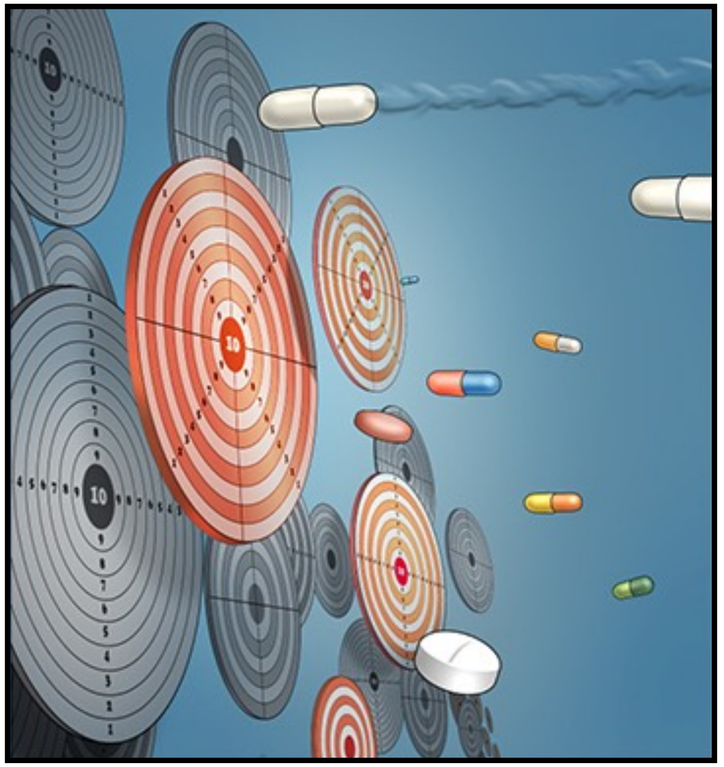
Polypharmacology: A Brief History of Drug Design Philosophy



Sean Huth

MacMillan Research Group

Group Meeting

May 6th, 2024

Outline

- What is polypharmacology?
- Historical context:
  - classical drug discovery
  - rational drug design
  - the modern era
- Case studies
  - PARP inhibitors
  - fragment-based drug design
- Lessons learned and looking forward

How do we define polypharmacology?

polypharmacology

the binding of a molecule to more than one target at therapeutically relevant concentrations

≠

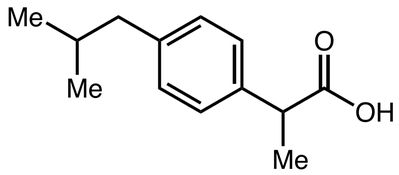
polypharmacy

the regular use of more than 5 medications at once in a single patient

What kinds of molecules qualify as exhibiting polypharmacology?

Anighoro, A.; Bajorath, J.; Rastelli, G. *J. Med. Chem.* **2014**, 57, 19, 7874.

How do we define polypharmacology?

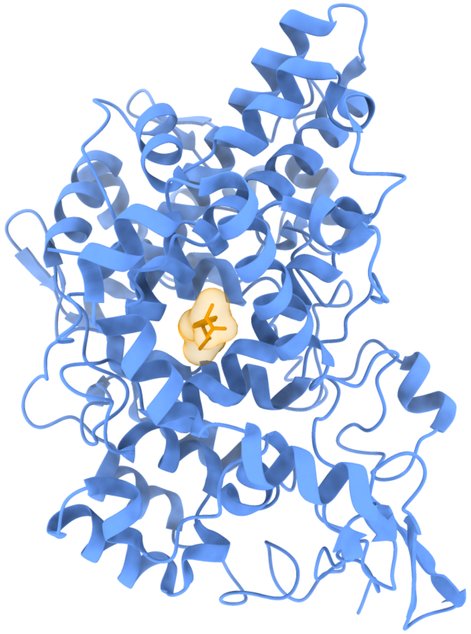


Ibuprofen

NSAID - Non-steroidal anti-inflammatory drug

COX

cyclooxygenase

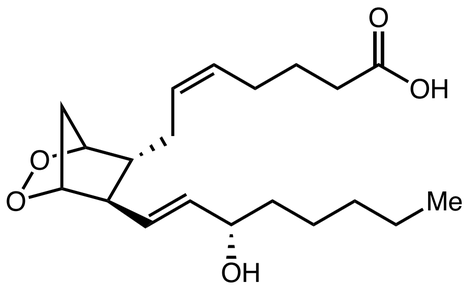


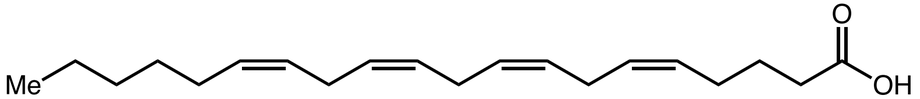
Morita, I. *Prostaglandins Other Lipid Mediat.* **2002**, 68, 165.

NSAIDs mechanism of action

Prostaglandin G2

mediator of pain/inflammation

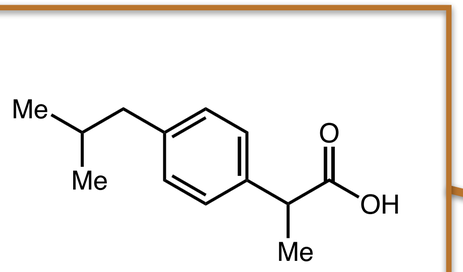




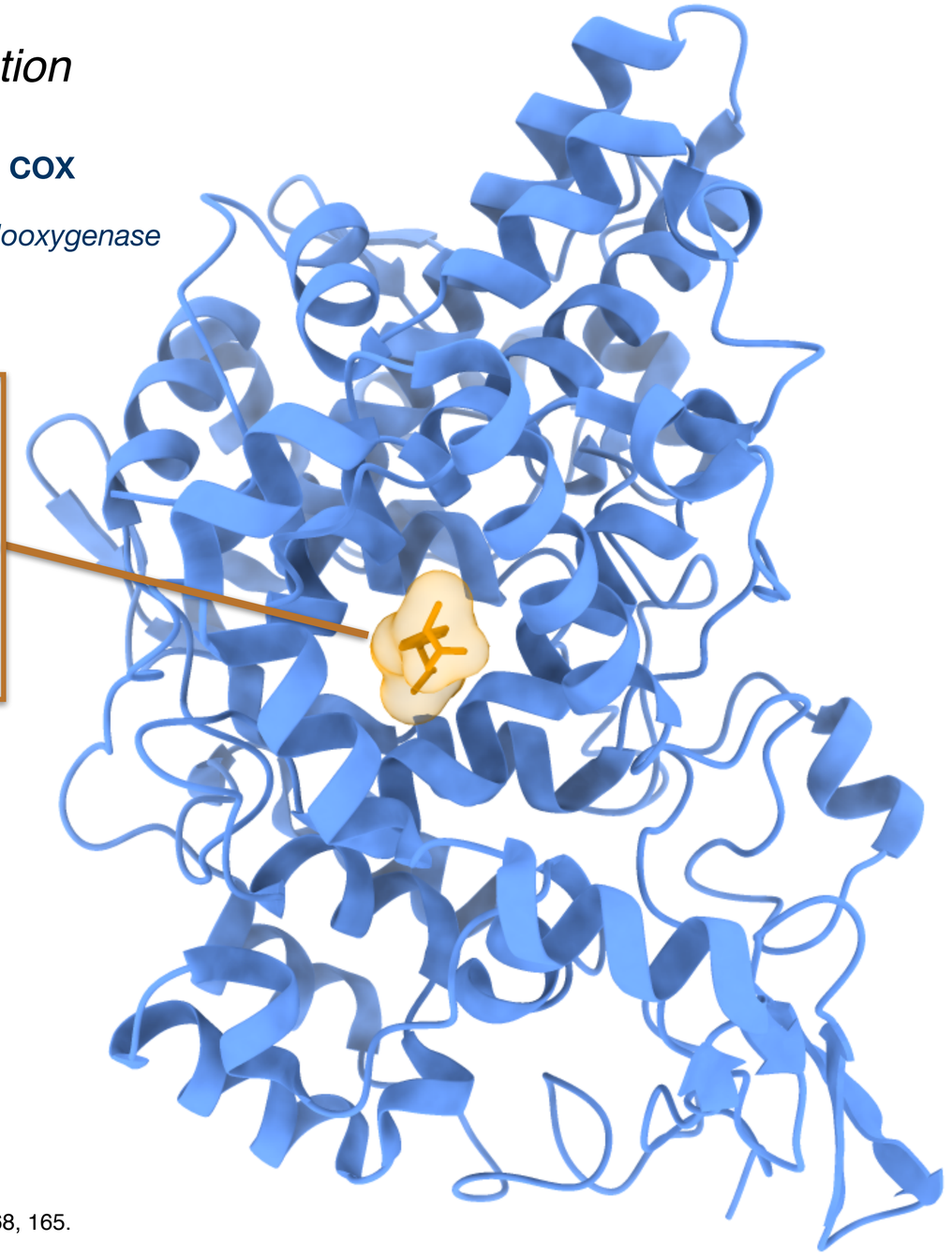
arachidonic acid

COX

cyclooxygenase



Ibuprofen



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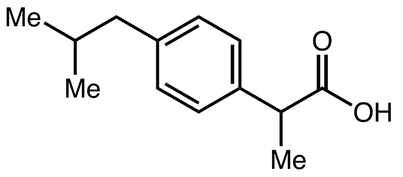
NSAIDs mechanism of action

Prostaglandin G2

mediator of pain/inflammation

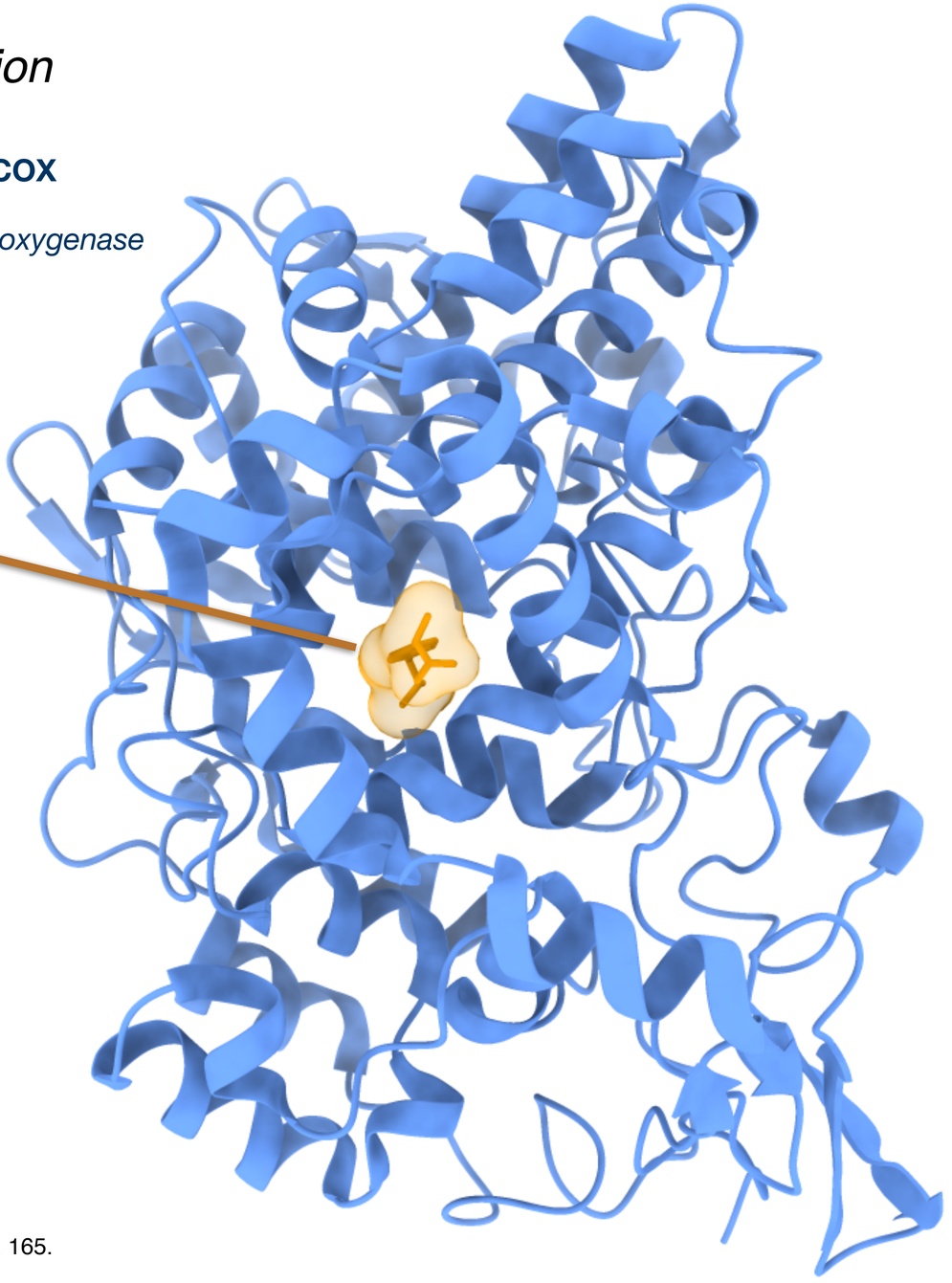
inhibition of prostaglandin synthesis

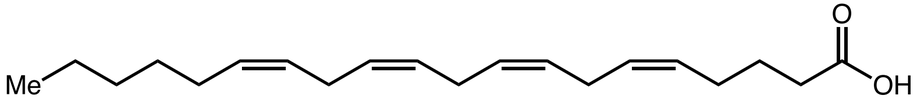


Ibuprofen

COX

cyclooxygenase





arachidonic acid

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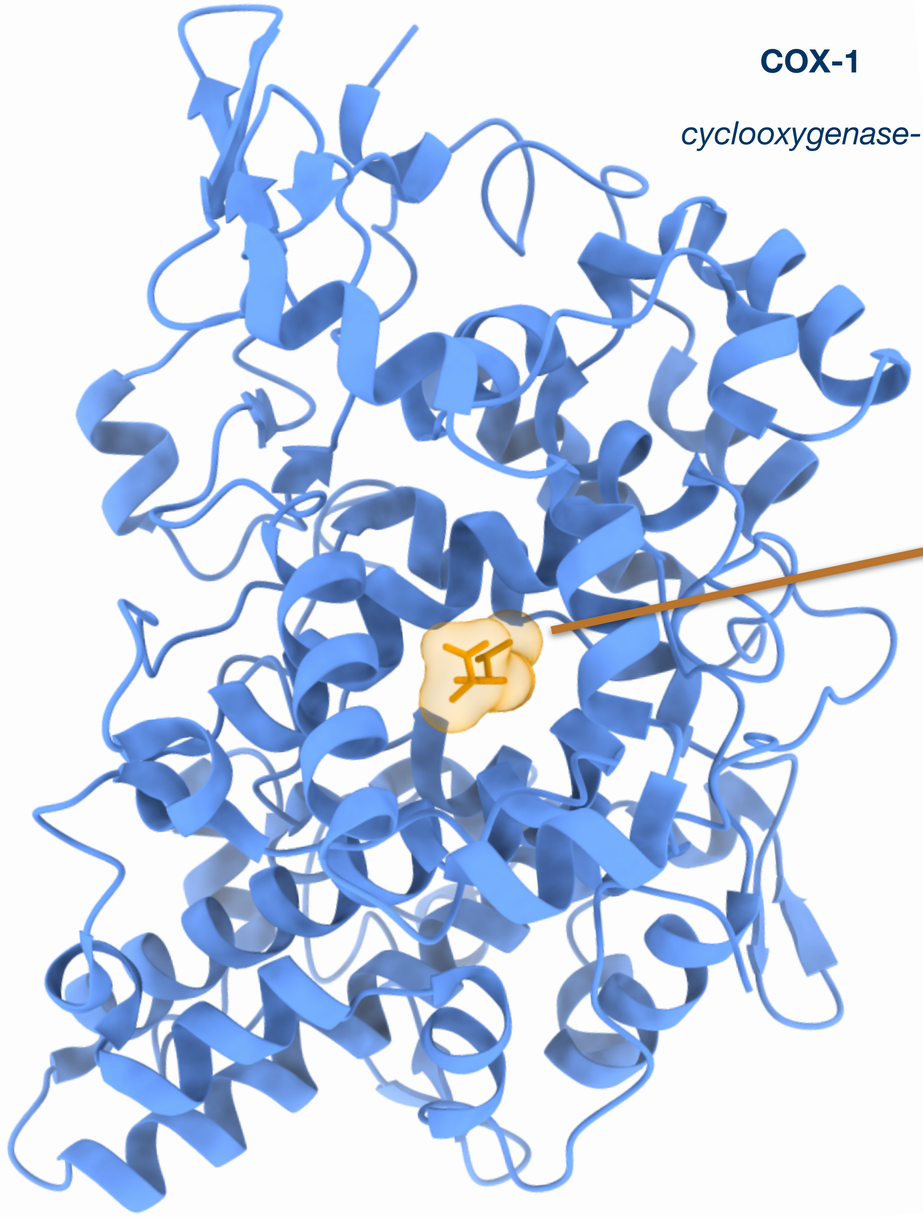
NSAIDs mechanism of action

