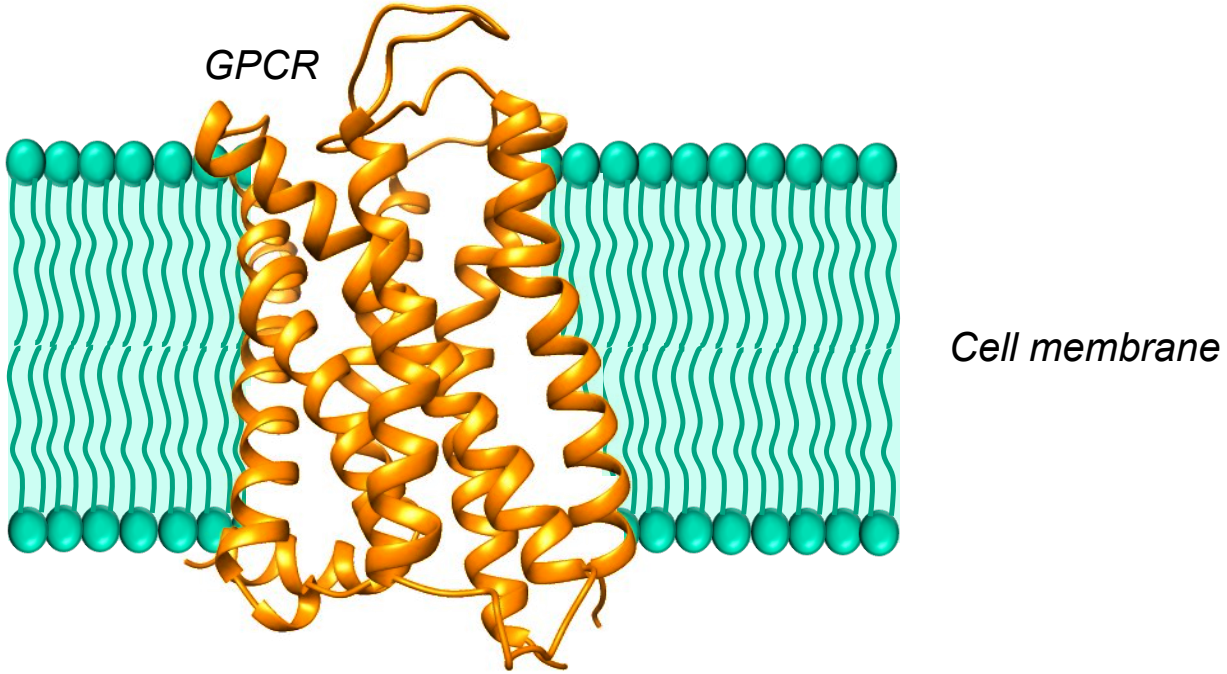
Between 30% and 40% of marketed drugs target GPCRs

Involved in several complex diseases

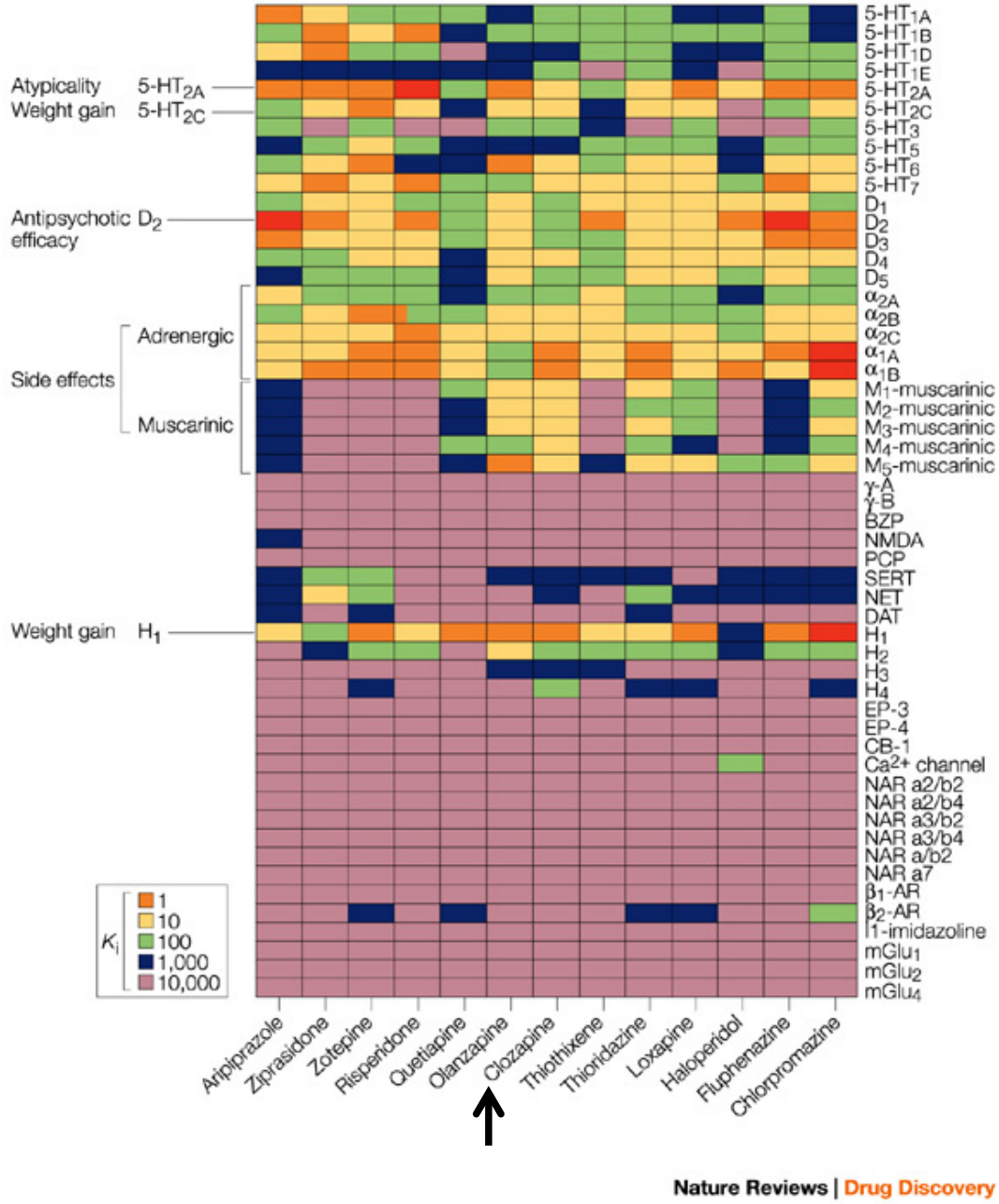
More than 800 GPCRs are expressed in human

