Exploiting polypharmacology in precision oncology: identification of differential kinase off-targets among clinical PARP inhibitors

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Introduction: Drug polypharmacology & PARP inhibitors

• A more comprehensive and systems-based approach to pharmacology is uncovering that drugs tend to bind to more than one target (Figure 1-2), a behaviour commonly referred to as polypharmacology with clinical implications that are still not well understood.¹

• The increasing availability of ligand-target interaction data in the public domain in resources such as canSAR² enables the development of computational methods to predict polypharmacology, that are becoming a cost-effective means to uncover new targets of drugs.

One-drug one-target

One-drug multiple-targets

• PARP inhibitors are a new class of targeted small-molecule cancer therapeutics that have showed unexplained differential effects in cellular models and clinical trials.¹

• Can we use computational methods to identify previously unknown off-targets of PARP inhibitors that can explain their observed differences?

Identification of differential kinase polypharmacology between PARP inhibitors

• PJ34 is a widely-used chemical probe to study the PARP protein family.²

• However, PARP-independent effects of PJ34 had been reported.²

• We used in silico target profiling to predict that Pim1 and Pim2 kinases could be off-targets of PJ34 due to the similarity with CHEMBL572783.³

• We subsequently validated our predictions in vitro.¹

• The newly-identified off-targets could have confounded many biological functions attributed to PARPs.⁴

Differential effects could be observed between several PARP drug candidates.⁵

• We explored whether the Pim kinase polypharmacology of the PARP chemical probe PJ34 was maintained among other PARP drug candidates and we expanded the off-target panel to 16 kinases sharing >60% of ligands with Pim1.²

• PARP drug candidates have a totally different in vitro affinity profile against this panel of kinases.¹

• Chemical probe polypharmacology can be used to identify new targets of drugs.³

Harnessing polypharmacology in precision oncology

• Off-targets of drugs have already been used to extend the uses of cancer drugs in the framework of precision oncology as illustrated by imatinib.⁶ However, these cases have arrived by serendipity and we aim at performing the first comprehensive analysis to exploit off-targets to extend the uses of cancer drugs.

• To this aim, we are currently analysing clinical trials performed at the Royal Marsden Hospital to identify molecularly targeted drugs taken by patients who had an exceptional response to the drug. Next, we will predict new targets and confirm them using in vitro experiments.

• Finally, we will use available clinical ‘omics’ data to try to identify associations with the newly identified targets and that can later on be validated as biomarkers to extend the uses of these cancer drugs in the framework of precision oncology.

Methods

• In silico target profiling using 2D feature-pair distribution descriptors and public sources of ligand-target interaction data to predict off-targets of selected drugs.

References