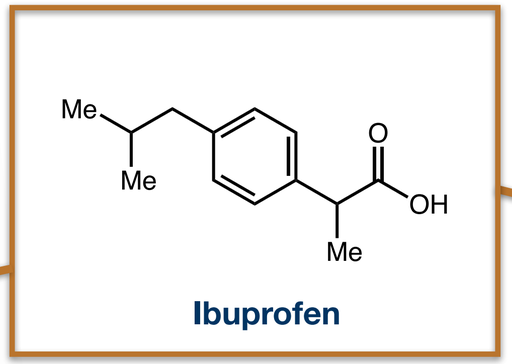
COX-1

cyclooxygenase-1

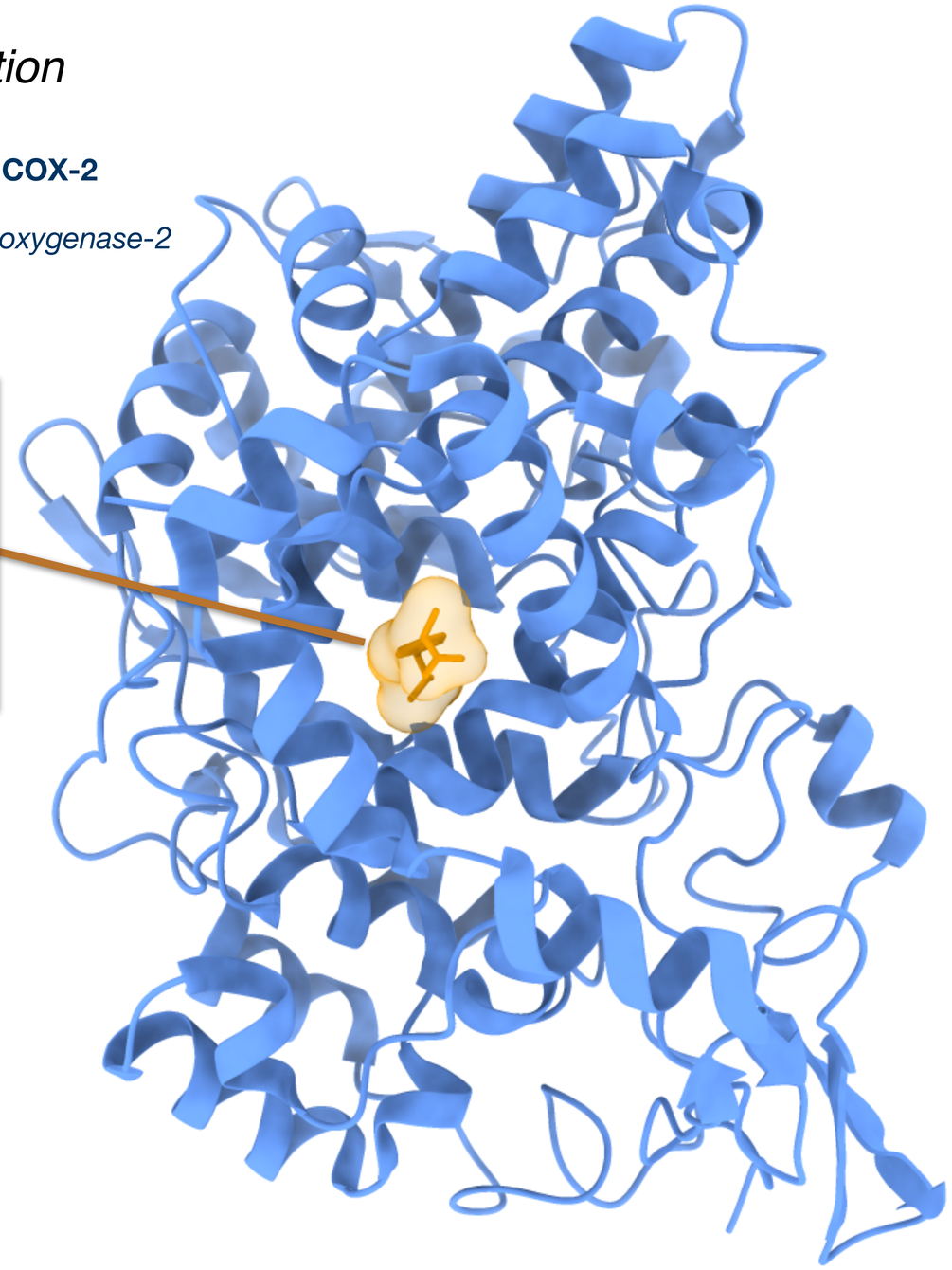
COX-2

cyclooxygenase-2





Ibuprofen



two distinct COX enzymes exist

BOTH are targets of NSAIDs

…so what's the difference?

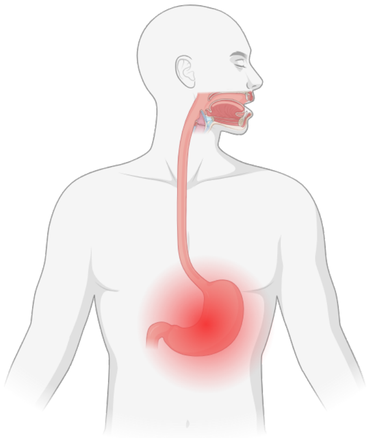
NSAIDs mechanism of action

COX-1

cyclooxygenase-1

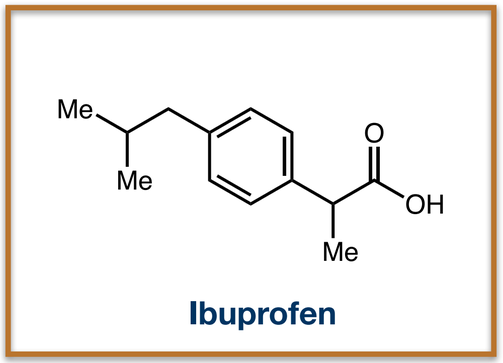
gastrointestinal prostaglandins

protect gastrointestinal mucosa



“off-target”

“anti-target”



Ibuprofen

“nonselective COX inhibitor”

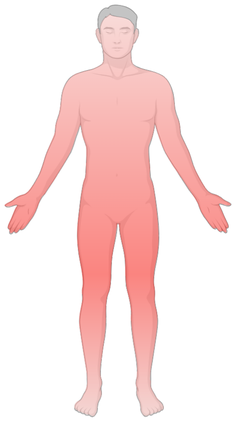
*exhibits **promiscuity***

COX-2

cyclooxygenase-2

inflammation/pain related prostaglandins

anti-inflammatory/pain relieving effect



target

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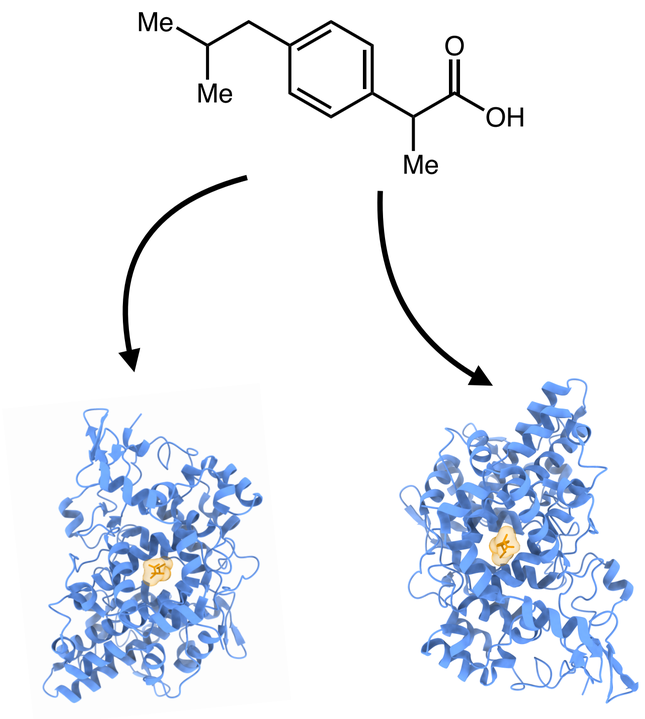


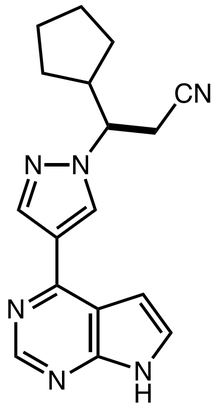
one drug, multiple
highly similar targets

ACS Med. Chem. Lett. **2018**, 9, 12, 1199.

Designer multi-targeting molecules

Yao, L.; Mustafa, N.; Tan, E.C. et al. *J. Med. Chem*. **2017**, 60, 8336.

Designer multi-targeting molecules

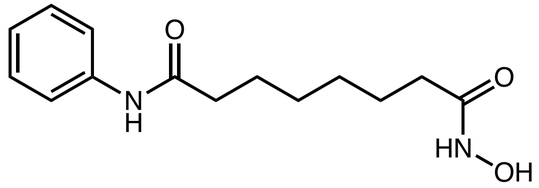


ruxolitinib

JAK 1/2 kinase inhibitor

anti proliferative, anti-inflammatory effects

IC_{50} = *3 nM*



vorinostat

pan-HDAC inhibitor

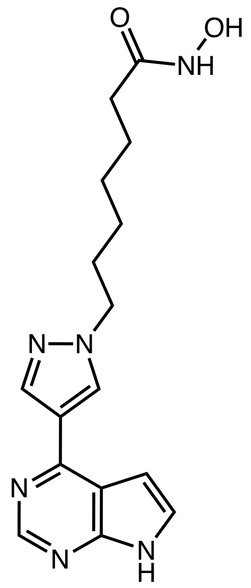
blocks de-acetylation of histones - epigenetic effects

IC_{50} = *10 nM*

Yao, L.; Mustafa, N.; Tan, E.C. et al. *J. Med. Chem*. **2017**, 60, 8336.

Designer multi-targeting molecules

Dual JAK-HDAC Inhibitor



excellent activity for both JAK and HDAC proteins

JAK IC_{50} = 75 nM

HDAC1 IC_{50} = 6.9 nM, HDAC6 IC_{50} = 1.4 nm

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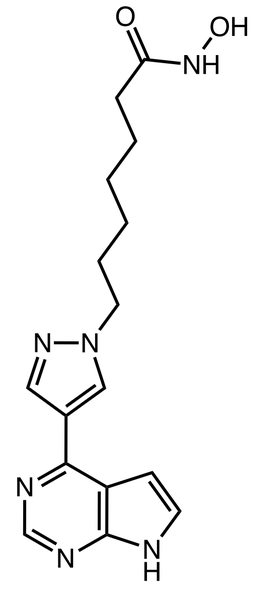

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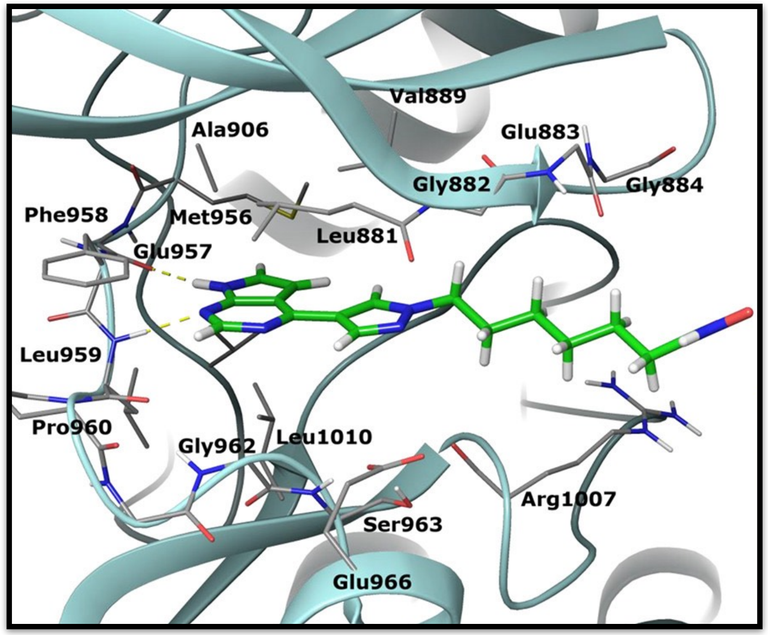
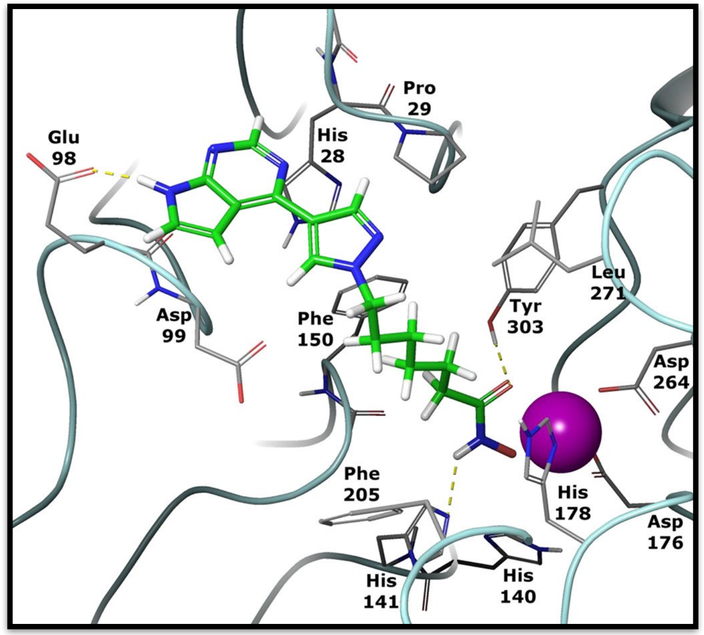
JAK-1 Molecular Docking



HDAC-1 Molecular Docking



dual HDAC/EGFR inhibitor strategy currently in clinical trials

Yao, L.; Mustafa, N.; Tan, E.C. et al. *J. Med. Chem*. **2017**, 60, 8336.

Meyers, J.; Chessum, N. E.A.; Cheeseman, M. D. et al. *ACS Omega* **2023**, 8, 19, 16532.

How do we define polypharmacology?

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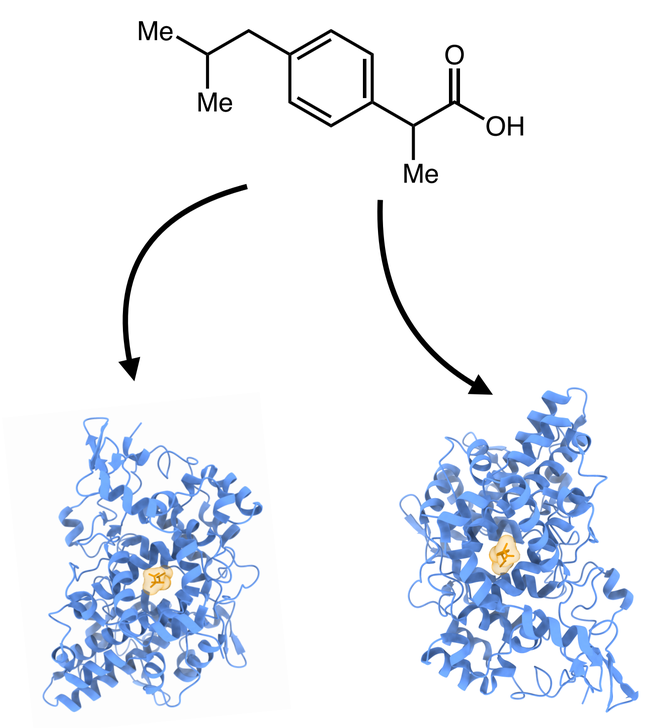
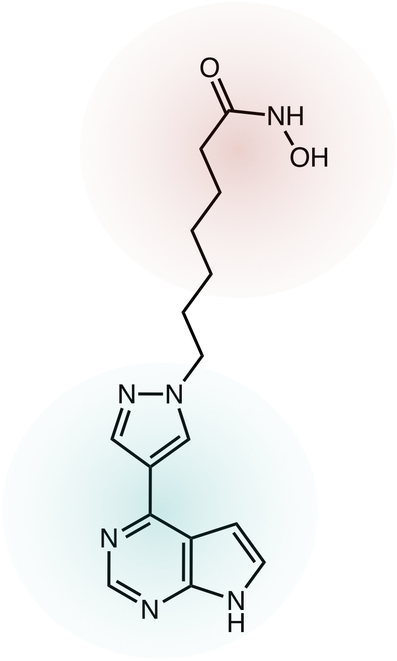


one drug, multiple highly similar targets

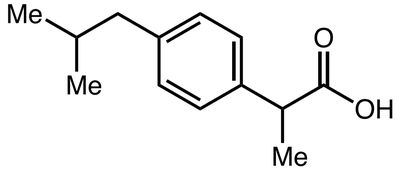
2. Multi-targeted by design



one drug, multiple targeting motifs

ACS Med. Chem. Lett. **2018**, 9, 12, 1199.