Recent progress in GPCRs X-ray crystallography

Drugs targeting these receptors are directed towards only few GPCR members



Selectivity profiling of GPCR ligands



Most of the presently approved antipsychotic drugs have a <u>complex pharmacology</u>, with appreciable affinity for a variety of GPCRs

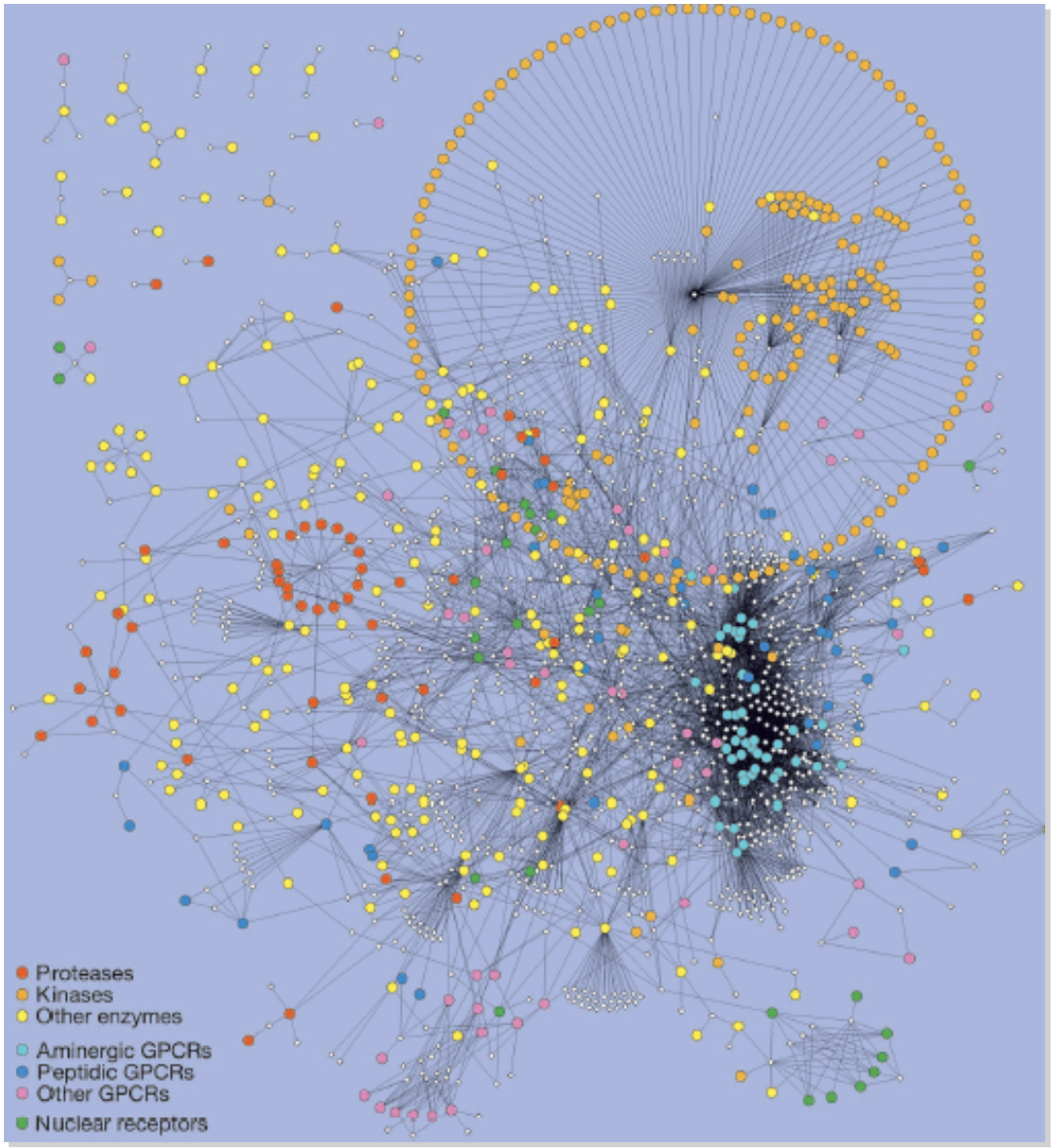
SIDE EFFECTS

TOXICITY

Drug–Target networks

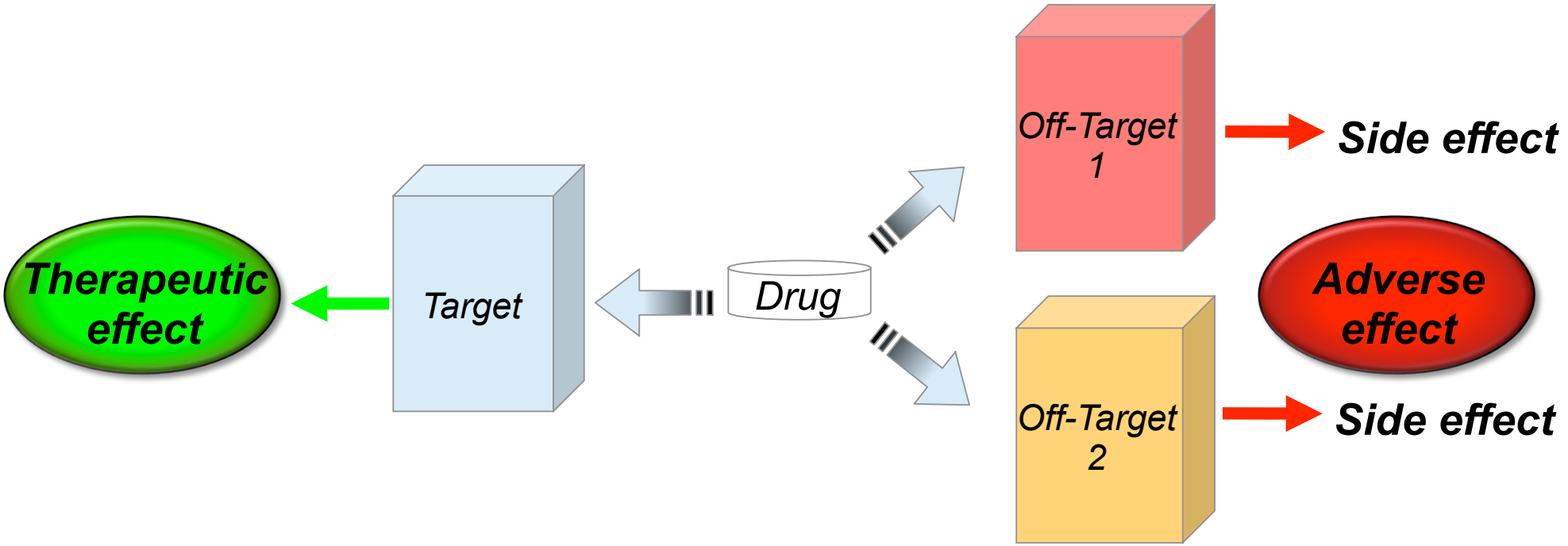
