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# Combine chemical probe resources to optimize biomedical research, scientists urge

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A new report urges biomedical researchers to use online web resources very carefully, taking into account their complementary benefits and weaknesses, when selecting small-molecule chemical probes to help answer their research questions.

In a 'special report' published today in the journal *Future Medicinal Chemistry* today (Thursday), scientists at The Institute of Cancer Research, London, carried out the first comprehensive assessment of all the publicly available resources on chemical probes.

The report strongly recommends that researchers should avoid general search engines and vendor catalogue information and instead use two kinds of online resource—expert reviews and computational Big Data approaches—in order to make the best decisions about which chemical probes to use in biomedical research, and also to avoid poor selection of tools that can lead to incorrect conclusions.

Small-molecule chemical probes are important tools that are widely used by scientists to modify—usually to inhibit—the activity of individual proteins in isolated cells or organisms and hence to determine their function. Chemical probes are also used to test the role of a particular protein in diseases such as cancer, and to help validate that protein as a target for future drugs.

Small-molecule probes provide an alternative approach to genetic technologies such as RNA interference and CRISPR—in fact the

chemical and genetic approaches are very complementary and highly effective when used in harness together.

Unfortunately, many small-molecule compounds that have been claimed as chemical probes, and often used very widely, are not sufficiently specific for the protein of interest—and using them can generate incorrect results. Some compounds hit a few extra protein targets while others hit very many others.

There is a pressing need to supply biomedical scientists with appropriate information so that they can select the best possible chemical probes for their experiments, helping to ensure that their research findings are robust.

A major challenge is that the information about potential chemical probes is scattered across many different scientific publications and other sources, making it difficult for scientists to make a fully informed choice—especially if the researcher is not an expert in chemical biology, pharmacology or drug discovery. Fortunately, help has been forthcoming over the last few years through the development of publicly available online resources on chemical probes.

The team of chemical probe researchers at The Institute of Cancer Research (ICR) discuss the various different web resources that supply information to guide the choice of chemical tools—finding that they all have their own strengths and limitations. They provide user-friendly advice on how to navigate these resources to select the best possible chemical probes for a researcher's needs.

The report stresses the value of resources that provide reviews written by chemical probe experts. It especially highlights the Chemical Probes Portal where chemical biology experts currently provide assessments on 192 chemical probes for 181 different proteins of interest and offer

advice on how best to use them. The portal also has information on around 200 other small-molecule compounds that should no longer be employed, even though many of these may have been used extensively in the past.

But there are also some limitations to resources that rely on expert peer review. For instance, most of the probes assessed on the Chemical Probes Portal act on particular protein families (kinases, G-protein-coupled receptors, phosphodiesterases, epigenetic proteins and BCL2 family members) and many other protein families are not yet covered. In addition, it is not so easy to keep such resources up to date, since they rely on manual input from volunteer reviewers. Changes are under way to address these points and make other enhancements to the portal.

The report also emphasises the usefulness of resources that provide objective assessment of chemical probes using large-scale, quantitative computational analysis. It highlights Probe Miner, a public web-based resource that was launched by the ICR research team in 2017 with funding from Wellcome. Probe Miner has several key advantages. It is objective, data-driven, quantitative and very comprehensive—based on bioactivity data for more than 300,000 small molecules acting on more than 2,300 human proteins. The underlying databases are frequently updated, ensuring that analyses are carried out using the latest information.

But the researchers also warned that some data sources and chemical probes could be missed from these computational systems—and also that the rankings of probes could be difficult to interpret for biologists lacking detailed expertise in chemical biology.

The report concludes that the continued enhancement of online resources will improve the selection of high-quality chemical probes and increase the robustness of biomedical research. It recommends that the

complementary expert-reviewed and computational data-driven resources should be used alongside each other to ensure the best decisions about which chemical tools to use—and that this could go a long way to addressing the major problems with the current misuse of chemical probes in biomedical science and drug discovery.

The authors also acknowledge that there is a significant challenge to make biologists aware of the resources available and to encourage their use. They encourage the wide dissemination of the recommendations in the report and uptake by researchers, research funders, journals and vendors to improve the quality and robustness of biomedical research.

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

"Chemical probes are vital tools in biomedical research, playing a key role in understanding how proteins work and what impact they have in cancer cells. These chemical tools frequently also power the start of campaigns to discover new cancer drugs. So it's of the utmost importance that scientists are careful and thorough when choosing chemical probes for their experiments. Failure to do so can result in unreliable or misleading results.

"In the past five years, we have seen a rise in efforts to pull together all available data on the characteristics and quality of chemical probes in publicly accessible databases, including our own data-driven resource, Probe Miner.

"In our review of the various online chemical probe resources available we found that they all have their own merits, and that Big Data approaches are a major step forward in bringing together the most up-to-date evidence. We really need to be combining the different sources of information so that researchers can get the best possible information

about chemical probes."

Study co-leader Dr. Albert Antolin, Sir Henry Wellcome Postdoctoral Fellow in Systems Pharmacology at The Institute of Cancer Research, London, said:

"To be useful for research, chemical probes actually have to be more selective for a target than many drugs used to treat patients, where the effectiveness and safety of the treatment are the most important criteria. If researchers want to find out the exact role of a particular protein in the body, or in disease, then action on several targets can be misleading or completely unacceptable.

"There is a vast volume of information on potential chemical probes but this information is spread around in different formats, so biomedical researchers need help to find the best high-quality chemical tools for their research."

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

"The poor selection and use of chemical probes can lead to incorrect and misleading results. There have been cases where use of poor-quality compounds has led scientists down entirely the wrong track, wasting precious time and funding, and even at times slowing down the discovery of drugs for the treatment of patients.

"It's incredibly important that we spread the word about the importance of prudently choosing the best possible chemical probes in biomedical research, so we can put a stop to the ongoing use of outdated tools, and ensure that biomedical science leads to robust, reliable results.

"Using chemical probe resources curated by experts alongside those

powered by Big Data approaches is the best way to select the right probe on the basis of the most recent evidence. We urge researchers, funders, scientific journals and vendors to utilise the recommendations in the report."

Provided by Institute of Cancer Research

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