Further targets of NSAIDs



Ibuprofen

COX1, COX2 inhibitor

anti-inflammatory, anti-pain

1990s - it was noticed that users of NSAIDs showed reduced instances of Alzheimers

Early 2000s - efforts to study why this trend was observed

Kopp, M.A.; Liebscher, T.; Schwab, J.M. et al. *Cell Tissue Res*, **2012**, 349, 119.

Weggen, S.; Eriksen, J.L.; Koo, E.H. et al. *Nature*. **2001**, 414, 212.

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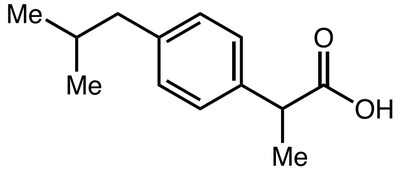

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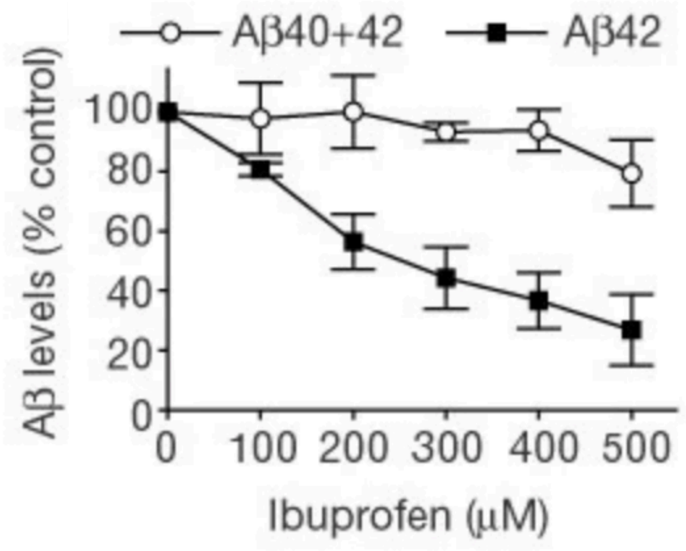
Nature, 2001 - Effect of NSAIDs on Amyloid Beta Levels



ibuprofen and other NSAIDs

reduce amyloid-beta 42 levels

Kopp, M.A.; Liebscher, T.; Schwab, J.M. et al. *Cell Tissue Res*, **2012**, 349, 119.

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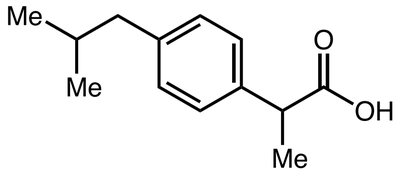

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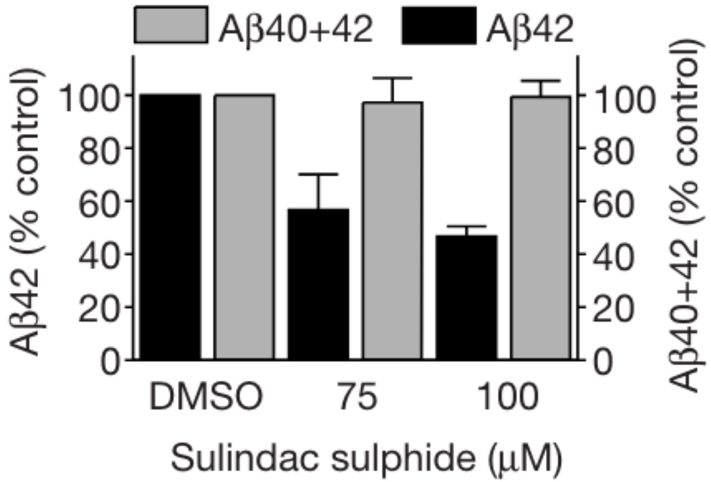

performed in COX1-/COX2- cell line

*reduction in Aβ42 is **independent***

of COX inhibition activity

Kopp, M.A.; Liebscher, T.; Schwab, J.M. et al. *Cell Tissue Res*, **2012**, 349, 119.

Weggen, S.; Eriksen, J.L.; Koo, E.H. et al. *Nature*. **2001**, 414, 212.

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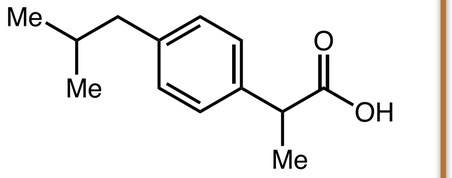

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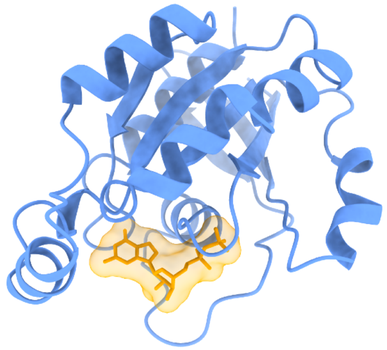
COX1, COX2 inhibitor

anti-inflammatory, anti-pain

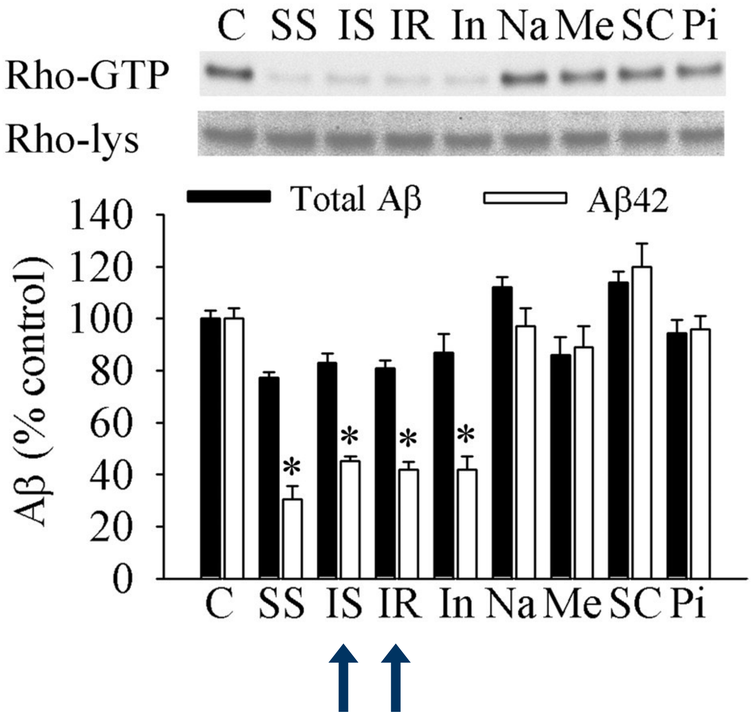
additionally targets Rho protein



RhoA

GTPase

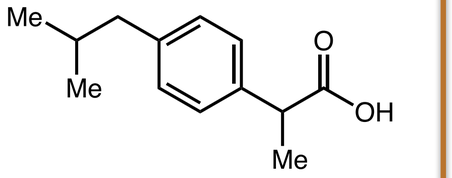
Science, 2003 - Mechanism of NSAID Amyloid Beta Reduction



Ibuprofen reduces Rho activity

Zhou, Y.; Su, Y.; Ni, B. et al. *Science.* **2003**, 302, 1215.

Further targets of NSAIDs



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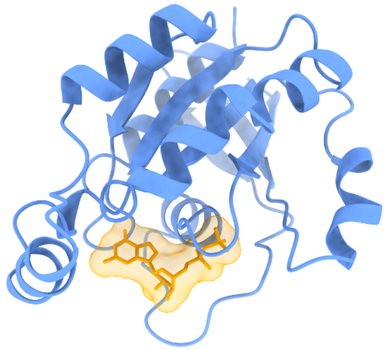
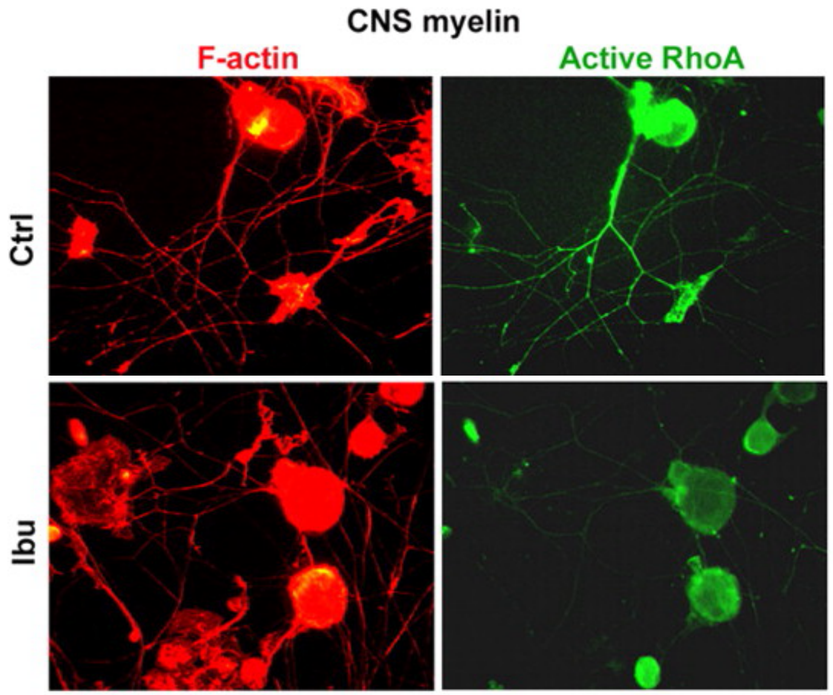


RhoA

GTPase

2007 - Ibuprofen, via RhoA inhibition, boosts neuronal growth

neuronal outgrowth model



Fu, Q.; Hue, J.; Li, S. *J. Neurosci.* **2007,** 27, 4154.

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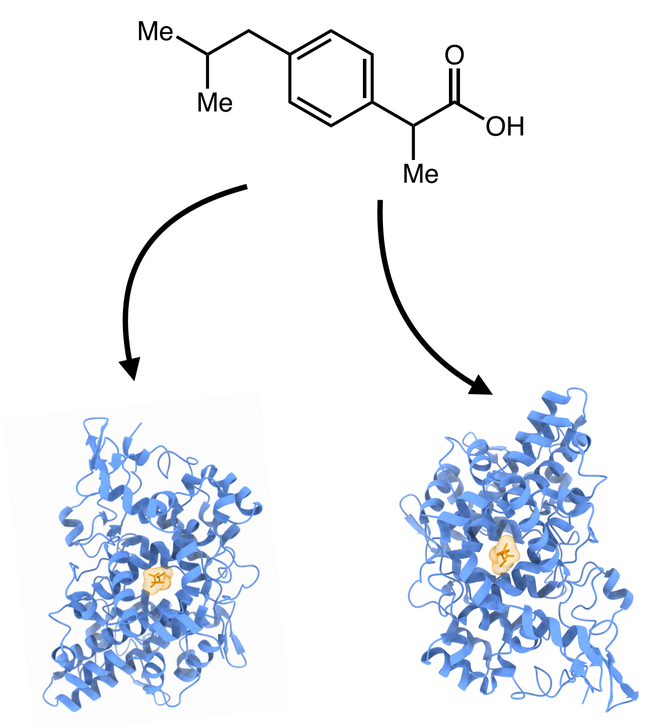
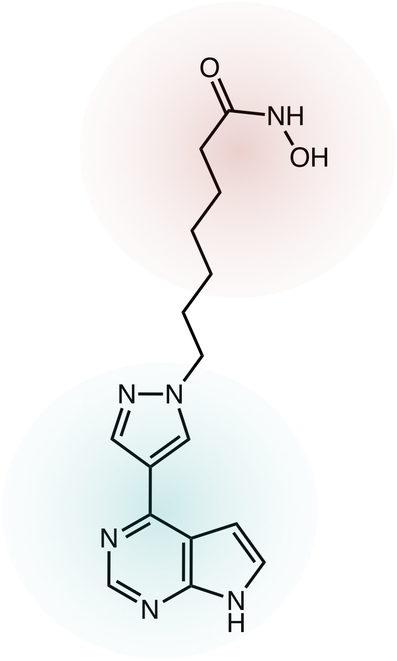


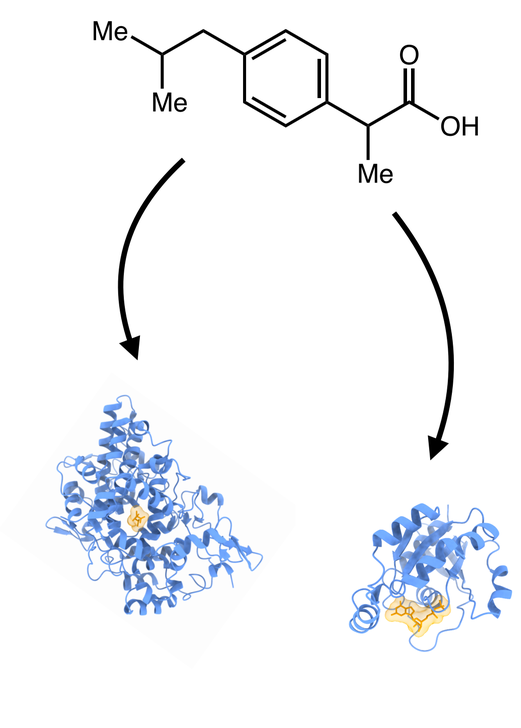
one drug, multiple highly similar targets

2. Multi-targeted by design



one drug, multiple targeting motifs

3. Multiple completely orthogonal targets



one drug, multiple totally different targets

ACS Med. Chem. Lett. **2018**, 9, 12, 1199.

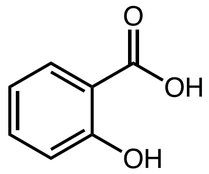
Historical context of polypharmacology in drug discovery

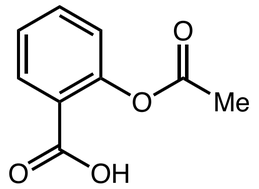
The Phenotypic Approach (????-late 1980s)

"observational" *"anecdotal"*

Willow tree bark

Salicylic acid





Acetylsalicylic acid (Aspirin)

first synthesized/registered by Bayer in 1899

mechanism wasn't elucidated until 1970s

Jalencas, X.; Mestres, J.Med. Chem. Commun. **2013**, 4, 80.

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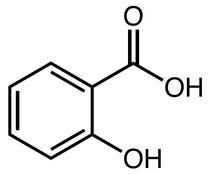
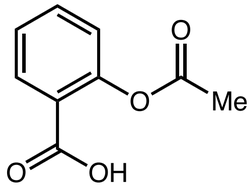


COX polypharmacology wasn't discovered until 1991



Acetylsalicylic acid (Aspirin)

1982 Nobel Prize in Physiology/Medicine

"for their discoveries concerning prostaglandins and related biologically active substances"

Sune K. Bergström

Bengt I. Samuelsson

John R. Vane

Brown, D. *Drug Discovery Today*. **2007**, 12, 23.

Historical context of polypharmacology in drug discovery

The Phenotypic Approach (????-late 1980s) → Why was this approach taken?

"observational" *"anecdotal"*

limitations in biochemical understanding

Advantages

- *lead compound, direct effect readout*
- *chemistry, biology are "in-sync"*
- *in retrospect: favors potential polypharmacology*

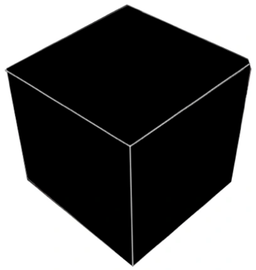
Disadvantages

- *phenotype =/= mechanistic insight*
- *no structural knowledge to guide optimization*
- *off-targets, toxicity hard to predict/measure*

chemistry

laborious

biology



"black-box"

concepts such as promiscuity, polypharmacology not widely appreciated/acknowledged

Brown, D. *Drug Discovery Today*. **2007**, 12, 23.

Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

enabled by two major advances in the late 1980s:

recombinant DNA technologies

fast-protein liquid chromatography

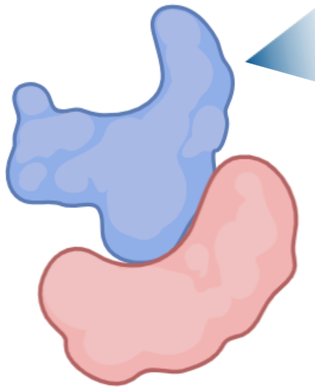
protein accessibility led to:

- quantitative assay data
- high-throughput screening
- metabolism/PK studies

Brown, D. *Drug Discovery Today*. **2007**, 12, 23.

Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*



BCR-ABL

ABL

tyrosine-protein kinase

BCR

breakpoint-cluster region protein

fusion-product of BCR and ABL genes

known as the Philadelphia Chromosome (Ph)

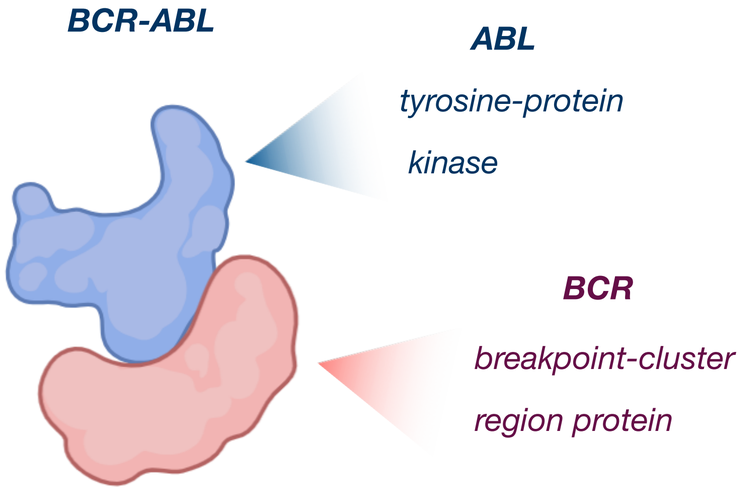
common in chronic myelogenous leukemia (CML)

early example of a specific protein-product that was directly linked to a cancer type

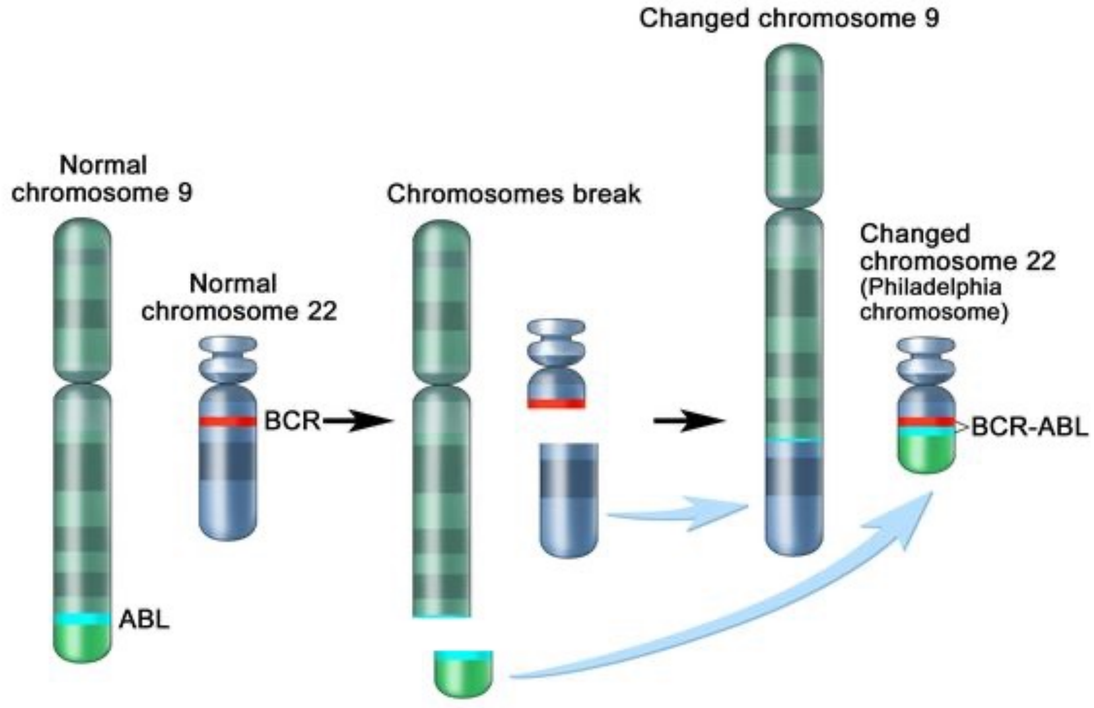
Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*



fusion-product of
BCR and ABL genes



late 1990s - campaign to screen for BCR-ABL inhibitors

Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

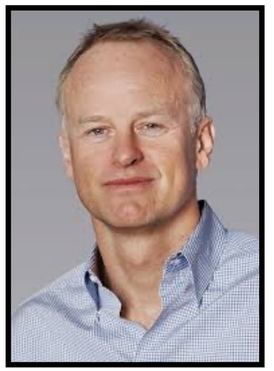
BCR-ABL

fusion-product of

BCR and ABL genes

CIBA-GEIGY GmbH, Wehr

NOVARTIS



Nicholas Lydon

performed high-throughput screening of molecules against BCR-ABL

Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

Survival statistics for chronic myeloid leukemia. *Canadian Cancer Society*, **2022**.

Historical context of polypharmacology in drug discovery

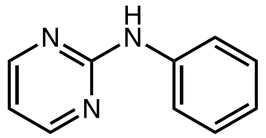
"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

BCR-ABL

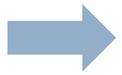
fusion-product of

BCR and ABL genes

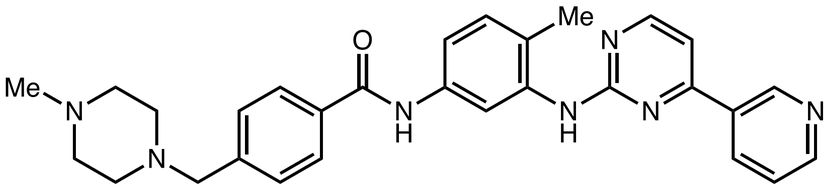
2-phenylaminopyrimidine



showed BCR-ABL inhibition



imatinib



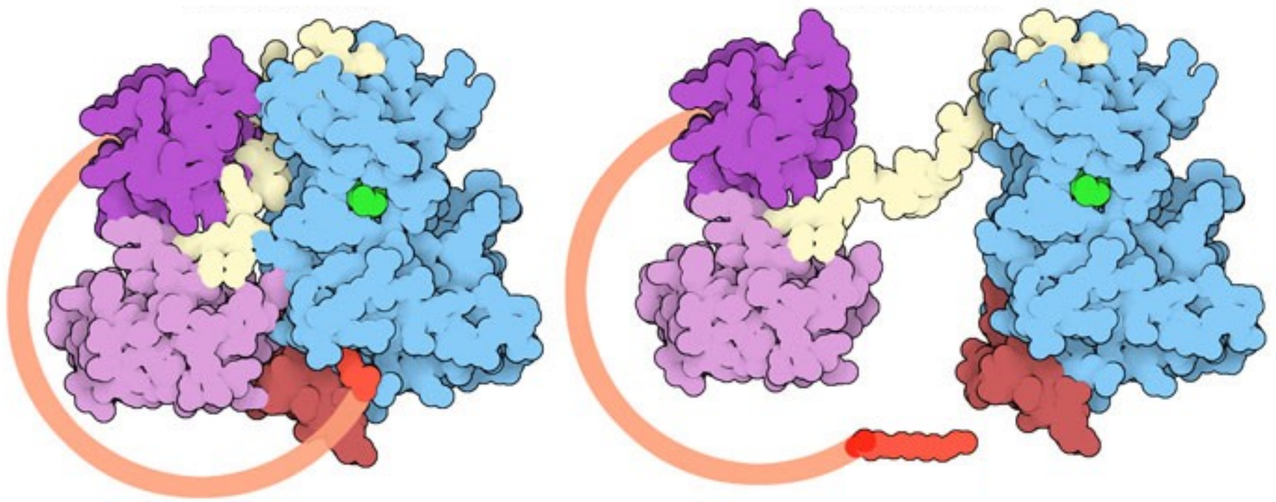
final optimized compound

Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

Historical context of polypharmacology in drug discovery

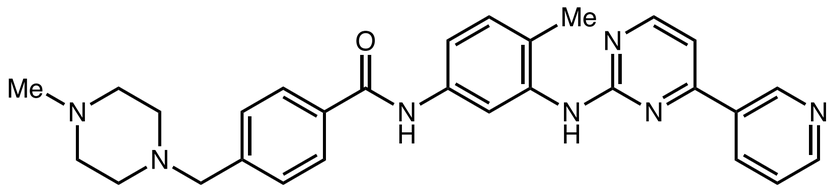
"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

Inactive ABL ***Active ABL***



auto-inhibitory region

imatinib



final optimized compound

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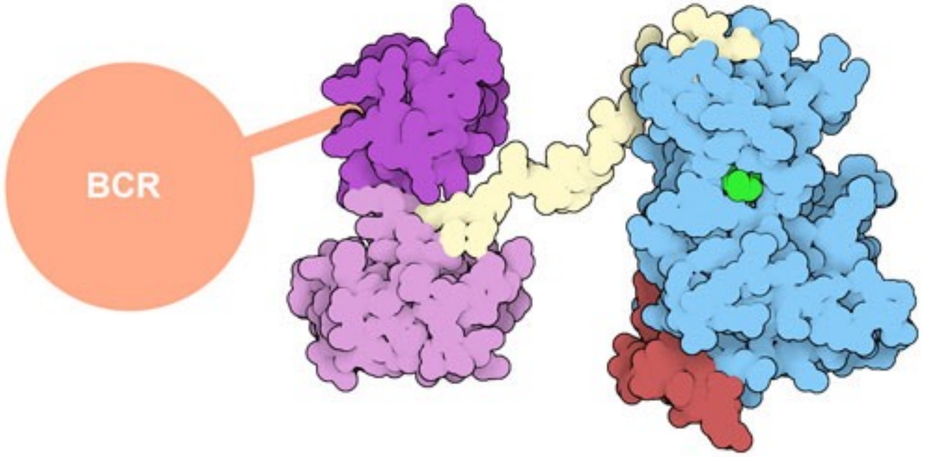
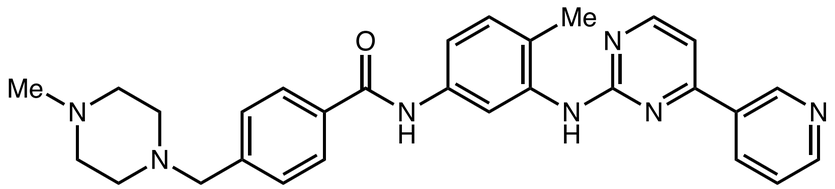
Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

BCR-ABL Fusion Protein



imatinib



final optimized compound

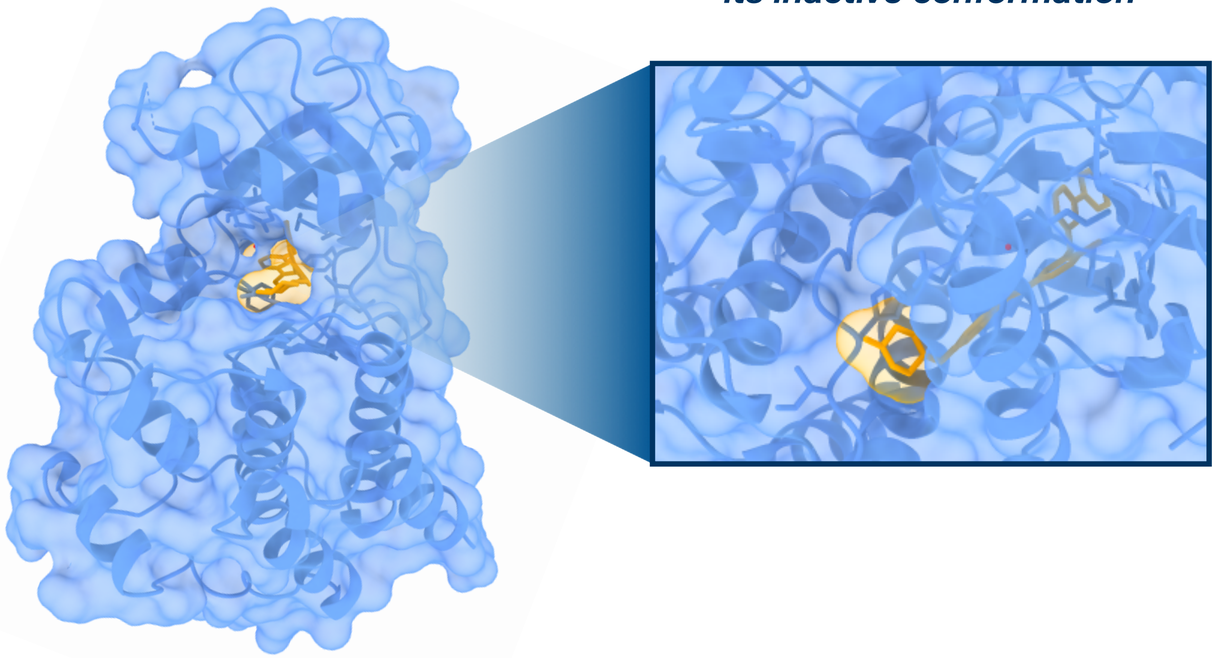
Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

Historical context of polypharmacology in drug discovery

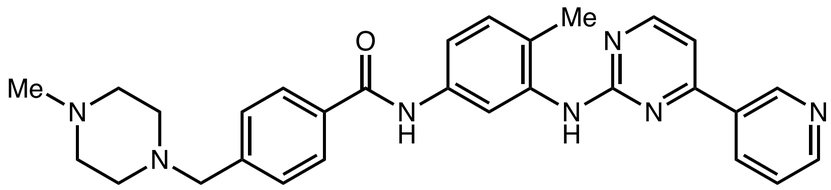
"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

ABL

imatinib locks ABL into its inactive conformation



imatinib



final optimized compound

FDA approved in May 2001 $4.6 billion peak sales in 2012

as of 2023, CML 5 year survival rate has surpassed 90%

Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

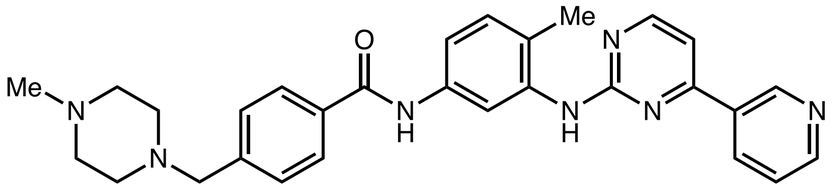
Survival statistics for chronic myeloid leukemia. *Canadian Cancer Society*, **2022**.

Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

Time Magazine, May 28, 2001

imatinib



final optimized compound

FDA approved in May 2001 $4.6 billion peak sales in 2012

as of 2023, CML 5 year survival rate has surpassed 90%

first "magic bullet", beginning of a new era

Druker, B.J.; Lydon, N.B. *J Clin Invest.* **2000,** 105, 3.

Survival statistics for chronic myeloid leukemia. *Canadian Cancer Society*, **2022**.

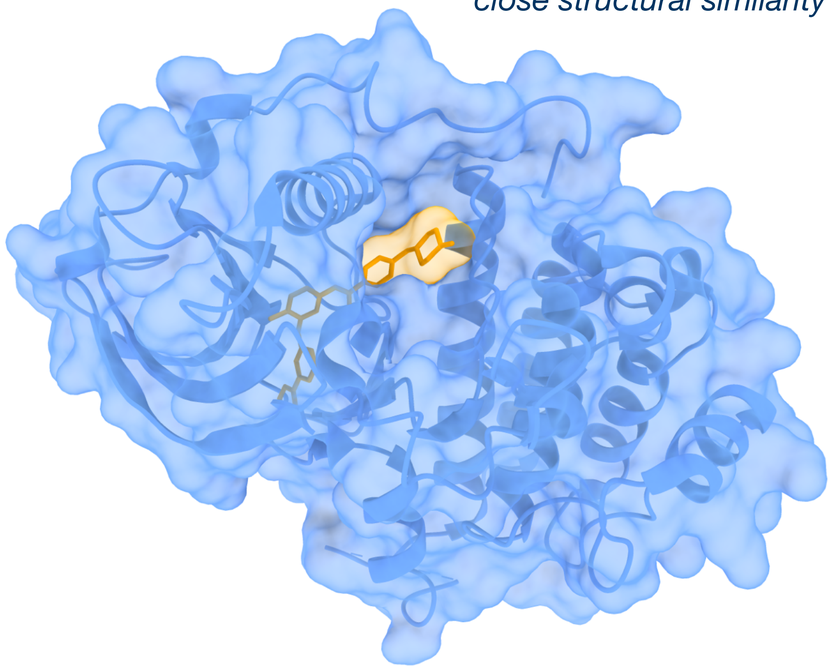
Historical context of polypharmacology in drug discovery

"target based" **Rational Drug Design (Late 1980s and onward)** *"hypothesis based"*

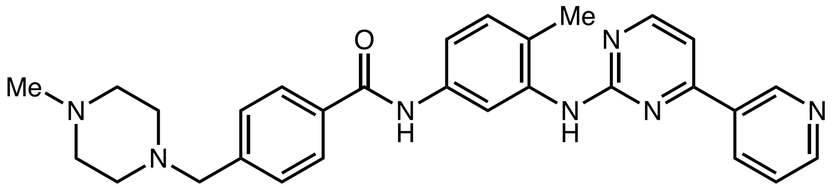
c-KIT

tyrosine protein kinase

close structural similarity to ABL



imatinib



final optimized compound

2002 - FDA approved for GIST (gastrointestinal stromal tumors)

imatinib also inhibited c-KIT

coincidental polypharmacology allowed for multiple oncology use-cases

Lopes, L.F.; Bacchie, C.E. *J. Cell. Mol. Med.* **2010**, 14, 42-50

Historical context of polypharmacology in drug discovery

"target based" ***Rational Drug Design (Late 1980s and onward)*** *"hypothesis based"*

Advantages

- *high-throughput screening possible*
- *direct structure-binding optimization possible*
- *allows high selectivity, mitigation of promiscuity*

Disadvantages

- *reductionist system, not 1:1 transferable findings*
- *relied upon single-target amenable diseases*
- *single-target compounds can lead to* ***resistance***

in acute lymphoblastic leukemia (ALL) - imatinib resistance within 6 months is as high as 70%

point mutations in ABL gene lead to failure of response

highly selective drugs are also more reliant on single-target efficacy

Gambacorti-Passerini, C.B.; Gunby, R.H.; Scapozza, L. et al. *Lancet Oncol.* **2003**, 4, 75.

