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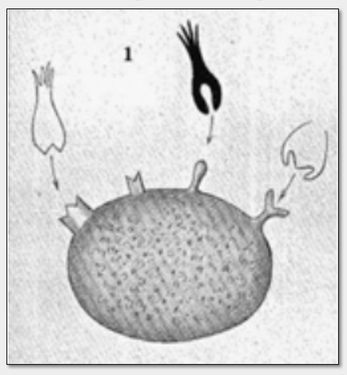
Exploiting polypharmacology in precision oncology: identification of differential kinase off-targets among clinical PARP inhibitors

Dr. Albert A. Antolin, Dr. Jordi Mestres, Prof. Paul Workman and Dr. Bissan Al-Lazikani

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 canSAR[2] 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

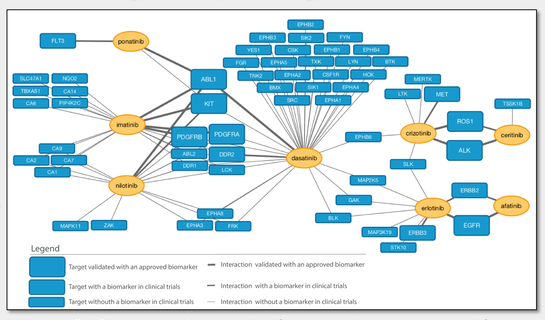


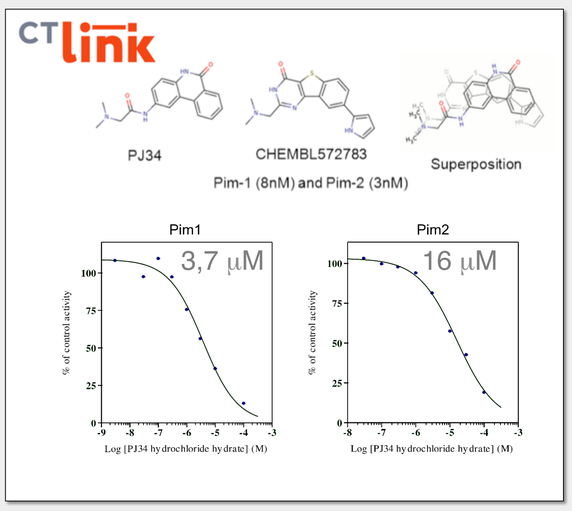
Figure 1. Early view of drug action proposed by Paul Ehrlich in 1901.[1]

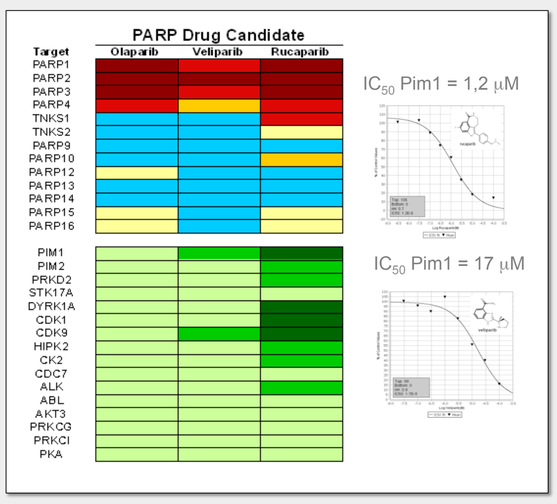
Figure 2. Drug–target network of cancer drugs approved for more than one indication due to their binding to multiple targets.[2,6]

- **PARP inhibitors** are a new class of targeted small-molecule cancer therapeutics that have shown **unexplained differential effects** in cellular models and clinical trials.[3]
- **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.[4]
- However, **PARP-independent** effects of PJ34 had been reported.[4]
- 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.[4]
- We subsequently **validated** our predictions ***in vitro***.[4]
- The newly-identified off-targets could have **confounded** many biological functions attributed to PARPs.[4]



