Study polypharmacology earlier in drug discovery, say researchers

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Polypharmacology—the ability of a drug to affect more than one protein—should be studied early in the drug discovery pathway, and constantly monitored as the chemical structure is optimized in the design of the clinical candidate, leading researchers believe.

New research demonstrates the importance of assessing polypharmacology from the outset to avoid undesirable off-target effects or potentially in future even to deliberately hit two or more desired targets at once.

The new study by scientists at the Institute of Cancer Research, London, used computational and experimental approaches to investigate the polypharmacology of a class of drugs called Hsp90 inhibitors, determining whether these inhibitors also affect another group of proteins, namely kinases.

The research showed the potential for the polypharmacology of a prototype drug to change as it is optimized for activity against one particular protein through the drug discovery journey—and reinforced the importance of keeping a careful track of which additional proteins a drug is hitting from the start.

Drugs with significant polypharmacology run the risk of being less specific in their effects on cells than those that only hit a single protein. The consequences of off-target effects are hard to predict and could include unexpected side effects and difficulty in understanding a drug's real mechanism of action, or could potentially increase the effectiveness of a drug if it was able to hit multiple cancer targets.

Studying Hsp90 inhibitors

Scientists at the ICR screened Hsp90 inhibitors against very large numbers of kinases—using both computer-based and experimental methods—in research published in *Cell Chemical Biology* and largely funded by Wellcome.

Although these inhibitors were initially designed to inhibit the activity of one cancer-driving protein, Hsp90, the researchers found that some of

the drugs were 'multi-tasking," affecting several kinases as well as Hsp90. They also showed that the kinases affected changed unexpectedly during the optimisation of one of the drugs.

Hsp90 is a protein chaperone—meaning it helps other 'client' proteins to fold correctly in the cell—and is therefore essential for the proper functioning of many biological systems.

Hsp90 works with hundreds of client proteins, including several potential cancer drug targets and also proteins involved in Alzheimer's disease and viral proteins from SARS-CoV-2. Hsp90 inhibitors have entered clinical trials for the treatment of cancer and also for Alzheimer's disease and COVID-19.

Predicting off-target effects

In the new work, the researchers studied six different Hsp90 inhibitors from different chemical families. Two clinical stage drugs, ganetespib and luminespib, showed significant off-target effects, meaning they affected kinases as well as Hsp90.

The scientists used computational approaches to predict the kinase polypharmacology of all six inhibitors and confirmed many of the predictions through large-scale experimental laboratory analysis. Luminespib and ganetespib showed off-target effects on several kinases, including some known to be involved in cancer development.

Kinases move phosphate groups onto proteins, affecting the activity of the protein. They play a key role in metabolism as well as cell signaling and are actual or potential targets for many cancer drugs.

Importantly, the computational 'in silico' methods predicted half of the off-target effects found in the lab for both ganetespib and

luminespib—underlining the usefulness of computational biology in drug discovery studies of this type.

Evolving polypharmacology

For luminespib, the original 'hit' compound and two 'lead' compounds—previous iterations of the chemical molecule that became the drug—are publicly available, and so the researchers were also able to study how the off-targets evolved during the discovery of this drug.

The researchers found that the off-target effects of luminespib changed significantly as the molecule was optimized. Unexpectedly, the final drug, luminespib, had significantly more off-targets than the lead compounds, and these included kinases that were not affected by the original hit compound.

The finding that the polypharmacology of a drug can change during the course of drug discovery suggests that off-target effects should be monitored from a much earlier stage and then throughout the project.

The researchers also provided evidence that Hsp90 inhibitors could bind to kinases in live cells.

The researchers believe that understanding a drug's polypharmacology will be essential to be able to properly investigate and establish its mechanism of action. It should be possible to design out unwanted off-target effects, or potentially in future drugs could be designed to deliberately hit two or more desired targets at once, in order to pack a stronger punch than just hitting a single protein.

Study lead author Dr. Albert Antolin, Sir Henry Wellcome Postdoctoral Fellow at the Institute of Cancer Research, London, said,

"The polypharmacology of a drug can influence the effects it has on cells, and the way it operates as a treatment. We found, to our surprise, that the polypharmacology of drug candidates created to target the protein chaperone Hsp90 changed during the drug discovery journey—with later-stage versions of the drug regaining off-target effects, and also gaining new effects different from earlier iterations.

"Our study underlines the importance of investigating off-target effects earlier in drug discovery, to be aware of potentially negative effects, and perhaps even to be able to exploit the benefits of off-target effects. It also demonstrates the growing value of in silico, computational methods in drug discovery."

Computational predictions

Study co-leader Professor Bissan Al-Lazikani, Head of Data Science at The Institute of Cancer Research, London, said:

"The systematic study of polypharmacology needs to become a crucial part of drug discovery. As computational approaches continue to improve, we can better predict how drugs will behave across the whole proteome, with an opportunity to understand much better how they exercise their effects on cells.

"Our new research underlines the potential of computational techniques to help discover off-target effects that may interfere with a drug's specificity, and even opens up future opportunities to design 'multi-tasking' drugs that hit more than one target involved in disease."

Study co-leader Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"At the ICR we are deeply interested in the extent to which drugs and

chemical tool compounds we use in the lab are able to interact with other proteins, in addition to the primary target of interest.

"It's important to be able to predict and characterize these targets in order to understand exactly how drugs and chemical probes work in cells and also to learn how to control this multi-tasking behavior to maximize the therapeutic benefit for patients and minimize side effects.

"Our current findings provide an important case study that we and other researchers can learn lessons from for future drug design."

More information: Albert A. Antolin et al, Evolution of kinase polypharmacology across HSP90 drug discovery, *Cell Chemical Biology* (2021). DOI: 10.1016/j.chembiol.2021.05.004

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