**HARNESSING DRUG METABOLITES IN PRECISION MEDICINE**

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**Abstract**

The comprehensive characterization of drug metabolites' polypharmacology is a seldom-explored aspect in drug discovery and development. Nevertheless, certain drug metabolites can achieve high concentrations in the bloodstream and exhibit noteworthy *in vivo* activities distinct from their parent drugs. In this study, we employ a combination of computational and experimental methods to thoroughly assess the multi-target pharmacological effects of M324, which is the primary metabolite of the FDA-approved PARP inhibitor, Rucaparib1. Our experiments convincingly establish that M324 has a different kinome profile when compared to its parent drug, showcasing potent inhibition of GSK3A and PLK2 at concentrations typically observed in clinical settings. These confirmed kinase activities of M324 may have significant implications for the effectiveness and safety of Rucaparib, thus requiring further clinical exploration. Significantly, we also identify a synergistic effect between the drug and its metabolite in prostate cancer cell lines, and a complete reduction of alpha-synuclein accumulation in patient-specific dopamine neurons from individuals with Parkinson's disease treated with the metabolite. These biological actions hold promise for potential clinical applications and may open up new avenues for drug discovery in areas where there are substantial unmet medical needs.

This study underscores the vital importance of thoroughly investigating the actions of major drug metabolites to gain a comprehensive understanding of drug responses in clinical settings and to fully harness the potential of our existing arsenal of drugs in the context of personalized and precision medicine.

**References**

(1) Hu H, Serra C, Zhang W, Scrivo A, Fernández-Carasa I, *et al*. Identification of differential

biological activity and synergy between the PARP inhibitor rucaparib and its major

metabolite. ***Cell Chemical Biology****, in press*. bioRxiv preprint available here:

https://www.biorxiv.org/content/10.1101/2022.11.22.517505v1