Historical context of polypharmacology in drug discovery

Recognition of Polypharmacology as a Strategy (early 2000s)

until this time, was mostly viewed as something to be avoided or coincidental

OPINION

Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia

Bryan L. Roth, Douglas J. Sheffler and Wesley K. Kroeze

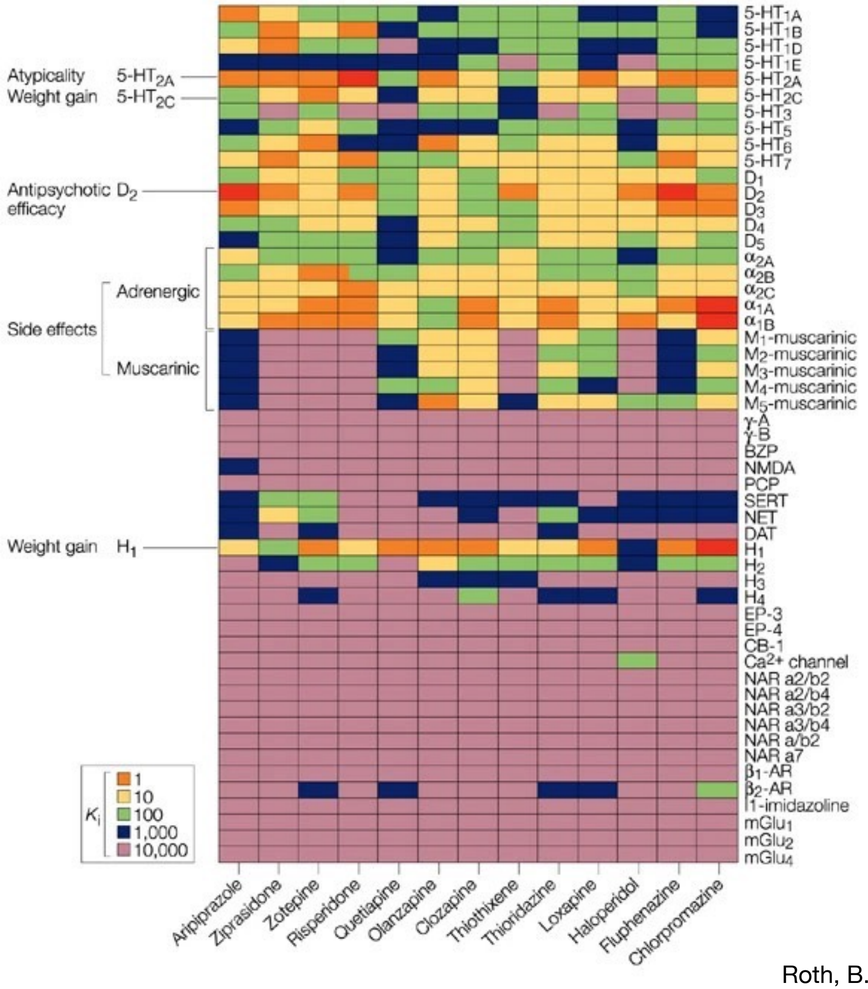
the idea that "dirty" drugs may actually be better

highly relevant in CNS contexts

Roth, B.L.; Sheffler, D.J., Kroeze, W.K. *Nat. Rev. Drug Discov.* **2004**, 4, 353.

Historical context of polypharmacology in drug discovery

Recognition of Polypharmacology as a Strategy (early 2000s)



majority of CNS drugs exhibit polypharmacology

literature outcome analysis of drugs for:

Schizophrenia

Depression

in both cases, “non-selective” drugs have better outcomes

Roth, B.L.; Sheffler, D.J., Kroeze, W.K. *Nat. Rev. Drug Discov.* **2004**, 4, 353.

Historical context of polypharmacology in drug discovery

Recognition of Polypharmacology as a Strategy (early 2000s)

"Clearly, conventional approaches relying on high-throughput screening (HTS) of cloned human molecular targets and the subsequent optimization of these 'single-target agents' is not likely to yield selectively non-selective agents, except, perhaps, by chance."

proposed combination of "behavioral" and genomics based screening, followed by med-chem lead optimization

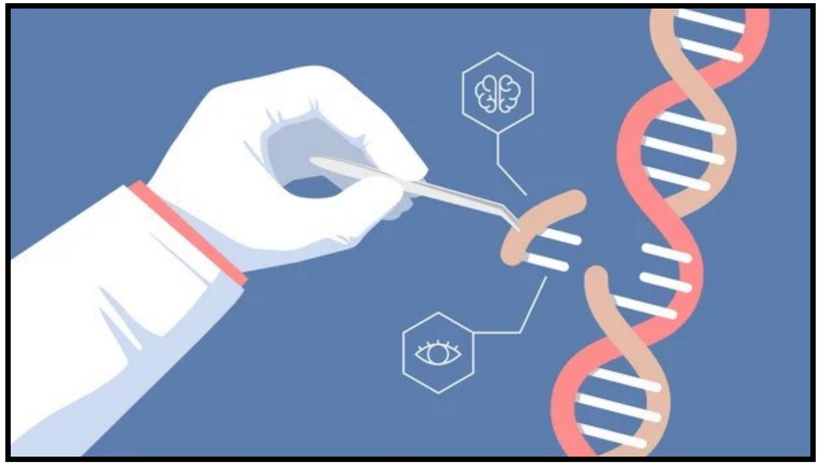
Roth, B.L.; Sheffler, D.J., Kroeze, W.K. *Nat. Rev. Drug Discov.* **2004**, 4, 353.

Historical context of polypharmacology in drug discovery

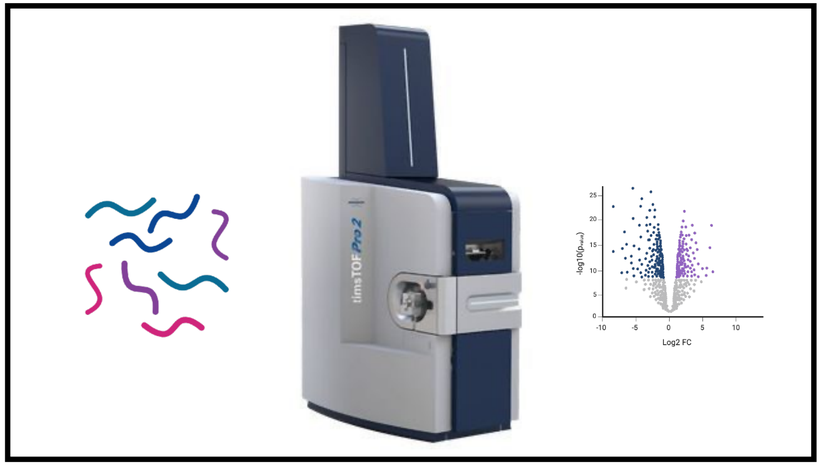
The Modern Era (2012 onwards)

new, powerful technologies for studying drug mechanism:

genetic screening/CRISPR



modern high-fidelity chemoproteomics



Schenone, M.; Dancik, V.; Wagner, B.K.; Clemons, P.A. *Nat. Chem. Biol.* **2013**, 9, 232.

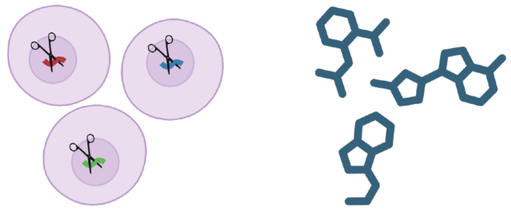
Historical context of polypharmacology in drug discovery

The Modern Era (2012 onwards)

new, powerful technologies for studying drug mechanism:

genetic screening/CRISPR

high throughput gene profiling

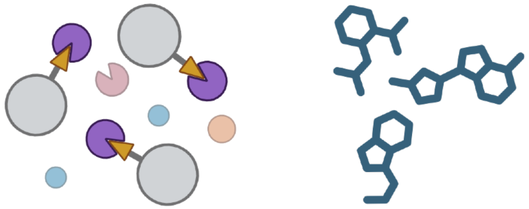


Which genes affect this drug's activity?

computation

modern high-fidelity chemoproteomics

protein-level interaction data

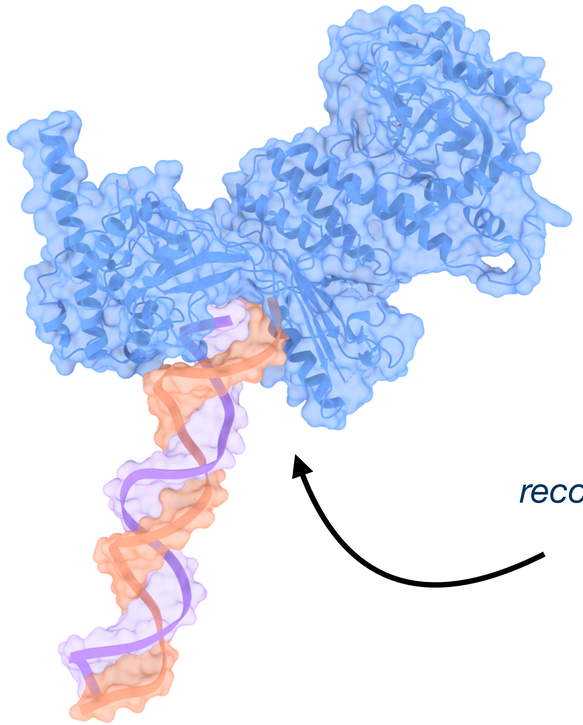


What proteins is this drug interacting with?

"How specific are these drugs really?"

Schenone, M.; Dancik, V.; Wagner, B.K.; Clemons, P.A. *Nat. Chem. Biol.* **2013**, 9, 232.

Case study: polypharmacology in PARP inhibitors

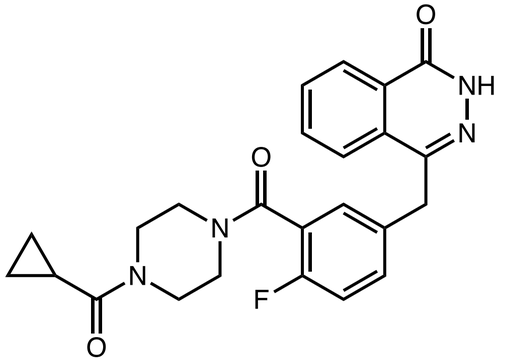


PARP

poly-(ADP) ribose polymerase

DNA repair, genomic stability

recognizes single strands breaks (SSBs) in DNA and recruits repair machinery



olaparib

FDA approved 2014

AstraZeneca MERCK

$2.8 billion in sales in 2022

PARP inhibition is a powerful anti-cancer strategy (BRCA ovarian/breast cancer)

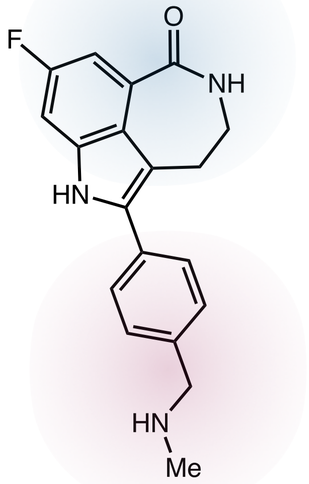
Antolin, A.A.; Ameratunga, M.; Al-Lazikani, B. et al. *Nat Sci Rep*. **2020**, 10, 2585.

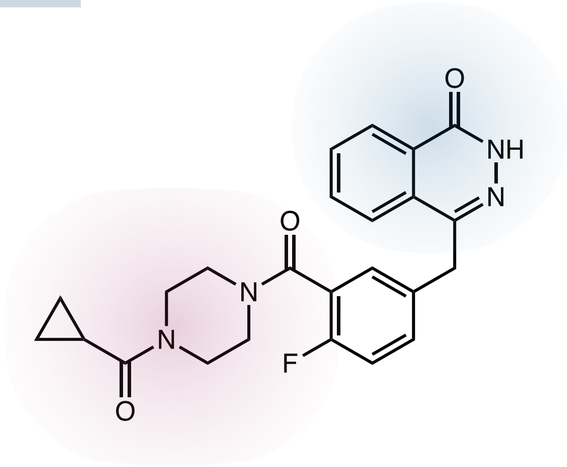
Case study: polypharmacology in PARP inhibitors

comparison of PARP inhibitors

rucaparib

FDA approved 2016





olaparib

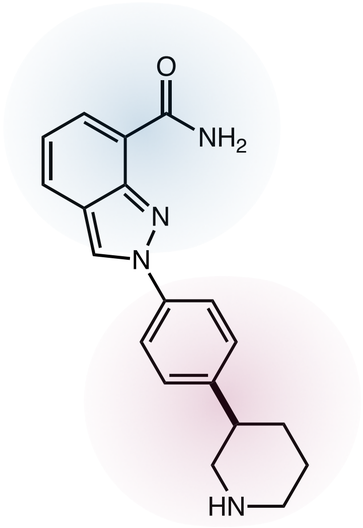
FDA approved 2014

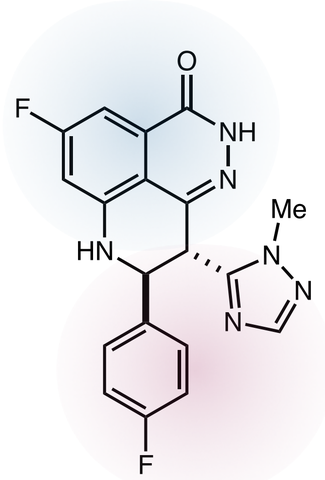
conserved benzamide motif - PARP binding

significant variability on rest of scaffold

niraparib

FDA approved 2017





talazoparib

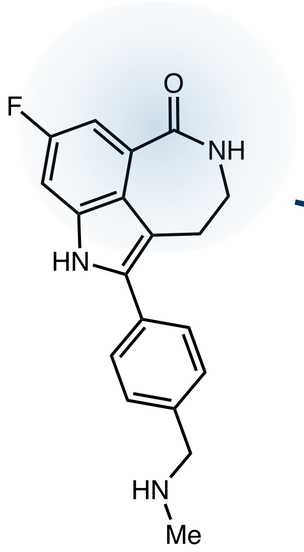
FDA approved 2018

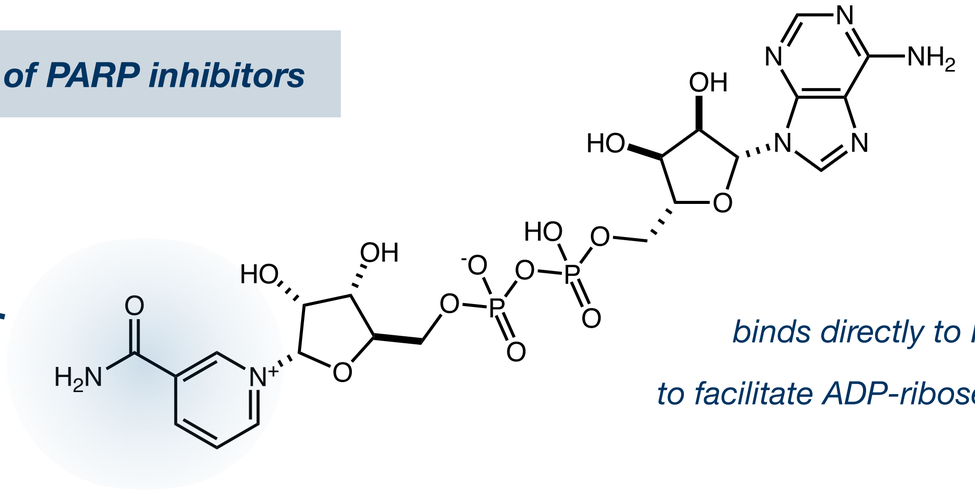
Case study: polypharmacology in PARP inhibitors

comparison of PARP inhibitors

rucaparib

FDA approved 2016





NAD+

Nicotinamide adenine dinucleoetide

binds directly to PARP

to facilitate ADP-ribose synthesis

clinically, there is no strong rationale for selecting one PARP inhibitor over another

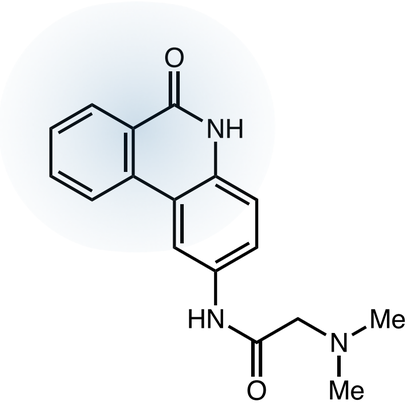
…but they have different structures

So are there differences?

