SPANISH Drug Discovery Network

HARNESSING DRUG METABOLITES IN PRECISION MEDICINE

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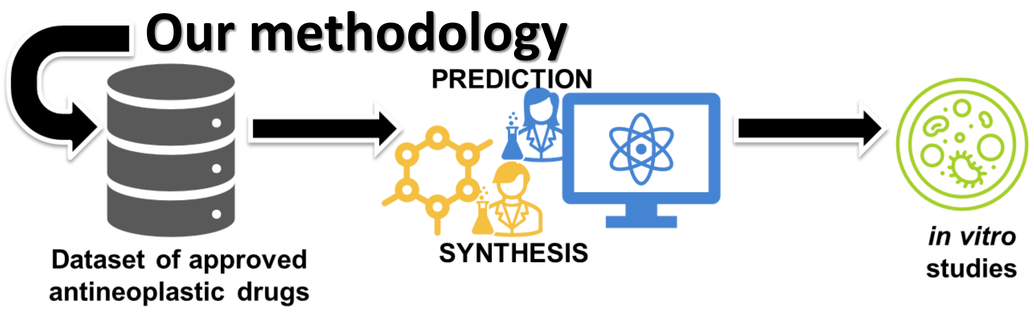
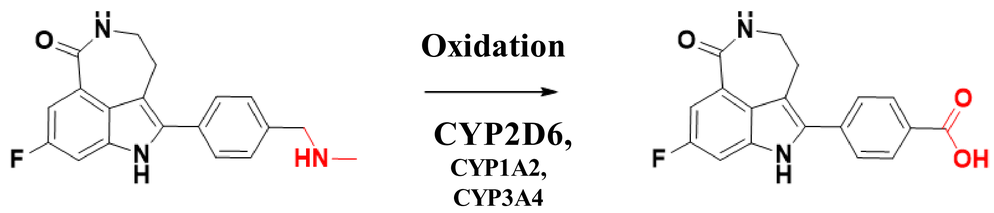
Introduction

Drug **metabolites can modulate different proteins than their parent drugs** that could be quickly translated into **meaningful clinical applications**. Approximately 20% of drug metabolites are believed to possess the necessary characteristics for exhibiting cellular activity[1]. Among these metabolites, certain ones have been proven to present the same biological activity than their parent drugs and some have even advanced into becoming i**ndependent drugs**[2]. Furthermore, recent evidence highlights that metabolites once considered inactive due to their limited biological impact on the same target as the parent drug might actually exhibit notable activity against different targets[3]. This discovery underscores the need for deeper exploration.

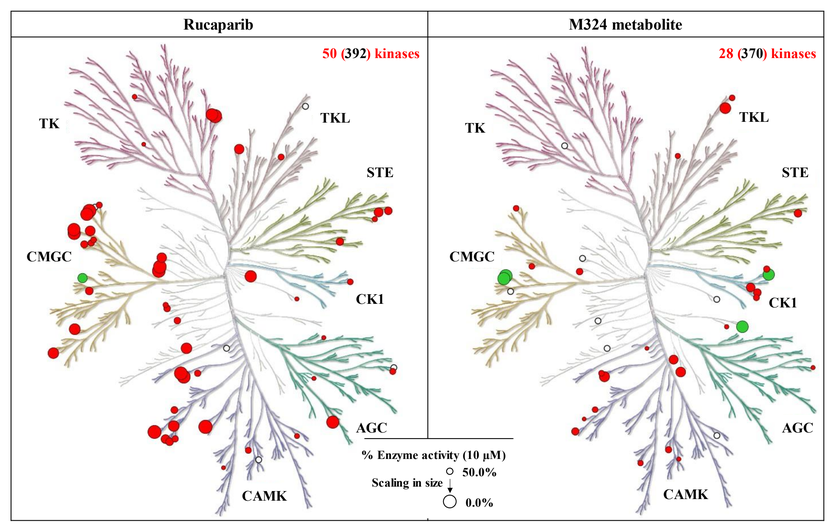
Our methodology



Rucaparib & M324 case of study

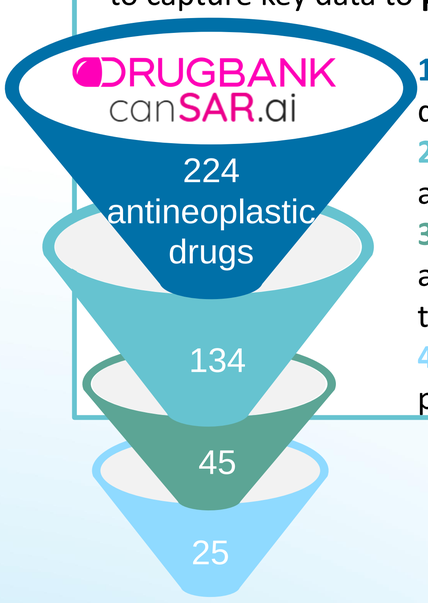


Rucaparib's primary metabolite, **M324**, and **Rucaparib** exhibit inhibition of distinct off-target kinases. Notably, M324 demonstrates a **distinct kinase polypharmacology profile**, notably marked by potent inhibition of GSK3A and PLK2 (IC_{50} < 600 nM), both of which are not strongly inhibited by rucaparib[4].