D-T networks generated by using known associations between drugs and their target proteins.

A **link** is placed between a **drug node** and a **target node** if the protein is a known target of that drug.



Off-target effects

Drug **side effects** may be mediated by interaction with targets which are not intended to be perturbed by the drug (**off-target** or **antitarget**)



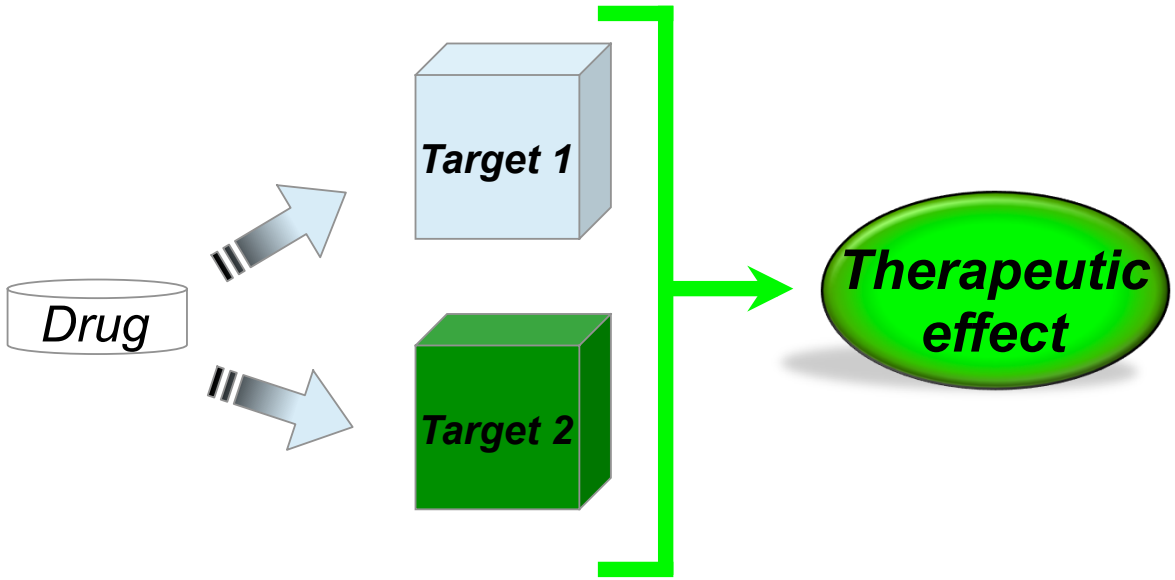
- **Biological assays on potential off-targets**
- **Develop predictive models**

