Screening and Beyond: New Opportunities to Advance Neuroscience Discovery

Without question, the technology, availability of highly selective small molecule tools, and access to behavioral models to study neuroscience targets have never been better. However, just for a moment, imagine that you possess a unique compound collection with no means to evaluate it for therapeutic relevance for central nervous system disorders. Or imagine that you have a novel molecular target or screening platform or assay but do not have access to a compound collection from which to identify lead compounds. The lack of this sort of information has been a drawback, and despite the notable advances in neuroscience research, the neuroscience community has been hampered by issues related to the development of novel molecular targets and pathways, novel mechanisms of action, and the evaluation of novel compounds for activity at neuroscience targets.

These issues have not gone unnoticed by industries, foundations, academic institutions, and the National Institutes of Health (NIH). In an uncommon move, pharmaceutical giant Eli Lilly and Company recently launched a free initiative called Phenotypic Drug Discovery (PD2) (*1*, *2*). PD2 is a web-based tool by which researchers all over the world can submit compounds from their laboratories for testing in four major disease areas, including Alzheimer's disease (AD). Under the terms of PD2, researchers or their institutions retain all rights to the compounds, but Lilly retains rights of first refusal for possible collaborations or licensing deals. Even more striking is that contributing researchers receive all data and retain the rights to publish the data or use it in any manner they choose. The goal is to accelerate discovery and identify new chemical entities that outperform internal positive controls for AD that might represent the next generation of therapeutics (*1*, *2*).

Academic institutions have not been far behind either. The Broad Institute and the Stanley Center for Psychiatric Research initiated a new program in 2009 under the Broad Institute Chemical Biology and Novel Therapeutics (CBNT) Program, called PsychHTS (*3*, *4*). The PsychHTS program's mission is to stimulate the discovery of new approaches for the treatment of schizophrenia and bipolar disorders. Experts within the Broad Institute will work with investigators that have novel ideas and approaches for psychiatric diseases to assist in developing new screens, optimizing and miniaturizing these screens for high-throughput screening (HTS), and to provide medicinal chemistry expertise to optimize screening hits. With new genetic data and identification of risk genes for schizophrenia, the PyschHTS program hopes to move beyond the D_2 antagonist dogma that has dominated the standard of care of schizophrenics for over 40 years and deliver fundamentally new therapies to treat the positive, negative, and cognitive symptom clusters of the disease (*3*, *4*).

Lilly and Broad are not alone. The National Institutes of Health and the Roadmap Initiative have been active in this arena since 2004 (*5*). The current Molecular Libraries Probe Production Centers Network (MLPCN) is the second phase of a program begun in 2004 as part of the Molecular Libraries and Imaging Initiative under NIH's Roadmap for Medical Research. The MLPCN currently is comprised of four Comprehensive Centers (Screening and Chemistry), three Specialized Screening Centers, and two Specialized Chemistry Centers, all staffed with drug discovery scientists with experience from the pharmaceutical industry. The MLPCN provides a grant mechanism, the RO3, to fund assay development and optimization, HTS of the MLSMR screening collection (> 350 000 compounds), and medicinal chemistry support to develop a potent and selective small molecule probe. Assay and compound data is housed in an open access database called PubChem; however, to address intellectual property concerns, data is embargoed until patents are filed. Importantly, all MLPCN small molecule probes are free and available upon request in milligram to gram quantities, with the goal of advancing basic research within the community. A significant portion of the MLPCN probes currently available are for neuroscience targets for which potent and selective small molecule tools did not previously exist (*5*).

In addition, neuroscience funding opportunities are at an all time high from both NIH/NIMH and private and nonprofit foundations. To help you in your quest to secure resources, on the *ACS Chemical Neuroscience* homepage, we have compiled a comprehensive list of neuroscience-focused funding sources. We encourage you to peruse this link, and if you find the list incomplete, please send us information on additional resources.

References

1. For information see, www.lilly.com.
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3. For information see, www.broad.mit.edu/science/programs/psychiatric-disease/psychhts
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