HARNESSING DRUG METABOLITES IN PRECISION MEDICINE:
Deeping into antineoplastic's major metabolites polypharmacology

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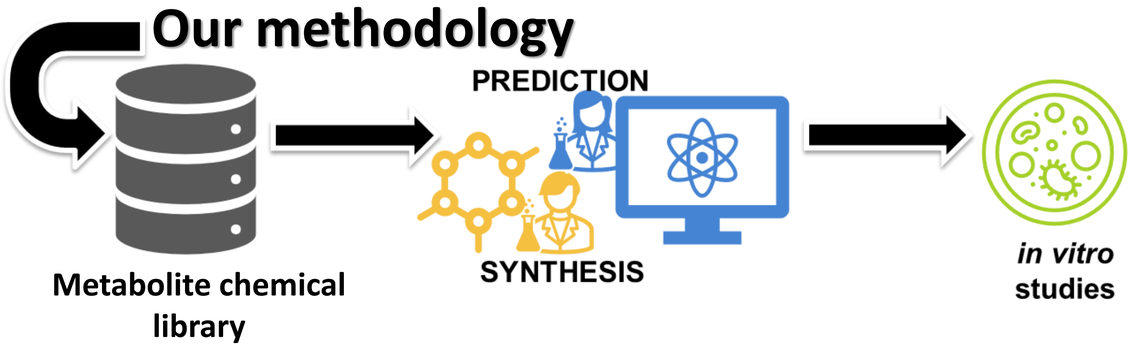
Introduction

Metabolites of drugs have the potential to modulate various proteins distinct from their parent drugs, leading to swift translation into valuable clinical applications. It is estimated that around 20% of drug metabolites harbor the essential traits to manifest cellular activity.[1] Within these metabolites, some have demonstrated equivalent biological activity to their parent drugs, with select few progressing to become standalone pharmaceutical agents[2]. Moreover, recent evidence underscores that metabolites previously deemed inactive due to their restricted biological impact on the same target as the parent drug may indeed demonstrate **significant activity against alternative targets**[3].

This discovery underscores the need for deeper exploration in the study of drug – and metabolites' – polypharmacology.

Our methodology



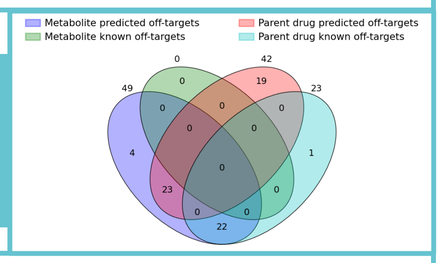
Methods: Computational approach

1 **Polypharmacology prediction methods** enable us to anticipate fresh activities against **novel off-targets** of small molecules by leveraging publicly available data linking drugs, metabolites, targets, clinical outcomes, and even side effects.

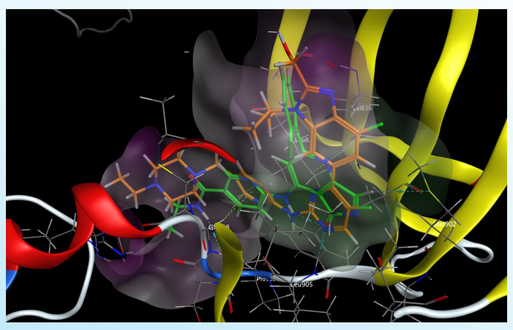
Some commercial and web-based tools:

Chemotargets CLARITY® v3.0

Polypharmacology Browser 2
GalaxySagittarius
SEA algorithm



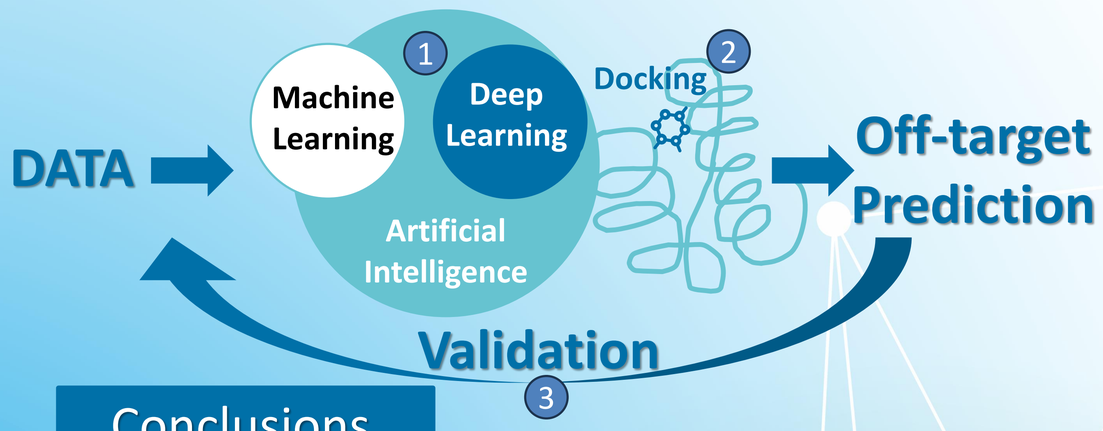
2 Additionally, the availability of **crystallized protein structures** in the RCSB Protein Data Bank empowers us to validate our predictions through modeling studies such as **docking**.



Abemaciclib metabolite docked in crystallized JAK3 structure (**PDB**: 7UVY).