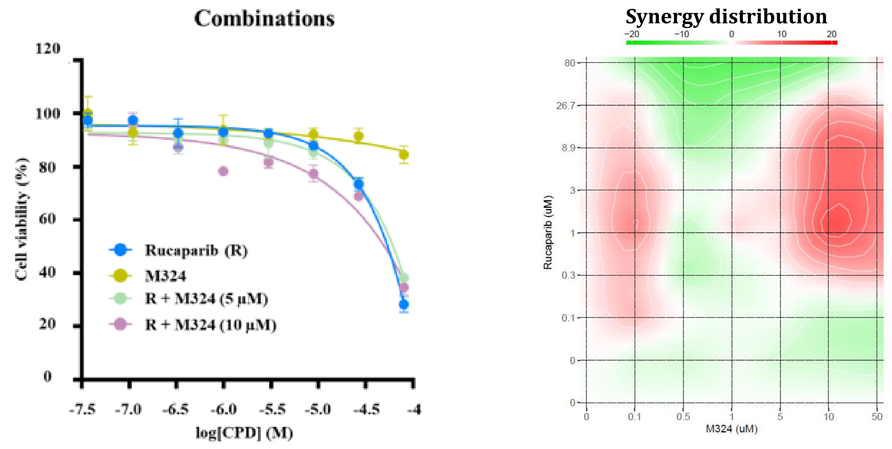
Major drug metabolite database

Aiming to discover **new applications** in precision medicine, a **curation** of a major **drug metabolite dataset** has been performed to capture key data to **prioritize** the most promising metabolites.



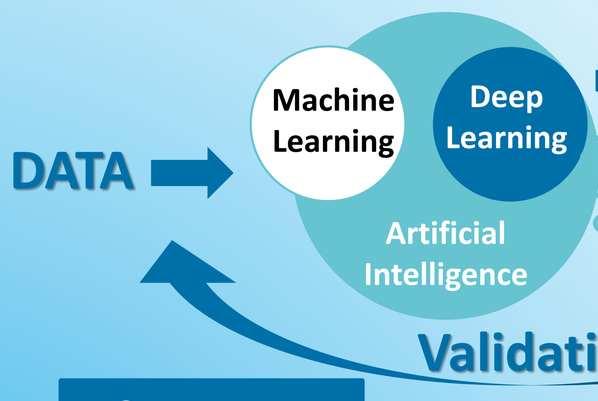
1st filter: Only FDA/EMA approved antineoplastic drugs that are small molecules were considered
2nd filter: Chemotherapy agents, photosensitizers and discontinued drugs were discarded.
3rd filter: Compounds presenting a metabolite accounting for >10% of in-plasma concentration of the parent drug were selected.
4th filter: Metabolites presenting off-target predictions different from its parent drug.

Intracellular kinase activity of M324 and drug-metabolite combinations in **prostate cancer lines**

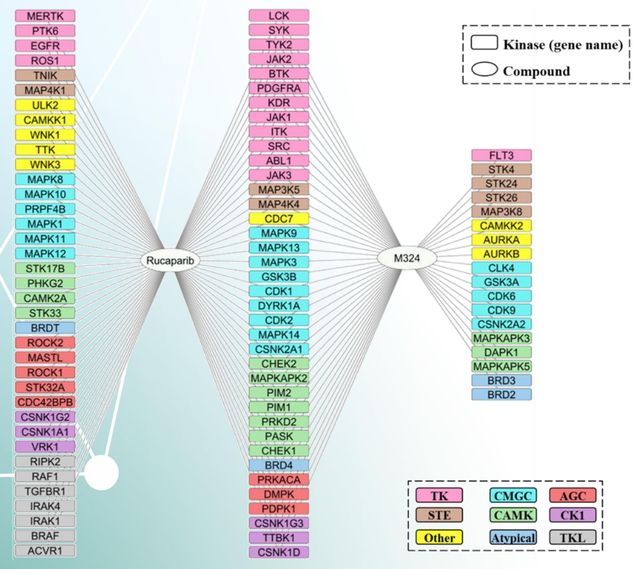


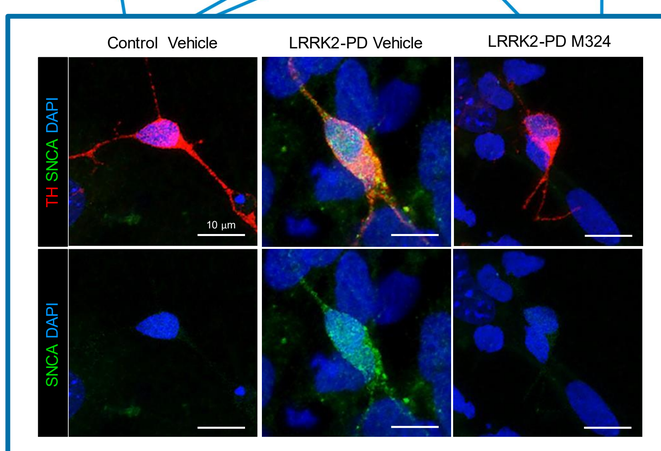
Computational approach

Through **polypharmacology prediction methods**, we can predict new activities against new **off-targets** of small molecules using public data connecting drugs, metabolites, targets, clinical outcomes, and even side effects. Plus, **crystallized protein structures** in the RSCB Protein Data Bank allows us to confirm our predictions through modelling studies such as **docking methodologies**. Finally, the **biological validation** gives us key information to better train the AI models in a looped process.



Commercial and web-based tools:
- Clarity
- Polypharmacology Browser 2 (PPB2)
- GalaxySagittarius
- SEA algorithm.





M324 reduces α-synuclein accumulation in hiPSC-derived neurons from a Parkinson's disease patient

Summary

M324 demonstrates that metabolites can be pharmacologically active and could potentially be used in precision medicine and repurposed for novel diseases like Parkinson's. Thus, the investigation of major metabolites opens a new promising approach for precision medicine, drug repurposing and side effect understanding.

References

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4. **Hu, H., …, Antolin AA.** ***Cell Chemical Biology, in press***. BioRxiv DOI: 11.22.517505

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