

Researchers call for improved use of chemical tools to enhance biomedical research

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Experts in biomedical research are calling for better use of chemical probes to improve our understanding of protein function and the foundations on which much of modern drug discovery and development are based.

In an interview in *Nature Communications*, Professor Paul Workman, Harrap Professor of Pharmacology and Therapeutics at The Institute of Cancer Research, London, and Professor Cheryl Arrowsmith, Chief Scientist for the Structural Genomics Consortium (SGC) Toronto laboratories and Professor of Medical Biophysics at the University of Toronto, outline the key problems using chemical probes in [biomedical research](#), and highlight new projects to increase the number and quality of chemical tools available to researchers.

Chemical probes are small molecules that are used to test the activity of a [protein](#) in a cell, often inhibiting it.

Expert guidance on chemical probes

One of the projects discussed is a new, enhanced version of an easy-to-use online resource for chemical probes. [The Chemical Probes Portal](#), relaunched in 2021, relies on expert review carried out by a 200-strong international community of researchers in [chemical biology](#), chemistry and pharmacology, and is supported by [big data analysis](#).

The Portal aims to address a central problem in biomedical research by encouraging the use in laboratory experiments of higher-quality, better-chosen chemical probes—the molecular tools, usually protein inhibitors, which facilitate understandings of biological processes, and which are important to underpin the conclusions of research.

A probe for every protein

[Target 2035](#) is a research community initiative to accelerate developing a chemical probe for every protein in the human proteome by 2035. Led by the SGC, Target 2035 brings together scientists from diverse areas of drug discovery including biochemists, structural biologists, medicinal

chemists, assay scientists and computational chemists.

With a focus on open, collaborative science and new technologies, Target 2035 aims to speed up the development of new, high-quality, chemical probes for the 90% of human proteins that have not yet been studied for potential drug discovery.

Powerful tools for biomedical research

Chemical probes are powerful tools used routinely to tease out how individual proteins are involved in health and disease, including in cancer, dementia, and recently COVID-19, and ultimately lead to the discovery of new drugs.

But the quality of these reagents varies widely and the use of sub-optimal tools in research is widespread. Using poor or badly selected compounds as tools can produce misleading results.

Better use of chemical probes could also save the biomedical research sector billions of pounds, by ensuring that new therapies for disease are developed from better, more robust understanding of their biological effects, and therefore are less likely to fail in costly clinical trials.

Providing expert information quickly

Developed by scientists at the ICR with the support of bodies including the SGC, Wellcome and Cancer Research UK, the new Chemical Probes Portal aims to encourage the widespread selection and use of the most suitable high-quality chemical probes, particularly within the academic biology community.

One of the major updates from the Portal's previous iteration is a new

process to sift through massive datasets, recommending interesting compounds to consider as probes for subsequent expert analysis.

Researchers from across academia and industry can also submit promising tools to the Portal, which will be reviewed by an expanded panel of nearly 200 experts before information is published for free to researchers across the world.

Expanding and improving the data

Other major updates to the Portal include information and expert opinion on hundreds of new chemical tools.

They include inhibitors for proteins previously considered largely undruggable, such as KRAS, agonists for cell surface receptor molecules, GPCRs, including the serotonin receptor HTR2A, as well as new chemical tools such as PROTACs and molecular glues—dual functional molecules that guide proteins to the cellular degradation system to be broken down.

In the last year alone, the number of probes listed on the Portal has increased by 60% to 520. Hundreds of new protein targets have been added, increasing the variety of tools that researchers can use, and broadening the impact in different research areas, including neurology and immunology.

Data sources include the ICR's canSAR, the world's largest public cancer drug discovery resource, and Probe Miner, a leading community resource for the evaluation of chemical probes based on large-scale medicinal chemistry data.

The [artificial intelligence](#)-enabled canSAR contains data on 500,000 protein structures and three million cavities on the surface of nearly

110,000 macromolecules, which are all annotated and curated so that machine learning algorithms can easily parse through the data, as well as clinical and other data.

Probe Miner has evaluated more than 1.8 million [small molecules](#) for their potential to act as chemical probes against 2,200 human protein targets.

Laying solid foundations for research

Dr. Albert Antolin, ICR Fellow and Junior Team Leader at the ICR, and one of the lead researchers in the Chemical Probes Portal, said: "The Chemical Probes Portal has a host of new updates including detailed information on hundreds of new molecules, a more efficient use of big data and, most importantly, renewed support from hundreds of leading international experts in the best use of chemical probes in research.

"The [portal](#) provides all the key information to support the selection of chemical probes in an easy-to-use way. It helps guide the use of chemical probes in thousands of experiments, laying more solid foundations for fundamental research and drug discovery in a wide range of diseases including cancer."

Professor Paul Workman, Harrap Professor of Pharmacology and Therapeutics at the ICR, and Executive Director of the Chemical Probes Portal, said:

"The incorrect selection and use of chemical probes is widespread in biomedical research and, unfortunately, leads to misleading or wrong conclusions being drawn from the results of experiments. In extreme cases, it can derail drug discovery and clinical trials and lead to the unnecessary waste of hundreds of millions of pounds of research funding.

"With the Chemical Probes Portal, and its close interaction with the Target 2035 initiative, our aim is to give the research community an accessible resource, underpinned by the best data and world-leading experts in the use of the best [chemical probes](#) for the study of particular proteins. The new developments on the Portal will now further improve the selection and use of the best tools available for experimental research and thus increase the quality and robustness of biomedical research."

More information: A conversation on using chemical probes to study protein function in cells and organisms, *Nature Communications* (2022). DOI: [10.1038/s41467-022-31271-x](https://doi.org/10.1038/s41467-022-31271-x)

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