Antolin, A.A.; Ameratunga, M.; Al-Lazikani, B. et al. *Nat Sci Rep*. **2020**, 10, 2585.

Case study: polypharmacology in PARP inhibitors

clues to promiscuity



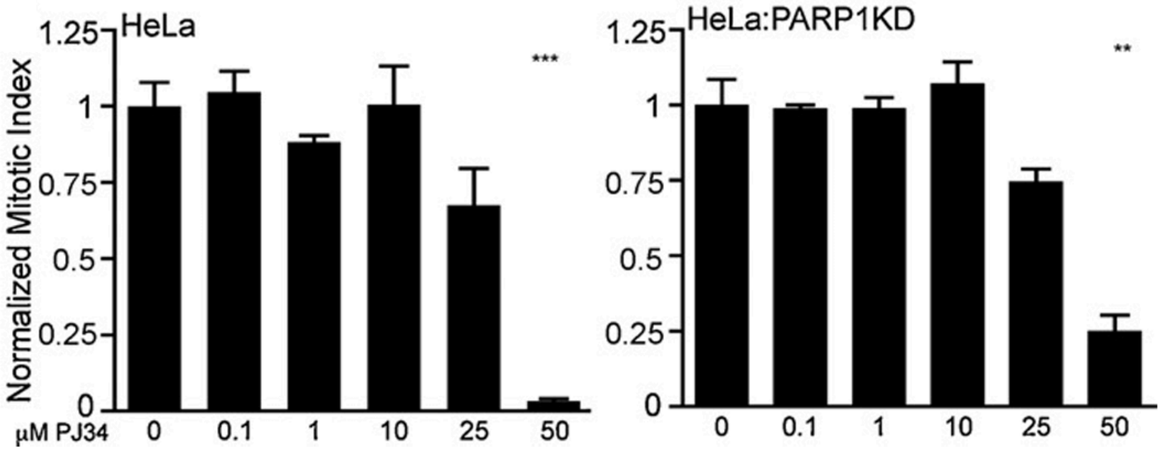
PJ34

- “test” molecule, known PARP inhibitor
- discovered in 2001
- used in 100s of studies for PARP biology

assumed to be highly selective PARP1 inhibitor

IC_{50} = 20 nM

PJ34 has unique properties, unexplainable solely by PARP binding



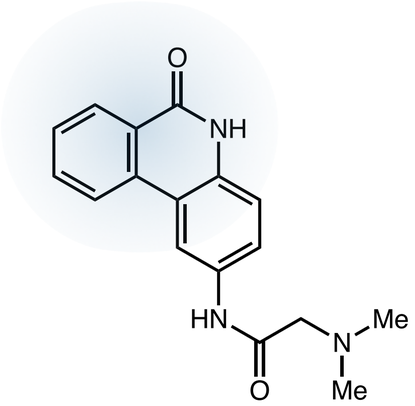
PJ34 leads to mitotic arrest (cell cycle stoppage)

PARP1 knockout does not affect mitotic arrest activity

Madison, D.L.; Stauffer, D.; Lundblad, J.R. *DNA Repair*. **2011**, 10, 1003.

Case study: polypharmacology in PARP inhibitors

PIM1 inhibition and its implications



PJ34

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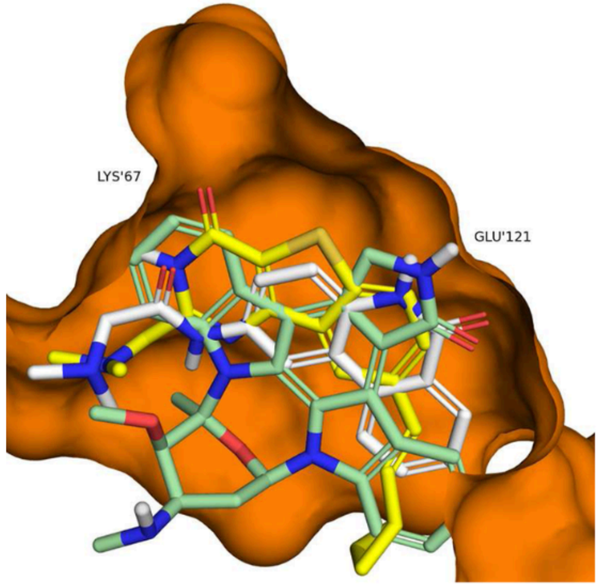
assumed to be highly selective PARP1 inhibitor

IC_{50} = 20 nM

PJ34 had unique properties, unexplainable solely by PARP binding

in-silico screen of potential targets reveals PIM1, PIM2 as predicted off-targets



PJ34 binding mode shown in white

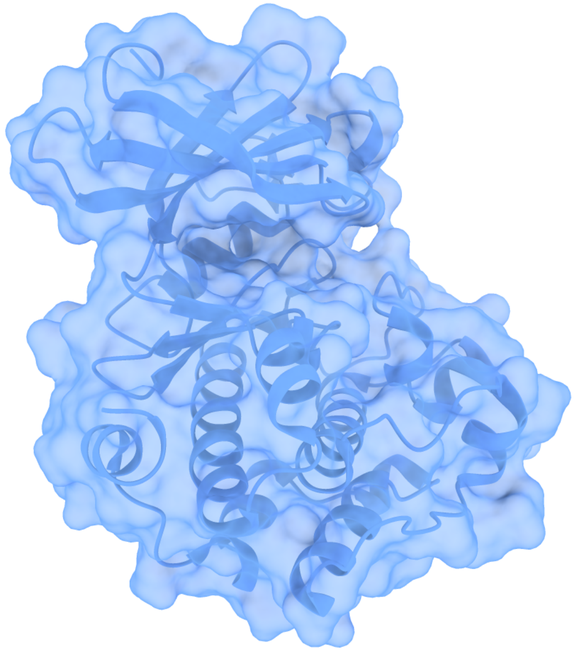
contrasted with other kinase inhibitors

no similarity in PARP1, PIM1 binding motifs/rationales

Antolin, A.A.; Jalencas, X.; Mestres, J. et al. *ACS Chem. Biol*. **2012**, 7, 12, 1962.

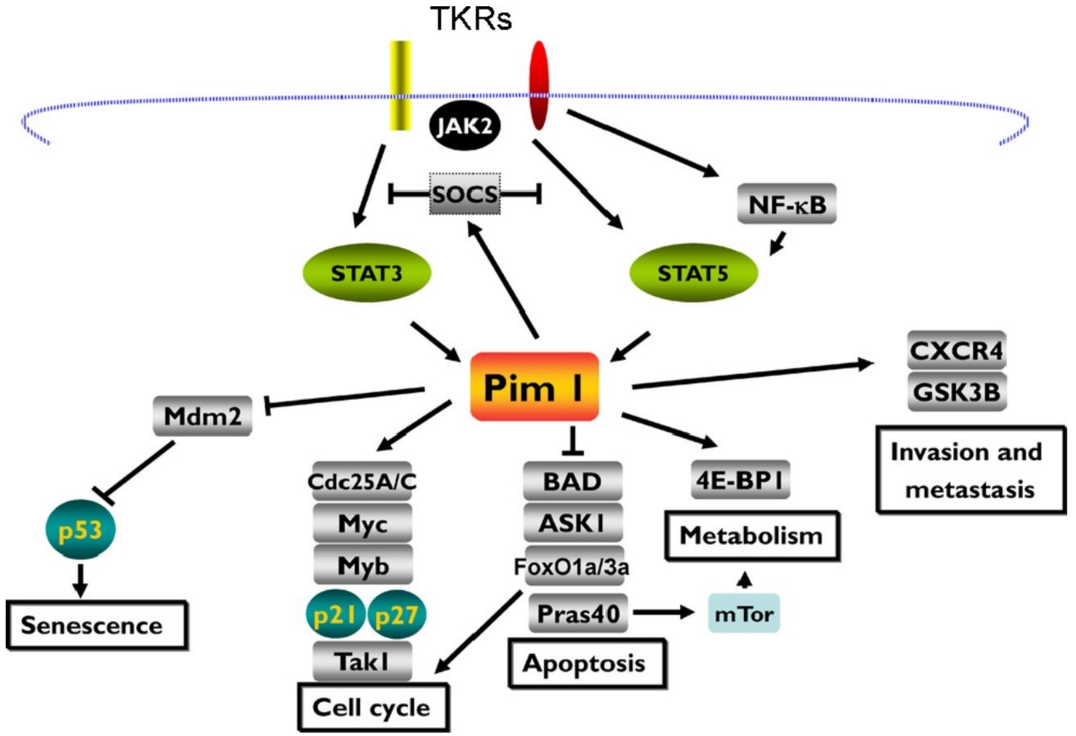
Case study: polypharmacology in PARP inhibitors

PIM1 inhibition and its implications



PIM - proto-oncogene serine/threonine kinase

overexpressed in many cancers, target for cancer therapy



Does this activity extend to FDA approved PARP inhibitors?

Antolin, A.A.; Jalencas, X.; Mestres, J. et al. *ACS Chem. Biol*. **2012**, 7, 12, 1962.

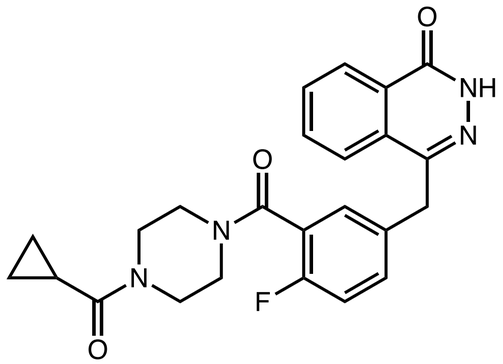
Case study: polypharmacology in PARP inhibitors

in-vitro kinome screen

screening of PARP inhibitors against 392 human kinases (76% of all known human kinases)

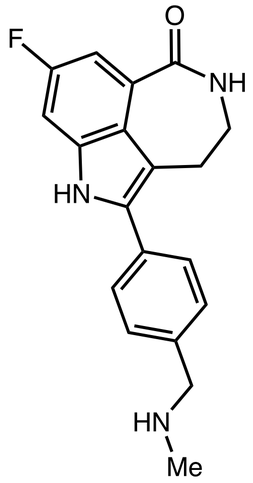
olaparib

FDA approved 2014

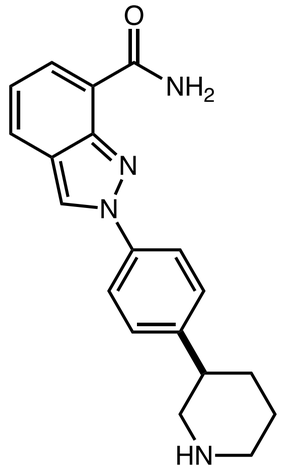


rucaparib

FDA approved 2016

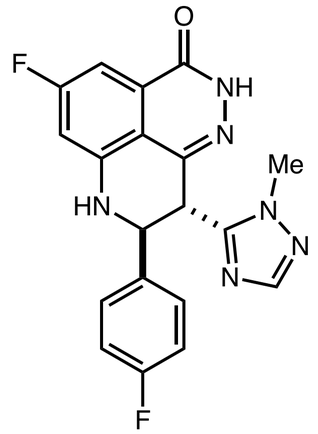


niraparib



talazoparib

FDA approved 2018



Antolin, A.A.; Ameratunga, M.; Al-Lazikani, B. et al. *Nat Sci Rep*. **2020**, 10, 2585.

Case study: polypharmacology in PARP inhibitors

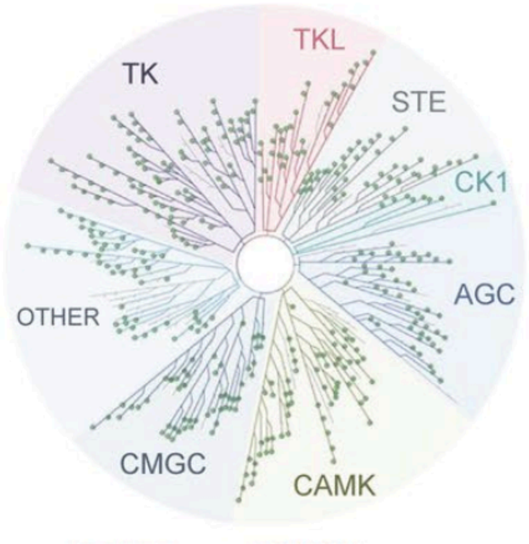
in-vitro kinome screen

screening of PARP inhibitors against 392 human kinases (76% of all known human kinases)

unique differences in kinase off-targets observed

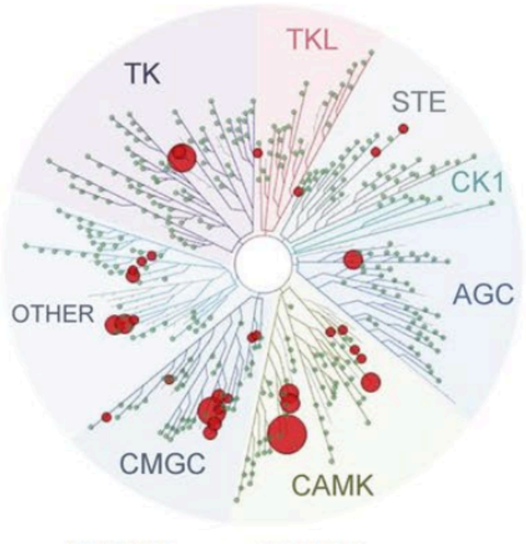
olaparib

FDA approved 2014



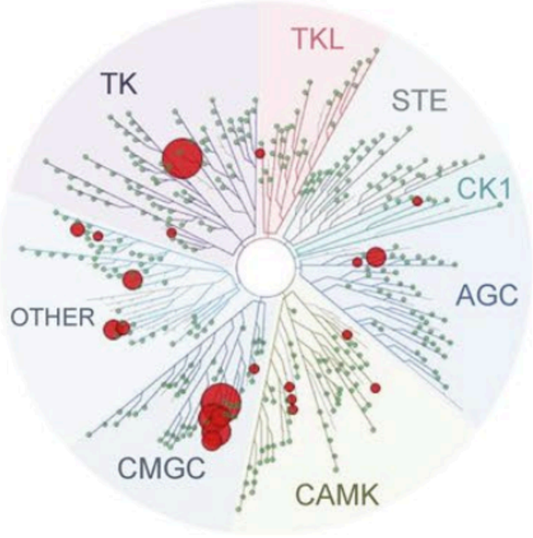
rucaparib

FDA approved 2016



niraparib

FDA approved 2017



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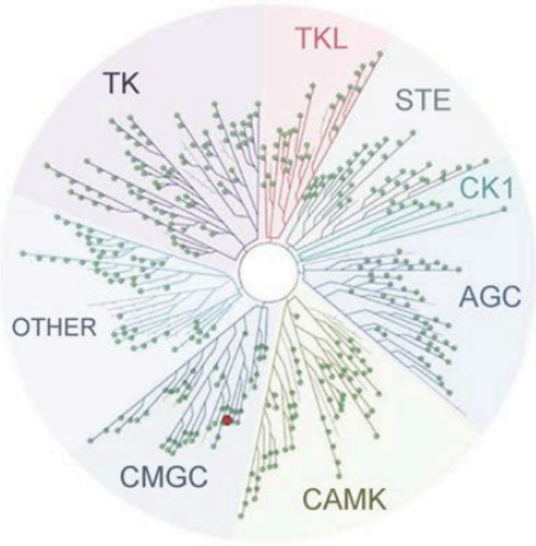

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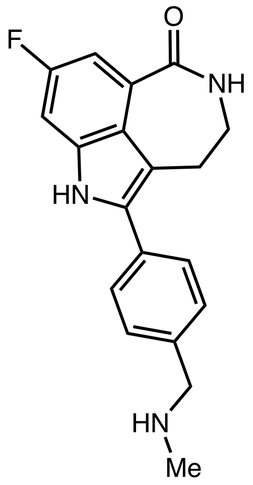

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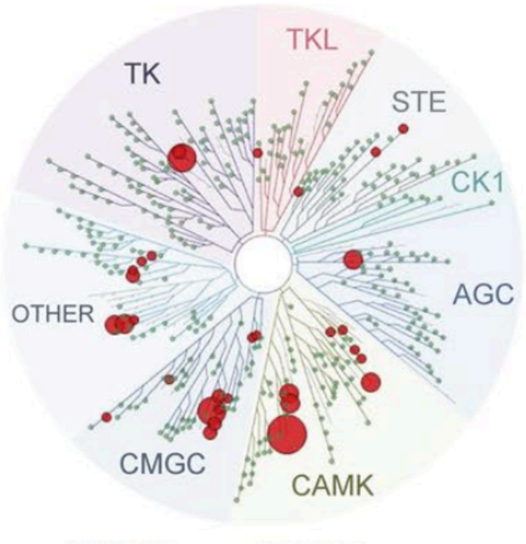