Therapeutic and Adverse Polypharmacology

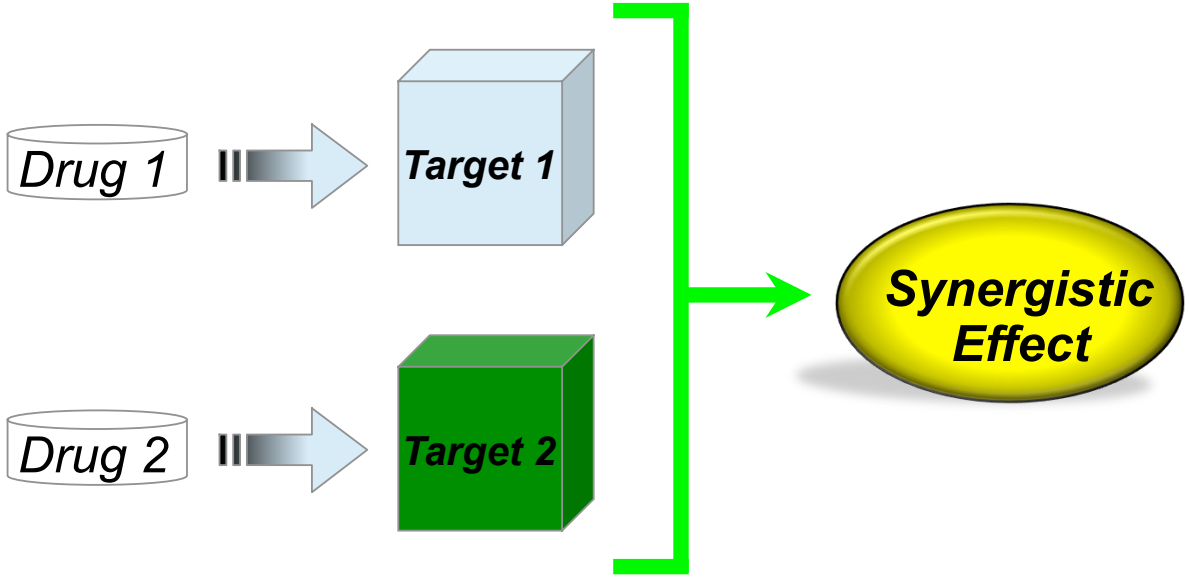
Therapeutic polypharmacology	Type of polypharmacology	Adverse polypharmacology
The treatment of **multigenic, complex diseases** based on the analysis of the **signaling networks of the disease state** and the systems-level effects of **modulating multiple protein targets** with one or more drug.	**Description**	The adverse, physiological effect caused by drug binding to protein **targets other than the therapeutic target** or binding to the therapeutic target in non-target tissue.
Enables **drug design** based on systems-level knowledge: involves the modulation of multiple nodes in one or more regulatory networks.	**Analysis of D-T networks**	Enables an understanding or prediction of the adverse event, including the effects of an **interaction with a non-target regulatory network** or signal propagation within the regulatory network that lead to an adverse phenotype.

Polypharmacology and Combination Therapy

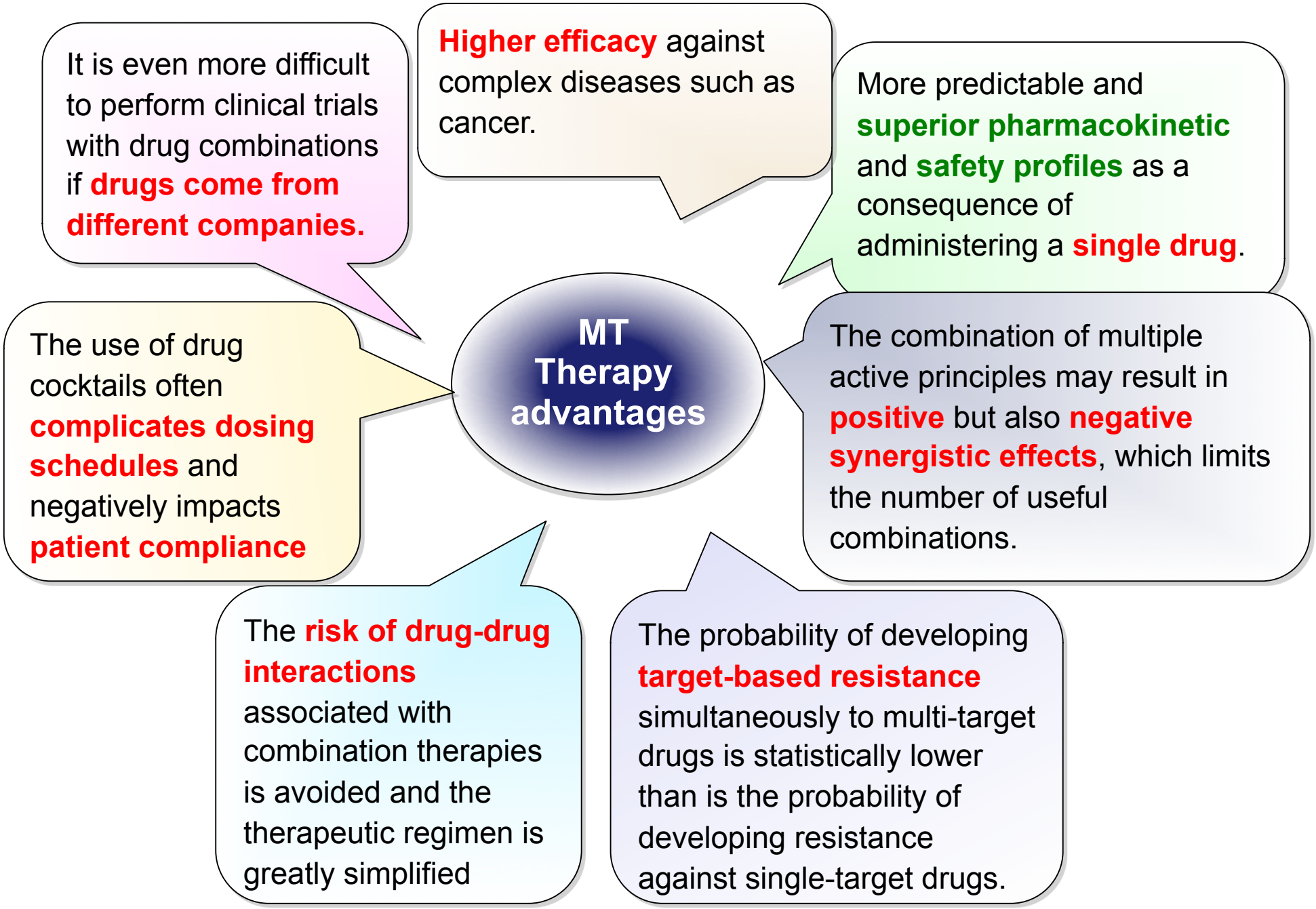
POLYPHARMACOLOGY (MULTI-TARGET THERAPY)