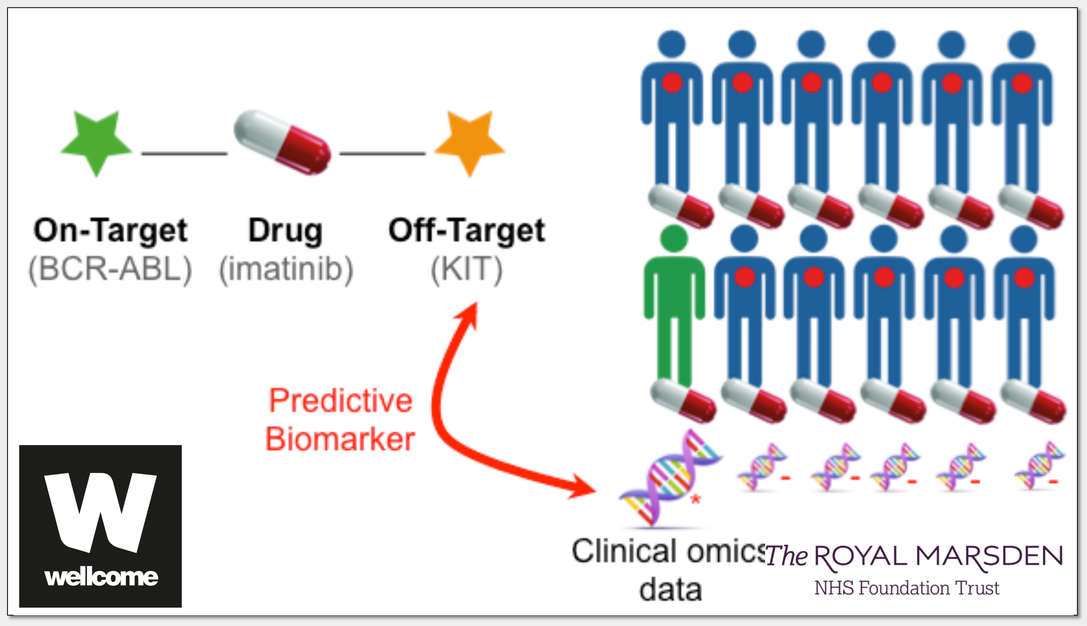


- **Differential cellular effects** had been also reported between several PARP drug candidates. [3]
- We explored whether the Pim kinase polypharmacology of the PARP chemical probe PJ34 was maintained among other PARP drug candidates and we expanded the off-target panel to 16 kinases sharing >60% of ligands with Pim1.[3]
- PARP drug candidates have a totally **different *in vitro* affinity profile** against this panel of kinases.[3]
- **Chemical probe polypharmacology** can be used to **identify new targets of drugs**.[3]

- There are now **3 PARP inhibitors approved by the FDA**. Therefore, clarifying if the observed differential off-targets have clinical implications is essential, to enable oncologists to prescribe the best inhibitor in each case.
- An analysis of reported side-effects uncovers **differences in their side-effect profile** that could be attributed to the identified off-targets.
- Specifically, **Pim-1** has been linked with **ALT/AST** upregulation in the liver.[5]
- The identified off-targets might be also used to extend the clinical uses of PARP inhibitors.

Harnessing polypharmacology in precision oncology

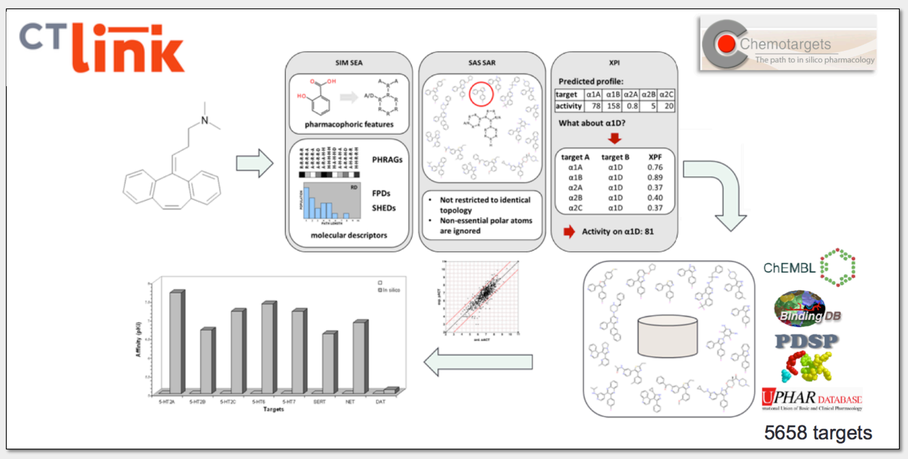
- Sir Henry Wellcome Postdoctoral Fellowship project funded by the **Wellcome Trust** as a collaboration between The Institute of Cancer Research, The Royal Marsden Hospital, Merck Sharp and Dohme and Benevolent.Ai.
- This unique **collaboration between academia and industry** aims to identify previously unknown targets of drugs to which some patients have had an exceptional response. This work may enable **the use of these drugs to be extended**, for the benefit or more cancer patients.



- 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.



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Contact

Cancer Research UK, Cancer Therapeutics Unit,
Division of Cancer Therapeutics and Division of Data Science,
The Institute of Cancer Research,
15 Cotswold Road, Belmont, Surrey SM2 5NG
Email: Albert.Antolin@icr.ac.uk

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