Metabolite	Tanimoto Index	Score S (kcal/mol)
Hydroxyabemaciclib (in orange)	0.552	-8.4904
Ligand (in green)	1.000	-7.5046

3 Finally, the **biological validation** gives us key information to better train the AI models in a looped process.



Overview: Previous studies & hypothesis

Previous reported studies in the group evidenced that **Rucaparib** and its primary metabolite, M324, show a **distinct kinase polypharmacology profile**[4]**.**

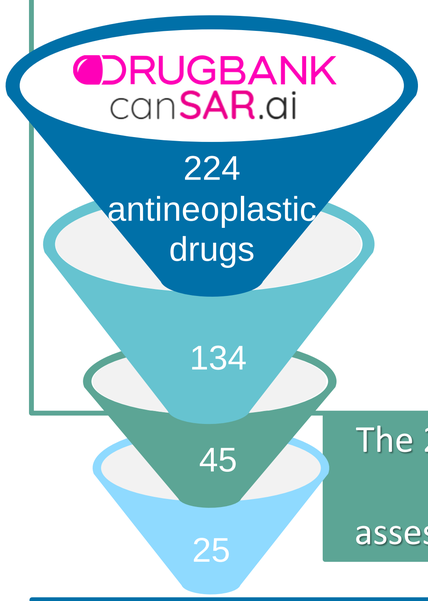
The total characterization of the metabolite has evidenced two potential beneficial effects:

- Synergistic effect in prostate cancer lines for Rucaparib-M324 combination
- Potential metabolite repurpose for Parkinson's Disease treatment

Thus, we hypothesize that **the investigation of major metabolites opens a new promising approach for precision medicine, drug repurposing and side effect understanding**.

Major drug metabolite library

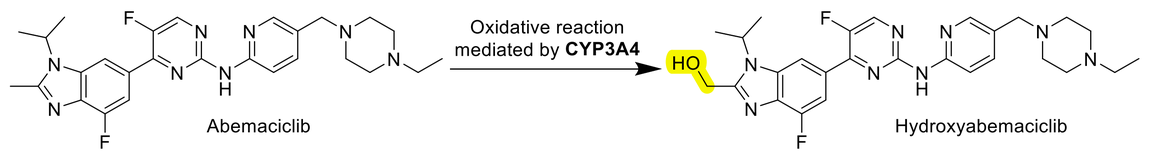
Aiming to discover **new applications** in precision medicine, a **curation** of a major **drug metabolite dataset used in CANCER therapy** has been performed to capture key data to **prioritize** the most promising metabolites.



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.

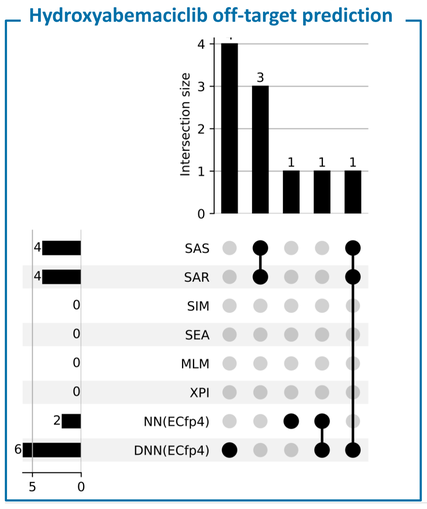
The 25 study-case set of parent drug-metabolites have been synthesized and are ready for biological assessment to proof their polypharmacological profile.

Results: Abemaciclib & hydroxyabemaciclib

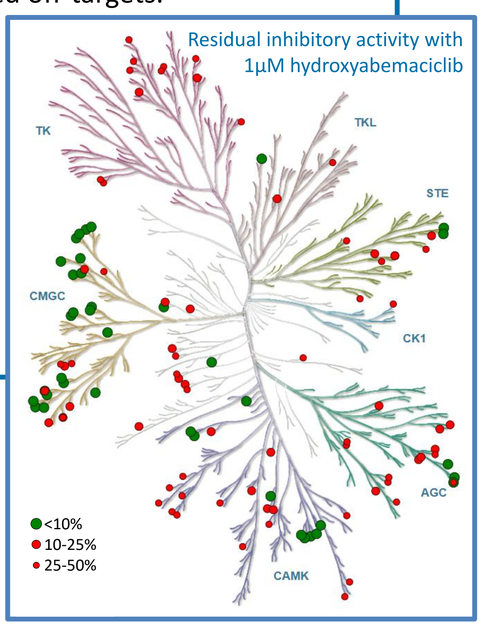


Abemaciclib's metabolite is considered **active** against the parent drug's targets (CD4 and CDK6) and is present in **26%** of in-plasma human concentration.

Hydroxyabemaciclib off-target prediction



- Through 8 polypharmacology predictive models, **10 distinctive off-targets** from the parent drug's have been forecast.
- **JAK1, JAK3 and ABL1** stand out as three of the most coincident predicted off-targets.
- Preliminary evidence suggests that the metabolite would **potently inhibit one of the three predicted off-targets**. Confirmatory studies are underway



Conclusions

In conclusion, **investigating the effects of prominent drug metabolites** is of vital importance to achieve a comprehensive understanding of **drug responses** in clinical settings. It emphasizes the necessity to fully harness the potential of our existing arsenal of medications, particularly in personalized and precision medicine, to optimize patient outcomes.

Plus, there is a huge therapeutical opportunity in metabolite repurposing…

References

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ICR The Institute of Cancer Research