COMBINATION THERAPY

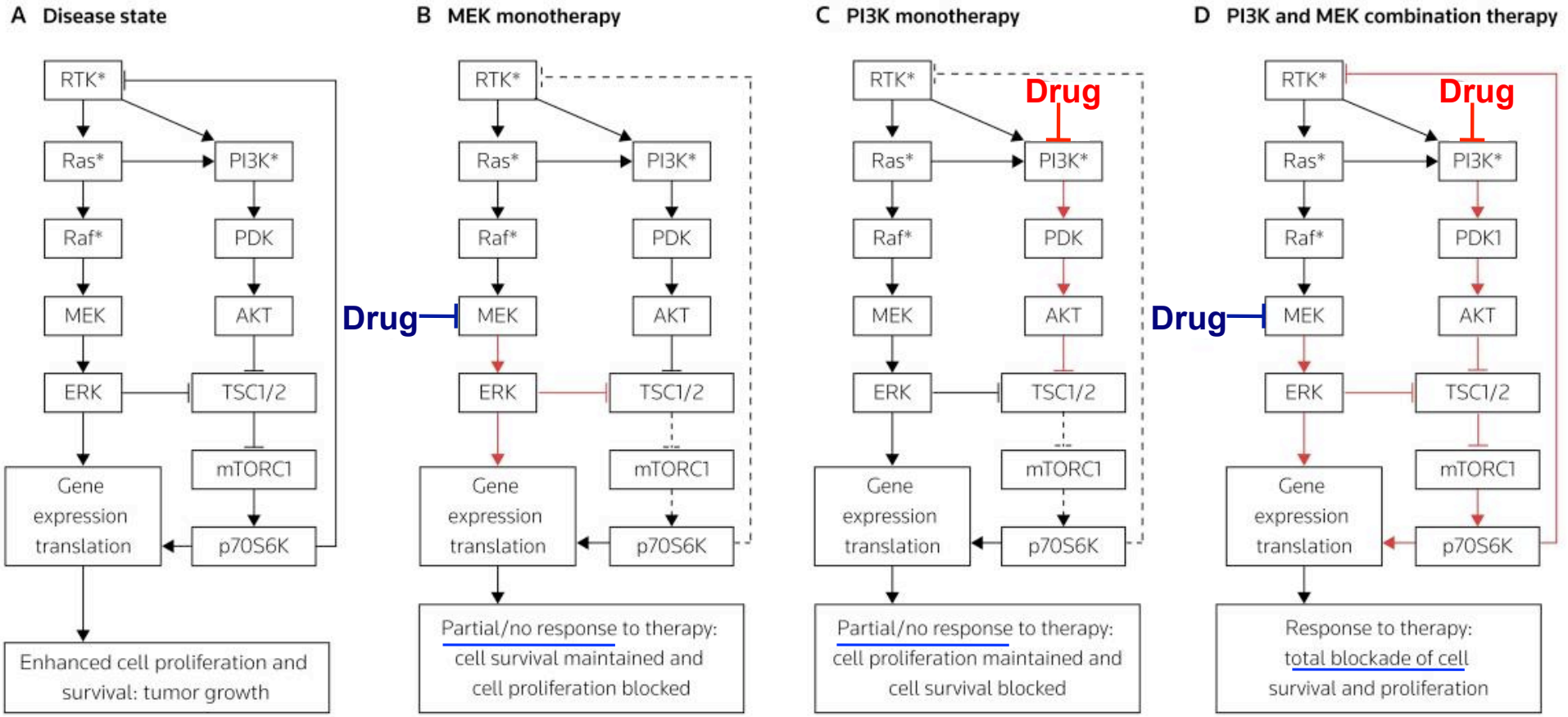


Potential advantages of MT vs single or CT

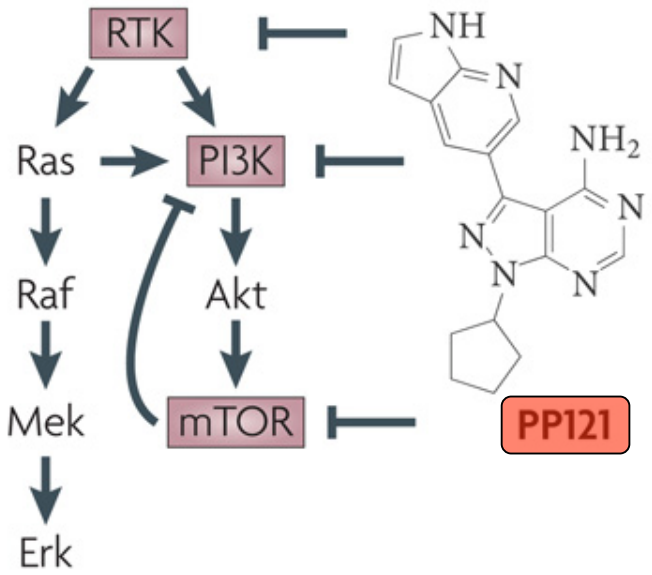


Combination therapy in kinases

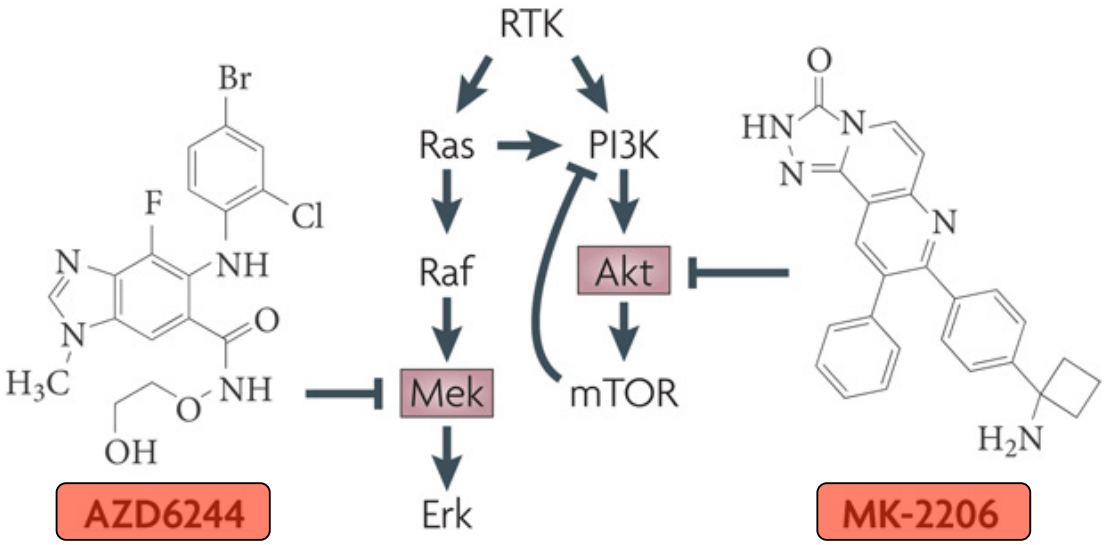
Mutations or aberrant expression of **RTK, MEK and PI3K** pathways in cancer. **Compensatory mechanisms** cause a limited or null response to monotherapies. **Combination therapies can overcome these compensatory mechanisms.**



Strategies for polypharmacological kinase inhibition



mTOR activates a **negative feedback loop** that inhibits **PI3K**.The dual inhibition of mTOR and PI3K may be more effective.