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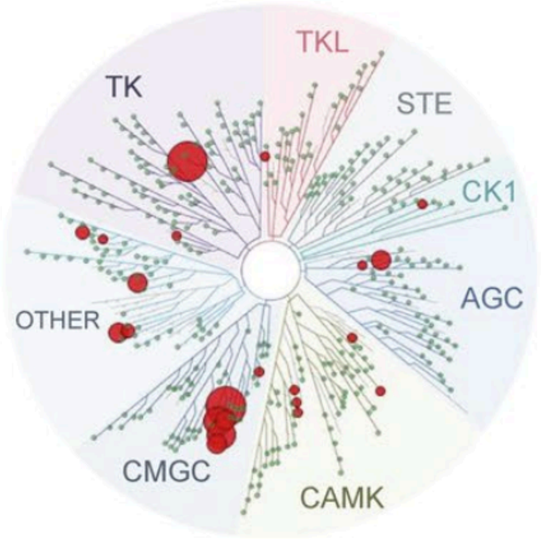

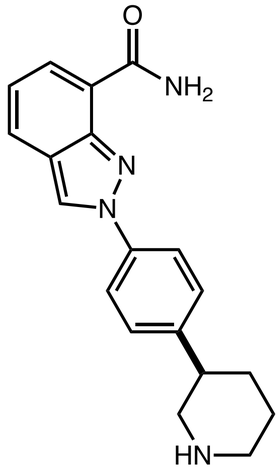

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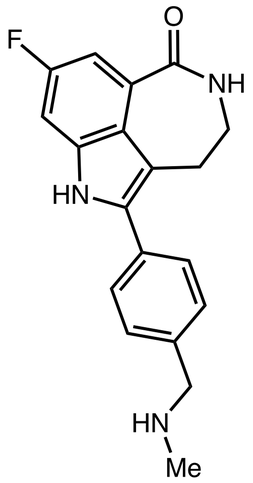

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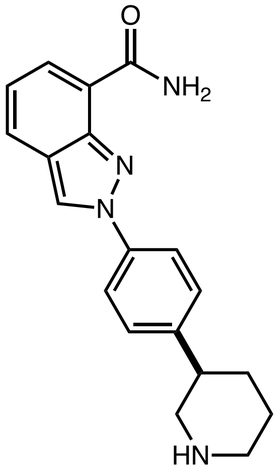


rucaparib inhibits CDK16 (IC_{50} = 381 nM)

cell cycle control protein

involved in cancer proliferation

both bind PIM1/PIM2

relatively weak (μM)

niraparib inhibits DYRK1B (IC_{50} = 254 nM)

cell cycle transition regulator

involved in cancer proliferation

Antolin, A.A.; Ameratunga, M.; Al-Lazikani, B. et al. *Nat Sci Rep*. **2020**, 10, 2585.

Case study: polypharmacology in PARP inhibitors

meta-analysis based upon differing polypharmacology

Differential adverse reactions between FDA-approved clinical PARP inhibitors

Side-effect	Olaparib	Rucaparib	Niraparib	Talazoparib
Dry mouth			●	
Anxiety			●	
Insomnia		●	●	
Hypertension			●	
Palpitations	●		●	
Increase in mean corpuscular volume	●			
Decrease in lymphocytes	●	●		●

side-effects may be patient-dependent based upon expression profile of off-targets

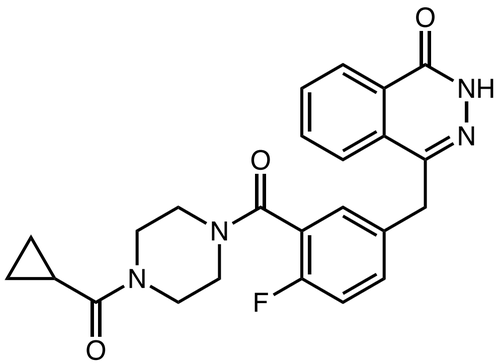
Antolin, A.A.; Ameratunga, M.; Al-Lazikani, B. et al. *Nat Sci Rep*. **2020**, 10, 2585.

Case study: polypharmacology in PARP inhibitors

2024 clinical trial comparison of PARP inhibitors

olaparib

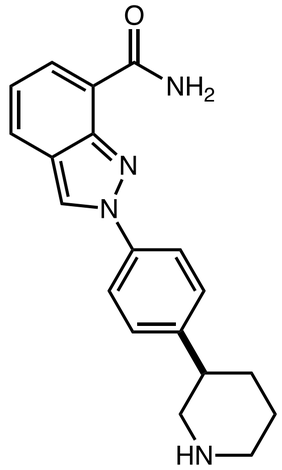
FDA approved 2014



few kinase off-targets

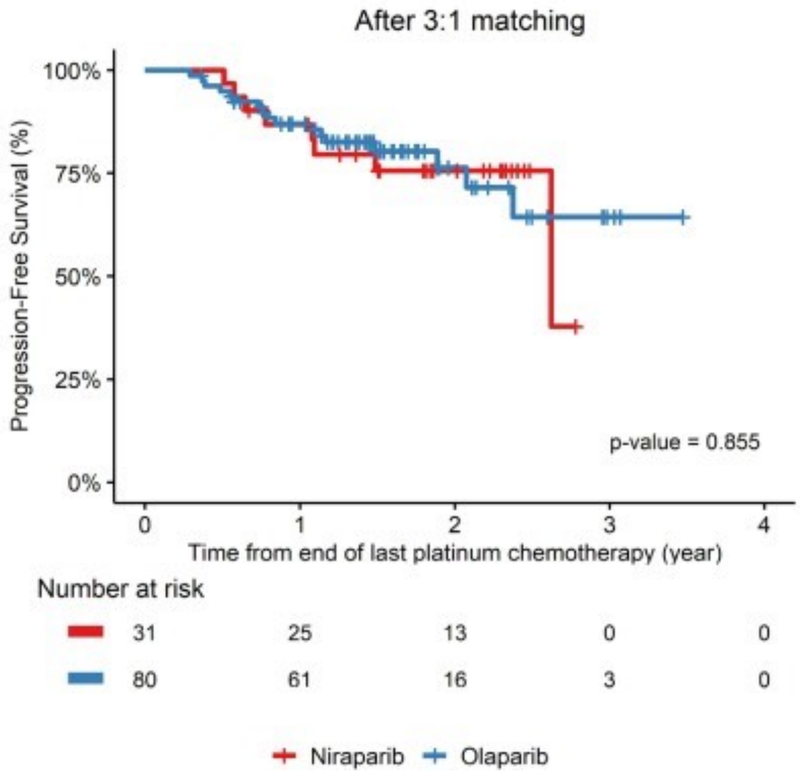
niraparib

FDA approved 2017



significant kinase off-targets

advanced ovarian cancer patients



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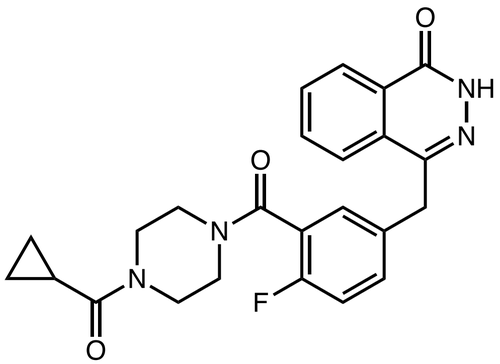

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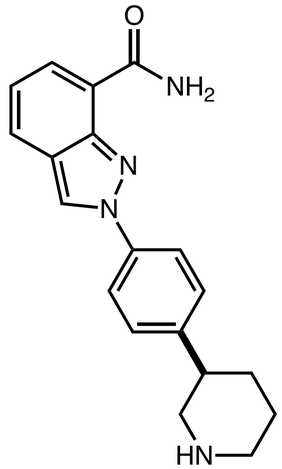


significant kinase off-targets

no statistically significant survival difference

but:

niraparib patients showed increased frequency of:

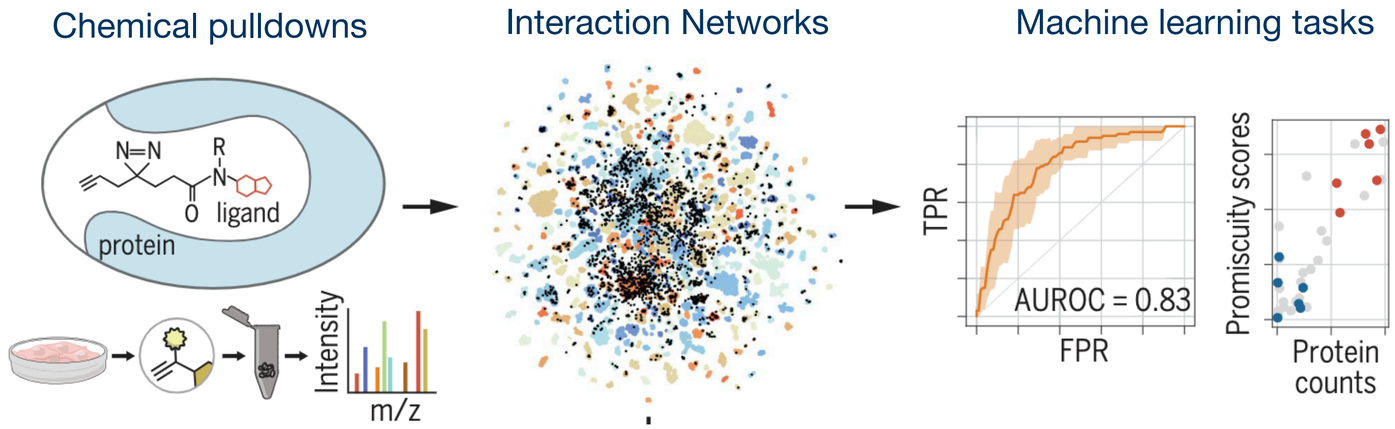
thrombocytopenia	neutropenia
p = 0.021	*p = 0.011*

hematological toxicity

Kim, J.H.; Kim, S.I.; Lim, M.C. et al. *Gynecol. Oncol.* **2024**, 181, 33.

Case study: large scale proteomics for ligand discover/prediction

April 26, 2024 - Pfizer, Georg E. Winter



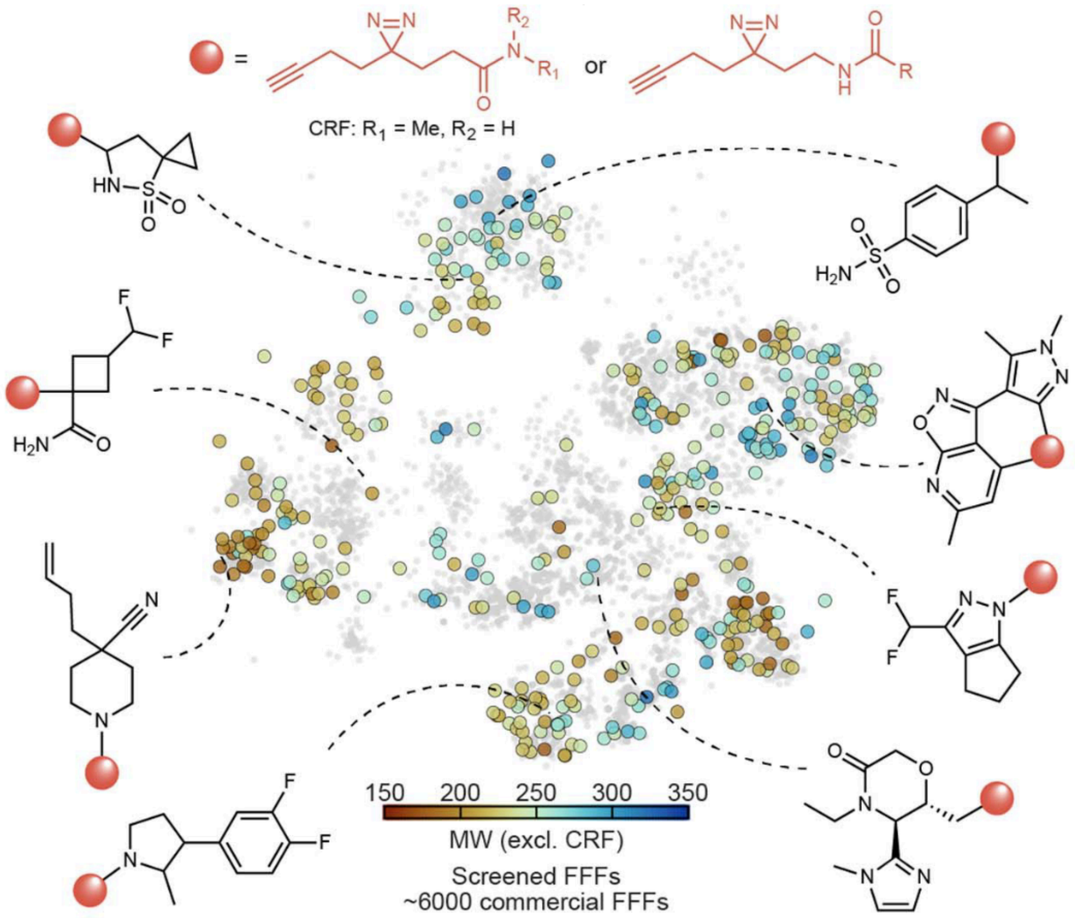
- *407 drug fragments encompassing a variety of chemical space*
- *each fragment linked to diazirine-azide moiety for PAL*
- *tested agains HEK293T cells at 50 µM*

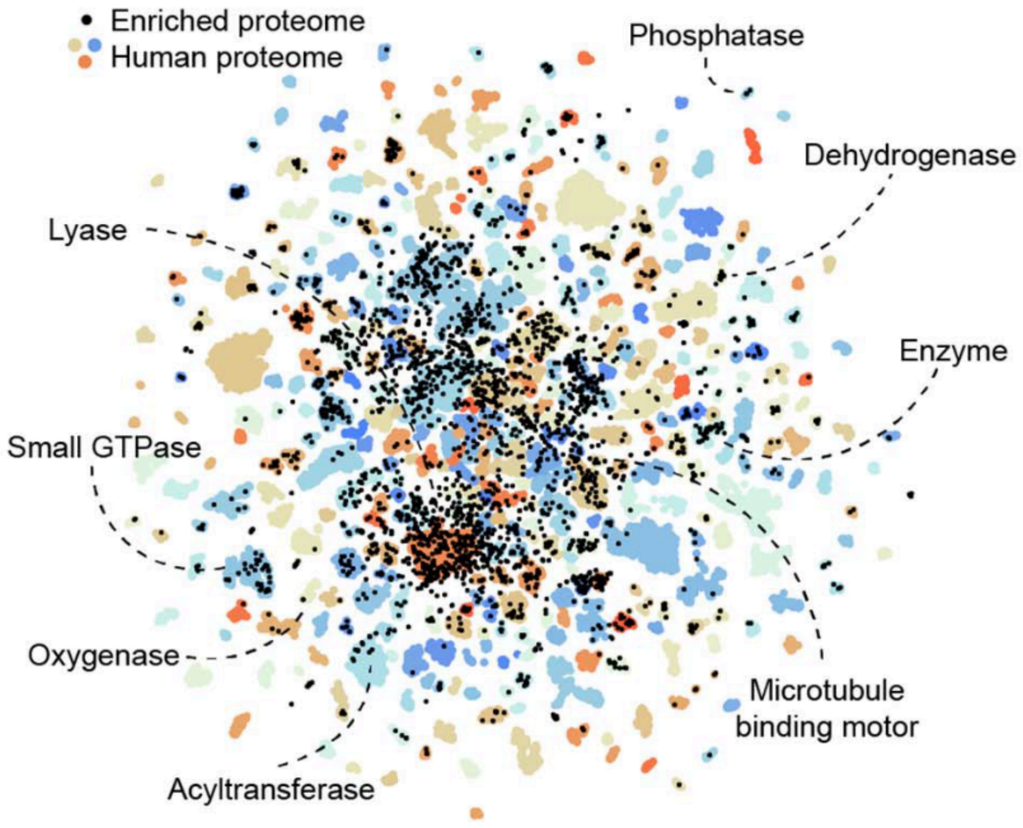
What if we could do FBLD in cells?

Offensperger, F.; Tin, G.; Winter, G.E. et al. *Science* **2024**, 384, 406.

