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More Precise Method For Rapidly Screening Chemical Compounds Will Help Identify Leads For Drug Discovery

A new screening approach can profile compounds in large chemical libraries more accurately and precisely than standard methods, speeding the production of data that can be used to probe biological activities and identify leads for drug discovery, the National Institutes of Health (NIH) Chemical Genomics Center, part of the NIH Roadmap for Medical Research's Molecular Libraries and Imaging Initiative, report.

"We are excited by the power of this approach, developed through the NIH Roadmap for Medical Research, to generate new chemical 'tools' for biological exploration. These tools will help researchers in both the public and private sectors unlock the mysteries of gene function and signaling pathways throughout the human body, opening the door to the development of new drugs," said NIH Director Elias A. Zerhouni, M.D.

In a paper published online in the Proceedings of the National Academy of Sciences (PNAS), a team from the NIH Chemical Genomics Center demonstrates the feasibility of a new paradigm for profiling every compound in large collections of chemicals. Traditional high-throughput screening measures the biological activity of chemical compounds at just one concentration. In contrast, the new approach, called quantitative high-throughput screening, or qHTS, tests the biological activity of chemical compounds at seven or more concentration levels spanning four orders of magnitude. The multi-concentration screen produces a pharmacological characterization of all the compounds that is far more complete and reliable than traditional methods.

"This advance is crucial to NIH's goal of efficiently profiling the range of biological activities associated with large chemical libraries and making that data swiftly available to the worldwide research community," said Francis S. Collins, M.D., Ph.D., director of the National Human Genome Research Institute (NHGRI). "Broad adoption of this paradigm should provide robust databases of chemical activity information that will be suitable for accelerating the early phase of the drug discovery process."

The NIH Chemical Genomics Center, which is based in NHGRI's Division of Intramural Research, is part of an NIH-supported nationwide research consortium of 10 groups, called the Molecular Libraries Screening Centers Network. The network has established a collection of 100,000 chemicals from a class of compounds known as small molecules. Such chemicals can serve as valuable probes in molecular, cellular and whole organism studies of biological functions. Furthermore, most medications used today are small molecules, and this class of chemicals is likely to offer attractive targets for future drug development.

Christopher P. Austin, M.D., the center's director and senior author of the study, explained what motivated his team to develop the new approach. "Traditional high-throughput screening frequently produces false positives and false negatives, and requires extensive follow-up testing. Furthermore, traditional methods often fail to detect compounds that exhibit partial activity or low efficacy, even though such compounds may represent important modulators of biological activity," Dr. Austin said. "To achieve our aim of speeding the discovery of biological probes and drug targets, we needed a method that offered far greater precision coupled with the capacity to identify chemicals with a wide spectrum of biological activities."

In their study published in PNAS, researchers from the NIH Chemical Genomics Center used quantitative high-throughput screening to test the activity of varying concentrations of more than 60,000 chemical compounds against pyruvate kinase, a well-characterized enzyme involved in energy metabolism that is deficient in a form of anemia and also implicated in cancer. The compounds were classified as either activators or inhibitors of the enzyme, with the degree of potency and

NHGRI's James Inglese, Ph.D., and Christopher Austin, M.D., right, with the Kalypsys robot used at the NIH Chemical Genomics Center. (Credit: Carla Garnett, NIH Record)

concentrations of each compound being

Of particular importance, the team was able to take advantage of the new approach to elucidate relationships between the biological activity of a compound and its chemical structure directly from the initial screen -- a feat not possible with the traditional method. "This new approach produces rich datasets that can be immediately mined for reliable relationships between chemical structure and biological activities. This represents a very significant savings of time and resources compared with current iterative screening methods," said the study's lead author James Inglese, Ph.D., director of the Biomolecular Screening and Profiling Division at the NIH Chemical Genomics Center.

For most of scientific history, researchers discovered new chemical compounds with medicinal qualities through a labor-intensive, time-consuming process that involved manually testing the compounds on tissue samples or laboratory animals. About 15 years ago, researchers in the pharmaceutical industry developed high-throughput screening systems that tested large numbers of compounds on engineered cell lines and proteins. Still, due to technical demands and limitations, such screening generally has remained focused on a single concentration of each compound.

To address the limitations of traditional high-throughput screening, the NIH Chemical Genomics Center set about developing a titration-based screening approach that combines a variety of advanced technologies, including microfluidics, low-volume dispensing, high-sensitivity detectors and robotic plate handling. In an experiment designed to test the feasibility, accuracy and efficiency of the new approach, the NIH researchers used sophisticated robotic systems to prepare 60,793 chemical compounds at seven or more concentrations across 368 plates, each containing 1,536 microwells. Over the next 30 hours in an automated format, the plated compounds were exposed to pyruvate kinase, and their biological activities were carefully recorded.

When the NIH research team compared their quantitative high-throughput screening results with those generated by screening the same chemical compounds with traditional, single-concentration methods, they found the new approach produced a much lower prevalence of false negatives. "Upwards of half of the compounds identified as active using the new approach were missed by the traditional screening method," said Doug Auld, Ph.D., co-author of the study and a group leader at the NIH Chemical Genomics Center. "This tells us that quantitative high-throughput screening is much more sensitive in uncovering chemicals with the potential to be used as biological probes or leads for drug development."

The researchers emphasized that miniaturization is essential to the efficiency and cost-effectiveness of their new approach. They noted that their miniaturized, seven-point concentration screen consumed less chemicals, used the same amount of enzyme and required only 1.75-times the number of plates as a traditional single-point concentration screen. Furthermore, the additional plate handling was offset by the elimination of the need to "cherry pick" and re-test compounds in separate experiments, which conserved time and chemical compounds.

In addition to its potential for identifying new biological probes and drug targets, the NIH Chemical Genomics Center will be using the new paradigm as a platform for its contributions to PubChem, the Molecular Libraries Roadmap's publicly available database of chemical compounds of relevance to genomic research. For more information on PubChem, go to http://pubchem.ncbi.nlm.nih.gov/.