The **single agent** **PP121** was shown to target both tyrosine kinases (VEGFR, BCR–ABL and RET), PI3K and mTOR. This dual inhibition disables the negative feedback loop.



The **combination** of the **MEK** inhibitor **AZD6244** and the **Akt** inhibitor **MK-2206** results in the inhibition of both the MAPK and PI3K pathways.

Knight, Shokat et al. *Nature Reviews Cancer* **2010**, 10, 130-137.

Target Fishing

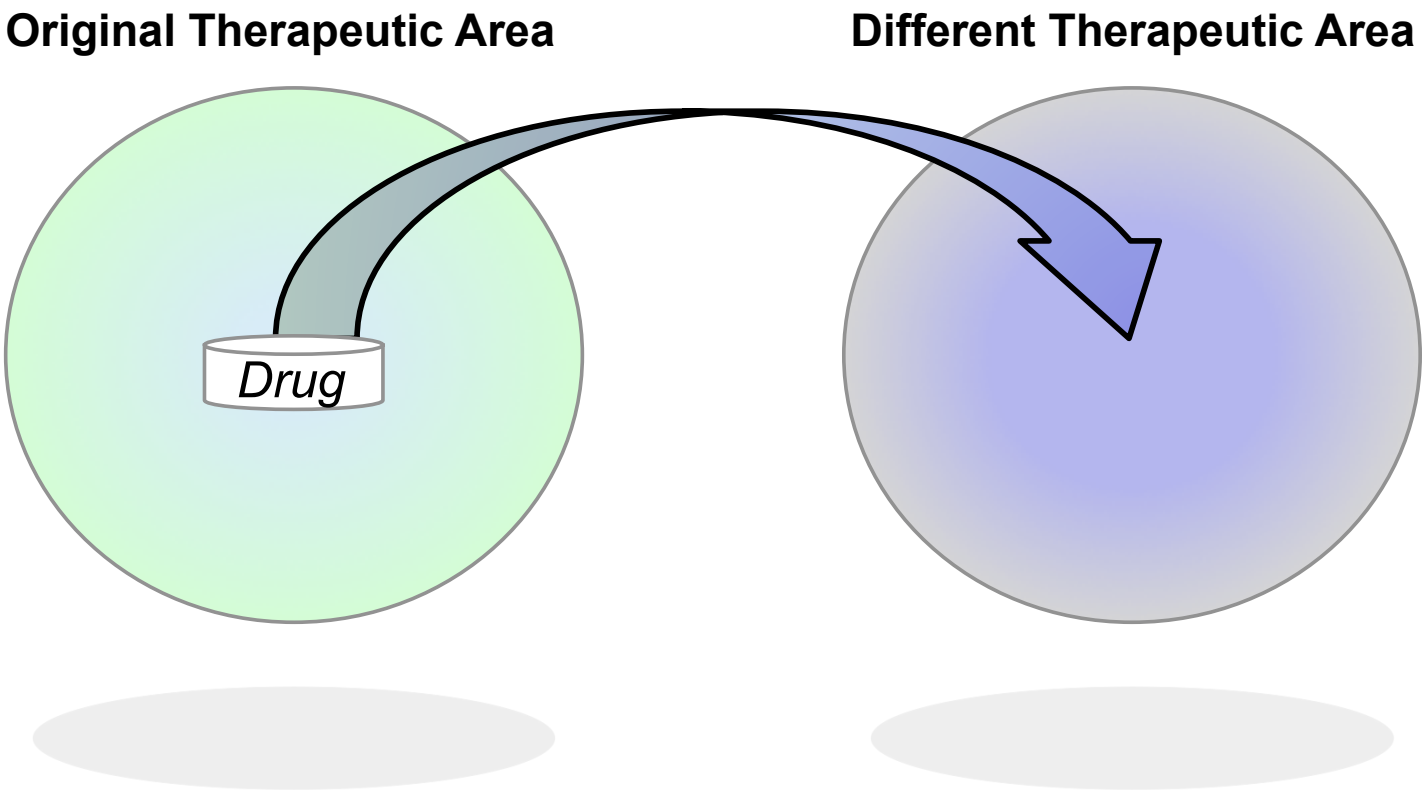
Identification of putative new targets for known ligands.

