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Innovations

The NIH Molecular Libraries Program: Identifying Chemical Probes for New Medicines

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In 2003, several program leaders within the National Institutes of Health (NIH) recognized that the results from the recently completed Human Genome Project were a launching pad for further study. Now that scientists knew the genome, how could they determine gene function? In particular, how could scientists find specific biological pathways and targets that could lead to new advances in biology and new drug therapies?

The Molecular Libraries Program (MLP), an NIH Roadmap Initiative first funded in 2004, has partially answered those questions. "At the time the term 'chemical genomics' was on the minds of NIH researchers," explains Carson Loomis, Ph.D., Program Director, Molecular Libraries. "The human genome was available and it was agreed that the NIH should become more involved in screening new small molecules to get better targets." The pharmaceutical industry had become frustrated by drug failures in development lacking the means to sufficiently validate potential targets. "They were at the breaking edge of science, yet when a new kinase was discovered and they developed a drug for it, it would often fail," explains Loomis. "The feeling was that we needed more basic research and that the NIH needed to further this cause of validating targets."

The act of Congress creating the MLP now includes the efforts of nine Molecular Libraries Probe Production Centers. They include one intramural NIH site, the National Center for Chemical Genomics (NCGC), and eight extramural sequencing and screening centers: the Broad Institute, the Sanford-Burnham Medical Research Institute, Johns Hopkins University, Scripps Research Institute, the University of New Mexico, Southern Research Institute, the University of Kansas, and Vanderbilt University.

The common purpose of these probe production centers is to generate new small molecule chemical probes by performing high throughput screening, secondary screens, and medicinal chemistry. The biological assays for these probes are sourced from the scientific community at large.

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Screening Library

The workhorse of the MLP program is its 350,000-strong library of unique chemical structures of the NIH's Molecular Libraries Small Molecule Repository (MLSMR). The MLSMR is screened with biological assays or bioactivity experiments looking for particular areas of biological activity.

Small molecule probes can be targeted to interact with extreme precision with a cell or cell byproduct. This specificity provides useful details about the steps in a cell's function and ultimately to its disease pathway. A "true positive active" compound found to be active against a biological target is classified as a chemical probe.

As part of the MLP mandate, all identified probes are immediately reported to the National Library of Medicine's PubChem, a chemical and biological activity repository. Full results may be withheld for up to year to allow investigators to publish their findings.

Though only 350,000 of the 26 million unique chemical structures found in PubChem derive from the MLP, they have generated a wealth of information when combined with the biological assays also deposited. Each participating MLP center receives the screening library and uses it to test a variety of biological questions. "The result is that over 90 million unique biological results have been placed in PubChem from the MLP sites, representing over 80% of the total," explains Steve Bryant, Ph.D., Program Director, PubChem. "It's the combination of the screening library with the unique bioassays that provide the information that lead to the designation of probe."

All of the centers deposit the entire screening experiment, even if most of the results showed no activity or low activity. "It's important to know what doesn't work as well as what does," explains Bryant.

Before victory is proclaimed, however, a probe has to be validated. Enrique Michelotti, Ph.D., who oversees this process within the MLP, says, "The assays and the probes identified have to address a very specific problem in biology." Assay providers need to supply the proposed assay to NIH for peer-review. The network runs the assay through high throughput screening against the 350,000 compound MLSMR collection. "Any new compound that is active in that assay is followed up by chemistry and has to be best in class in that it is addressing some particular issue in biology," he says. "That is what we are looking for in a probe."

One hundred fifty validated probes have been created since the $70 million, 4 year production phase of the effort began in 2008, but only about 120 are publicly available due to the 1 year embargo. Full details on the available probes can be found at the MLP website (http://mli.nih.gov/mli/).

Screening, Et Al.

The data coming from the MLP includes information on the chemical structures

as well as the assays and analytical tools regarding bioactivity.

"This lends real value to the program because each center in the MLP has a particular area of expertise regarding types of assays used or areas of research," says Loomis.

But the MLP includes a bit more than small molecule screening. It also funds technology development encompassing new instrumentation, chemical diversity efforts including natural products methods, and pilot scale libraries to generate novel new compounds to put into the screening library. For example, researchers at the University of New Mexico, an MLP center, are adapting flow cytometry to high throughput screening.

Probe = Research Tool

MLP defines a probe as a compound that can be useful as a research tool. "It does not have to work in animals but ideally it will work in cells," explains Loomis. "It could be a biochemical assay looking for a means to block a compound's phosphorylation ability, or phenotypic assays." The latter are of very high value to the MLP because these screens might point the way in finding a better target for a pathway.

The MLP emphasizes rare and neglected diseases, but they cover a large range of therapeutic areas including cancer, inflammation, infectious disease, and metabolic diseases. However, MLP funding is limited to the probe discovery process only. "If, with a little more study, some of these probes are found to be useful in animals and eventually becomes a lead for chemistry to develop a drug, that is a win/win for us, but our funding won't go that far," adds Loomis. If a probe discoverer believes it may represent a great opportunity for drug development, alternative funding is necessary.

"In my view, the most interesting and valuable part of the MLP program is the number of assays we have spanning multiple therapeutic areas or potential targets," says Michelotti. In MLP, the assays are designed in a way to capture multiple levels of biological activity. "They also include information on potential roles of agonists, antagonists, partial agonists, etc., as the information we receive is denser, more rich, because it is not limited to one particular target." And even within one target, Michelotti points out that the biological information is more comprehensive.

In the short time since full probe production began in September 2008, the MLP has become a go-to public resource in the burgeoning field of chemical probe production. With at least two more years of guaranteed funding, the number of new targets identified—and the probes to accompany them—will only rise in the hopes of quickening highly targeted drug discovery.

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