Case study: large scale proteomics for ligand discover/prediction

chemical space of fragments → ***proteome coverage***





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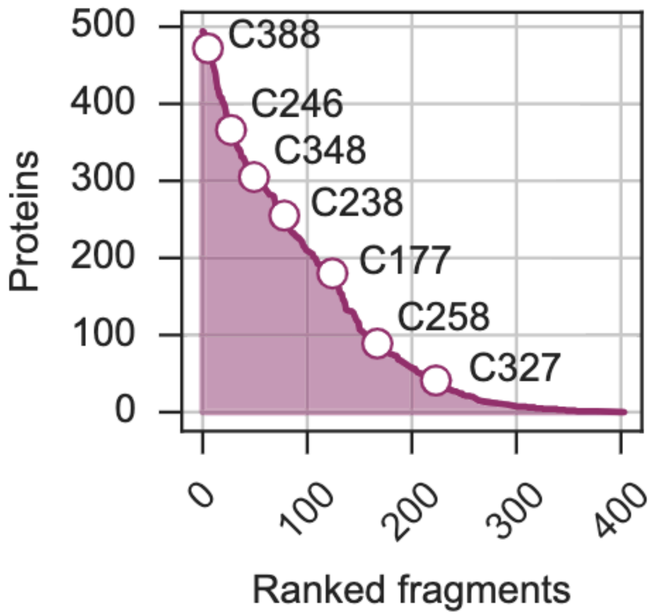
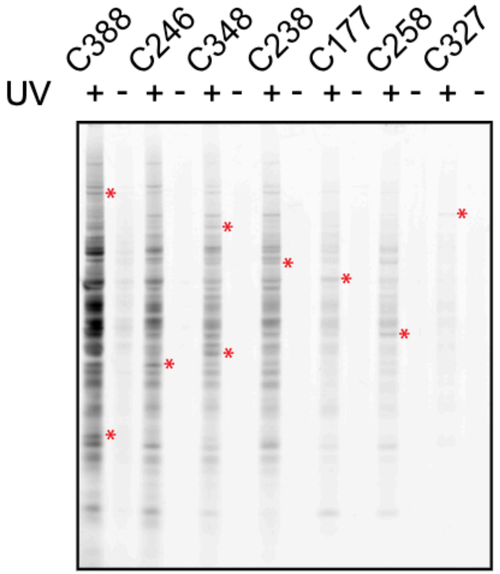
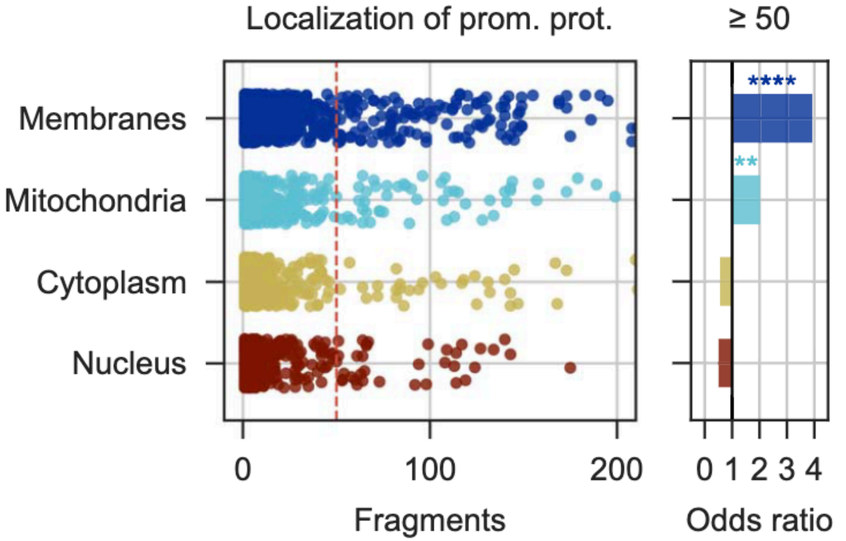
Case study: large scale proteomics for ligand discover/prediction

promiscuity ranking of drug fragments





localization of ligand targets



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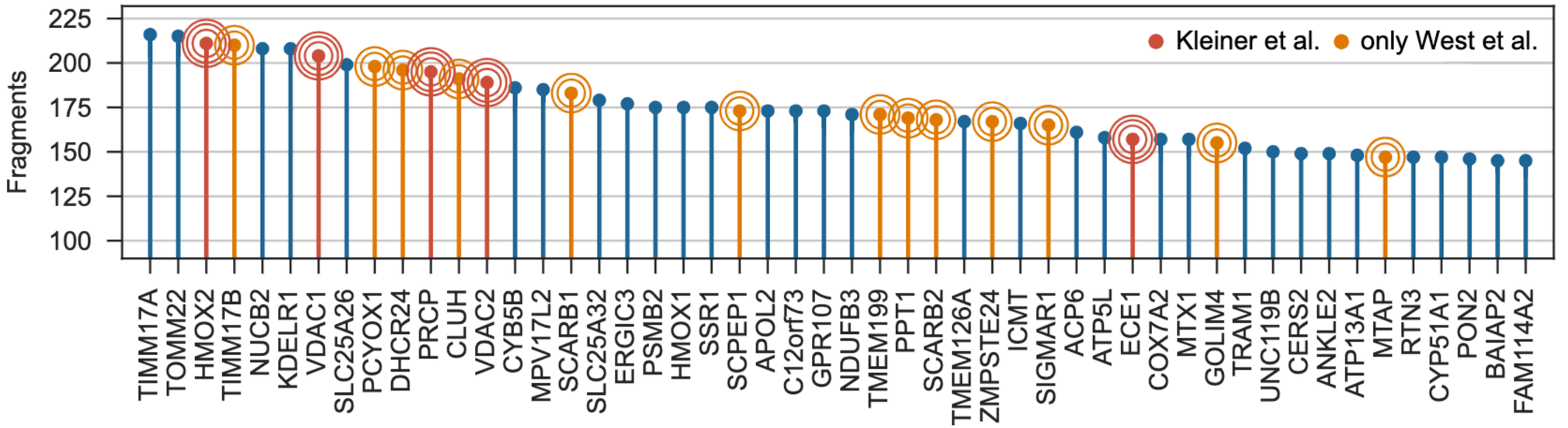
Case study: large scale proteomics for ligand discover/prediction

list of most commonly enriched proteins by fragments



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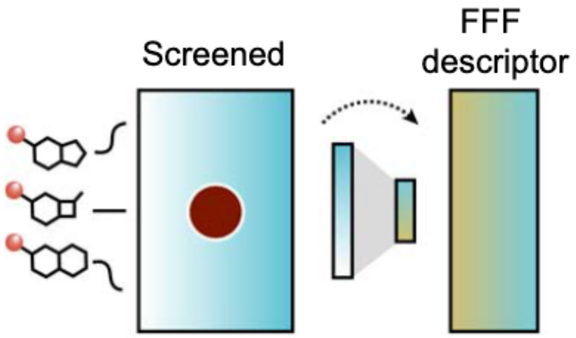
Case study: large scale proteomics for ligand discover/prediction

utilizing fragment data to predict promiscuity

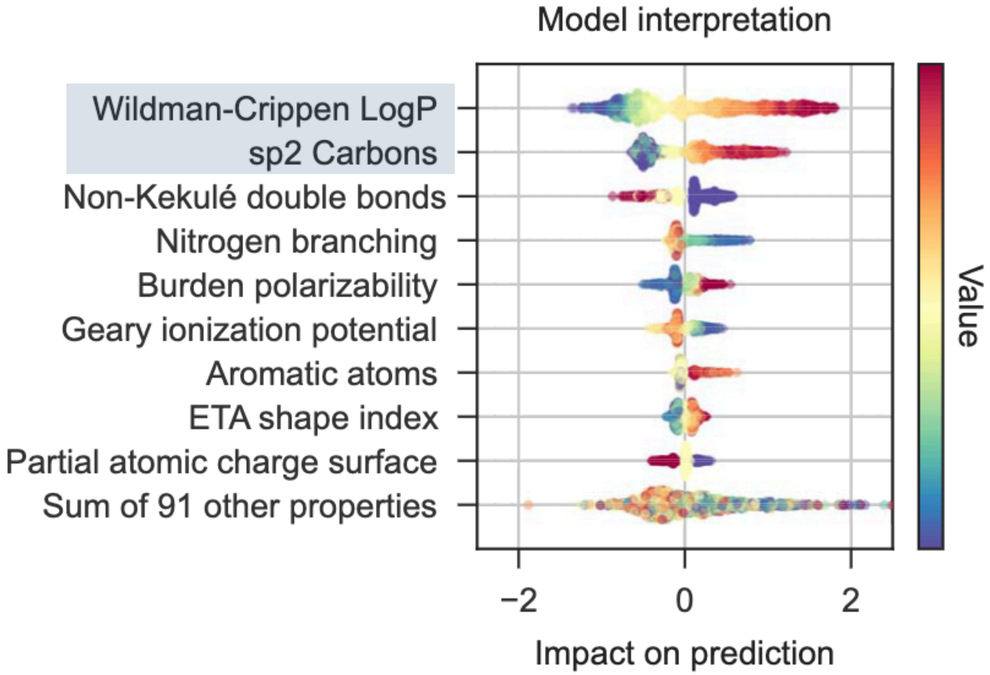
generate predicted promiscuity parameters

utilizing of fragment data
as a training set for machine learning



utilize 100 physiochemical properties
as predictors for promiscuity

analysis of most important molecular parameters



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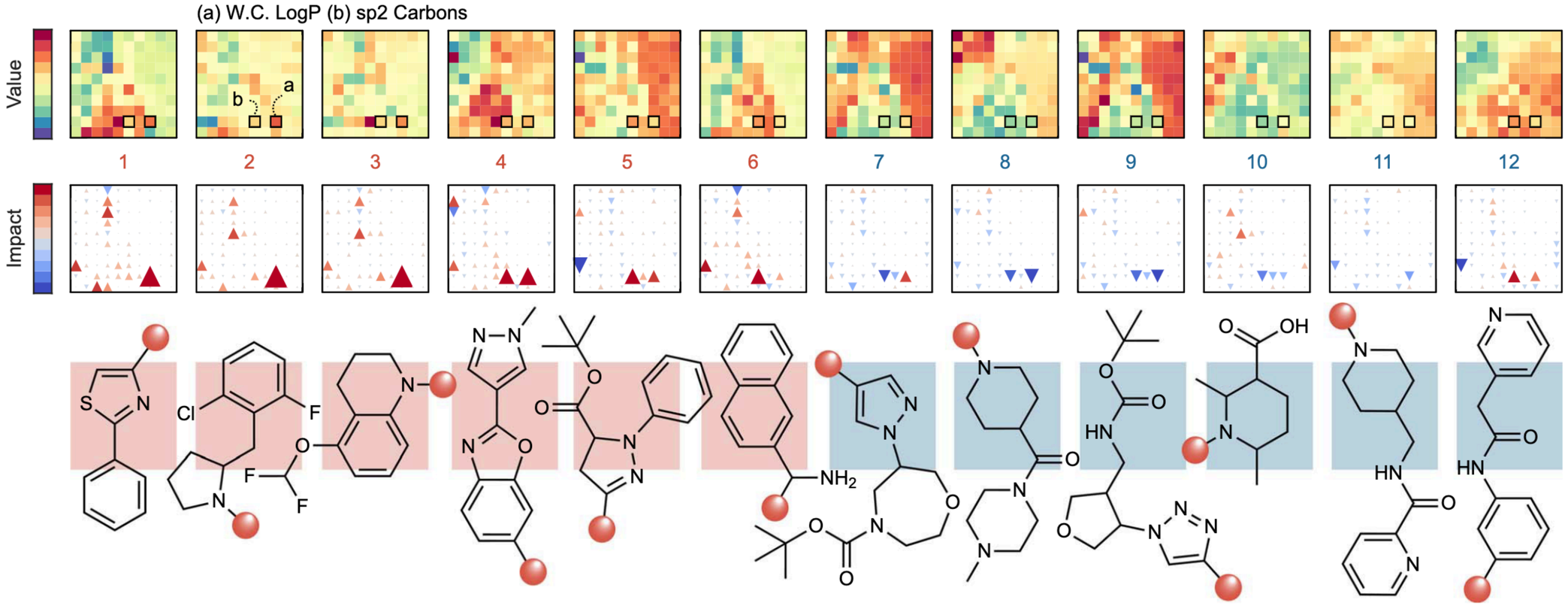
Case study: large scale proteomics for ligand discover/prediction

validation of promiscuity readouts

more promiscuous → *less promiscuous*



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Case study: large scale proteomics for ligand discover/prediction

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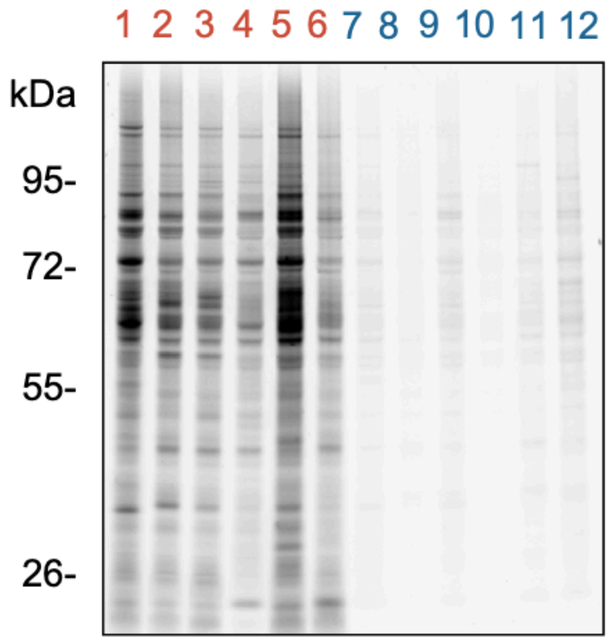
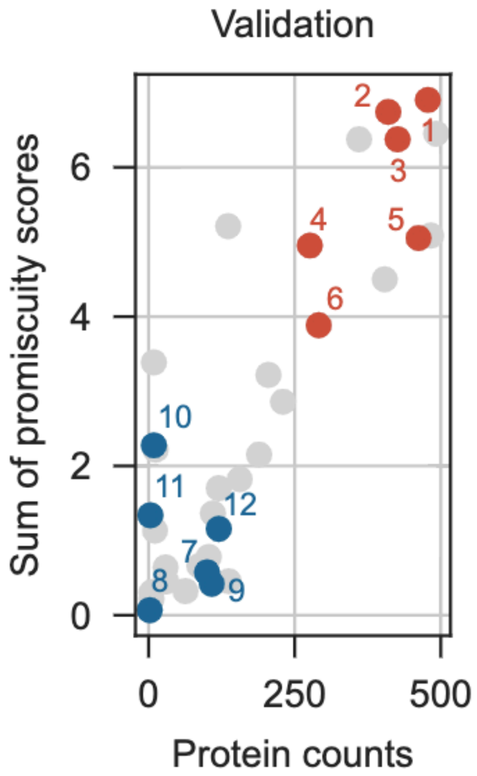
more promiscuous → *less promiscuous*

test compounds followed trend of promiscuity





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Polypharmacology takeaways

1. Polypharmacology isn't inherently good or bad

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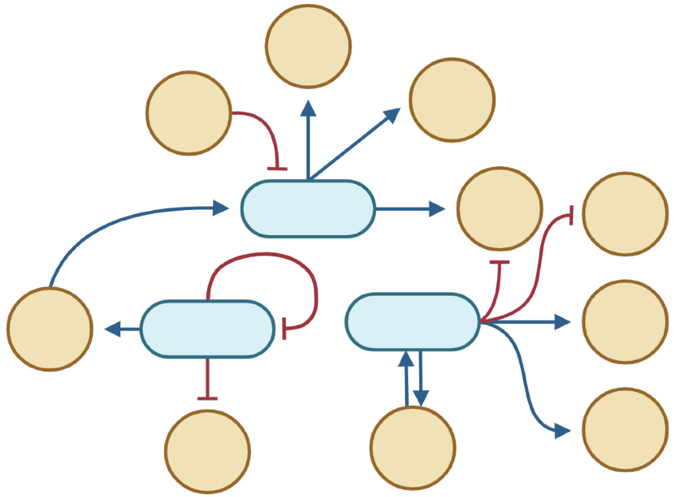
2. As our understanding of disease biology grows, so does the potential of polypharmacological approaches



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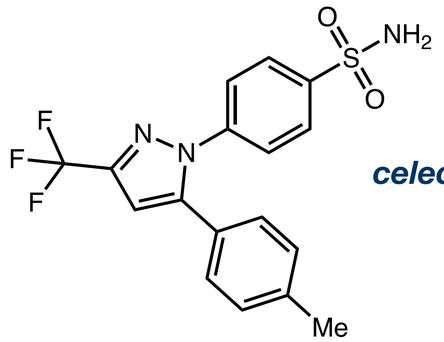
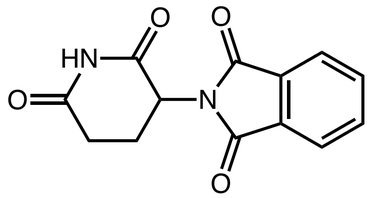
3. Revisiting of already approved drugs can uncover useful polypharmacology that can lead to drug repurposing



celecoxib

thalidomide



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2. As our understanding of disease biology grows, so does the potential of polypharmacological approaches

3. Revisiting of already approved drugs can uncover useful polypharmacology that can lead to drug repurposing

4. We are in a golden age for drug repurposing with new methodologies and opportunities

Questions?