Computational approaches:

- **Molecular docking**
- **Similarity searching**
- **Pharmacophore modelling**

Drug Repurposing (Repositioning)

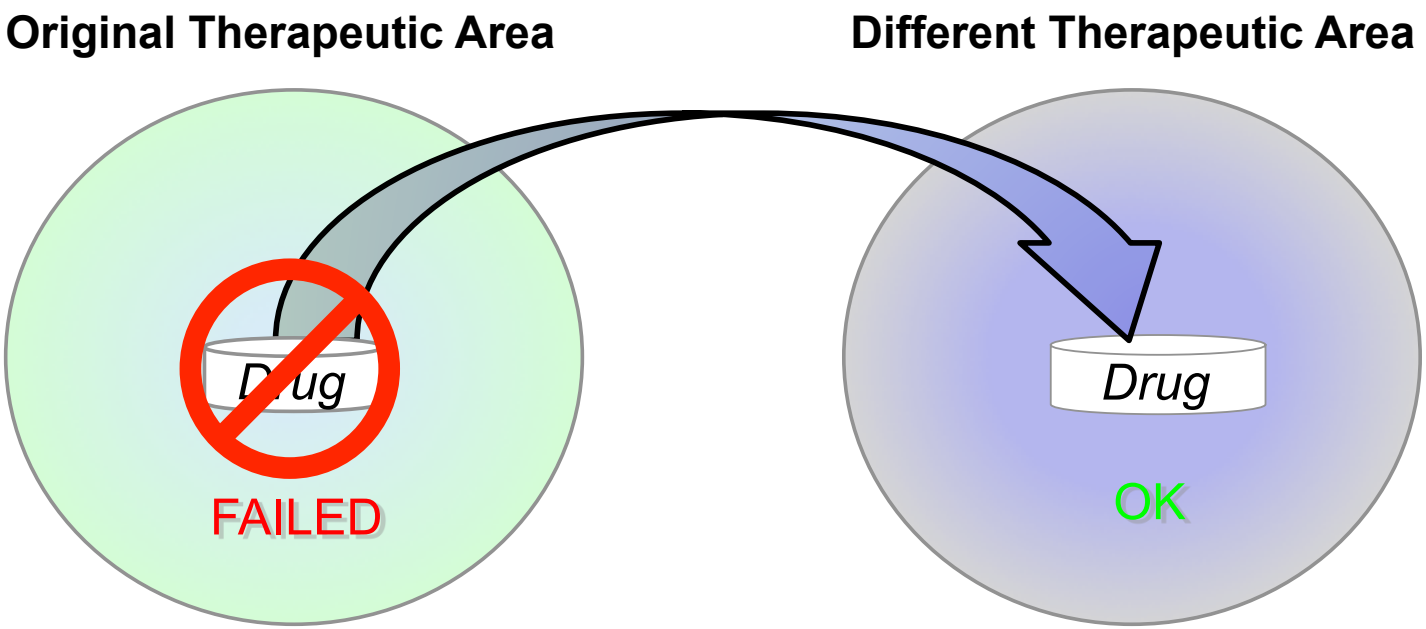
Drug rediscovery



Drugs that already satisfy basic toxicity, ADME and related criteria.

Drug repurposing promises to deliver significant value at reduced cost and in dramatically shorter time frames than is normally the case for the drug development process.

Drug Rescue



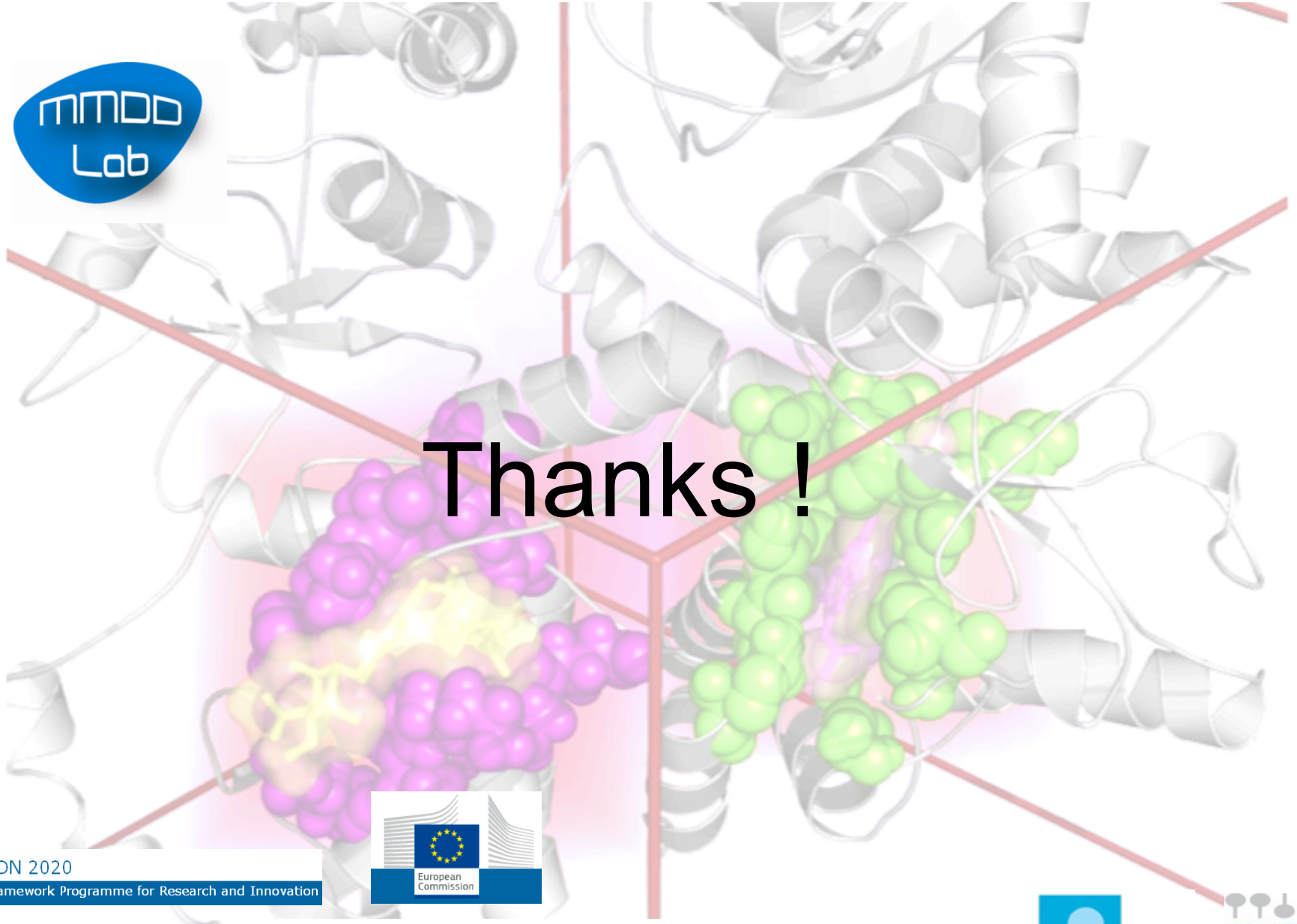
A drug that was not finally approved in a certain therapeutic area due to side effects may be “rescued” and applied in a new therapeutic area where the side effects may be acceptable or the dose needed is lower.

Polypharmacology: Next challenges

- ❑ Identify “ad hoc” combinations of targets
- ❑ Improve existing, or devise new methods for multi-target drug design
- ❑ Perform chemical optimization against multi-dimensional target profiles

Reading

1) Polypharmacology rescored: protein ligand interaction profiles for remote binding site similarity assessment. *Progr Biophys Mol Biol* 2014, 116, 174-186
2) Targeting the cancer kinome through polypharmacology. *Nat Rev Cancer* 2010, 10, 130-137
3) The efficency of multi-target drugs: the network approach might help drug design. *TRENDS Pharmacol Sci* 2005, 26, 178-182.
4) Drug promiscuity in PDB: Protein binding site similarity is key. *Plos one* 2013, 8, e65894
5) Systems approaches to polypharmacology and drug discovery. *Curr Opin Drug Discov Devel* 2010, 13, 297-309.
6) Predicting new molecular targets for known drugs. *Nature* 2009, 462, 175-181
7) Magic shotguns versus magic bullets:selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* 2004, 3, 353-359.
8) Structure-based approaches to target fishing and ligand profiling. *Mol. Inf*. 2010, 29, 176-187
9) Computational studies to predict or explain G protein coupled receptor polypharmacology. *TRENDS Pharmacol Sci* 2014, 35, 658-663
10) On the origins of drug polypharmacology. *MedChemComm* 2013, 4, 80-87
11) Polypharmacology: challenges and oppotunities in drug discovery. *J Med Chem* 2014, 57, 7874-7887
12) Computational polypharmacology comes of age. *Front Pharmacol* 2015, 6, 157
13) Design of multitarget activity landscapes that capture hierarchical activity cliff distributions. *J Chem Inf Model* 2011, 51, 258-266
14) Intifying the macromolecular targets of de novo-designed chemical entities through self-organizing map consensus. *PNAS* 2014, 111, 4067-4072
15) Compound promiscuity: what can we learn from current data*? Drug Discov Today* 2013, 18, 644-650
16) In Silico methods to address polypharmacology: current status, applications and future perspectives. *Drug Discov Today* 2016, 21, 288–298



Thanks !

HORIZON 2020
The EU Framework Programme for Research and Innovation

European Commission

SPINNER 2013
PERSONE AL FUTURO

Unione europea
Fondo sociale europeo
Investiamo nel vostro futuro

Ministero del Lavoro e delle Politiche Sociali
Direzione Generale per le Politiche per l'Orientamento e la Formazione

RegioneEmilia-Romagna
Assessorato Scuola, Formazione professionale, Università e ricerca, Lavoro

AIRC FIRC
Con la ricerca, contro il cancro.

CINECA
ISCRA