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Mining chemistry for psychiatry

A new initiative aims to jump-start drug development for psychiatric diseases by inviting neuroscientists with unconventional ideas to avail themselves of an established high-throughput chemical screening platform.

Schizophrenia, bipolar disorder and other severe psychiatric diseases usually strike at a young age and gravely impair people's quality of life and productivity. Although powerful antipsychotics are available, long-term treatment outcomes in many cases remain unsatisfactory. Despite massive research efforts in both academia and the pharmaceutical industry, the latest drugs still target the same neurotransmission mechanisms as those developed decades ago. Although new drugs are aggressively marketed, a US National Institute of Mental Health study found that they conveyed only minor benefits, if any, compared to older drugs (http://www.nimh.nih.gov/health/trials/practical/catie/phase1results.shtml). However, recent large-scale human genetics studies have revealed new genes seemingly associated with severe psychiatric conditions, and, interestingly, many of these genes are not linked to dopaminergic or serotonergic transmission. Motivated by these potential targets, the Broad Institute in Cambridge, Massachusetts has launched an initiative called 'PsychHTS' (http://www.broad.mit.edu/node/1218), inviting scientists with ideas and data suggesting novel mechanisms contributing to psychiatric disease to apply for access to the Broad's infrastructure and expertise for high throughput screening (HTS) of chemical compound libraries. This new initiative, aiming to overcome the long stagnation in psychiatric drug development, is very welcome.

PsychHTS is funded initially for three years by the Stanley Medical Research Institute, a private foundation with a mission to support focused research into schizophrenia and bipolar disease. For its first deadline in March, Ed Scolnick, the head of this project, says PsychHTS received six applications; two projects have been approved. Scolnick expects to run up to ten projects during the three-year pilot phase.

At its core, PsychHTS simply represents a mechanism to funnel mental illness–related projects onto the Broad's established 'Chemical Biology and Novel Therapeutics' (CBNT) screening and development platforms. Successful applicants—who may have no expertise with HTS methodology at all—are paired up with a Broad scientist 'chaperone' to develop an assay for their proposed mechanism that is amenable to 384-well plate robotic execution. Readouts may be anything from classical enzymatic reactions, through FRET for changes in protein interaction, up to subcellular changes captured by automated high-content imaging. An investigator may send a group member to the Broad to take advantage of its resources or may entirely 'outsource' assay development to the chaperone. Assay development typically takes two to three months, sometimes up to a year. The assay is then used to screen one or more compound libraries, encompassing at present up to 400,000 substances and growing. (PsychHTS pays for screening a 50,000-compound subset.) 'Hits'—compounds that affect the assay results in a way that indicates potential usefulness in a psychiatric research context—are automatically retested at several concentrations. The resulting collection of typically between 50 and 500 confirmed hits is then evaluated and prioritized according to criteria of scientific interest and potential drug promise, and thereby winnowed down to the top 10 or 20. The Broad Institute's organic chemists then synthesize and retest these compounds plus a series of their chemical derivatives, with goals such as improved solubility and more specific binding to putative targets. The goal of the entire procedure is to deliver small-molecule probes that modulate a specific cellular function—essentially tools for subsequent research into the initial hypothesis regarding a psychiatric disease mechanism.

At this point, the new small-molecule probes will need to be tested in animal models of mental illness. The dearth of such animal models, of course, constitutes its own bottleneck hampering psychiatric research. Many groups are engaged in efforts to develop new and better mouse models of psychiatric disorders; the Broad itself hosts a behavioral neurogenetics group that is dedicated to this work. Scolnick anticipates that PsychHTS investigators who obtain promising small-molecule probes may collaborate further with the Broad's mouse-model and medicinal chemistry groups for *in vivo* behavioral evaluation and chemical optimization, by way of inching closer to *bona fide* drug lead status.

PsychHTS is one of several recent efforts designed to advance disease-related research by giving academic scientists access to industry-grade chemical screening and medicinal chemistry technology. The US National Institutes of Health launched their Molecular Libraries and Imaging Initiative (http://nihroadmap.nih.gov/molecularlibraries) in 2003 to generate small-molecule probes for research, and last year, they committed to its continuance. A number of universities have also been setting up their own small-molecule screening cores in hopes of capitalizing on discoveries made in their labs. The PsychHTS initiative, however, seems to be unique in its focus on psychiatric disease.

Psychiatry is a large segment of the drug market, but innovation has languished nevertheless. This may in part be due to complacency at the pharmaceutical companies, but much of the problem is also because we have yet to fully understand the neurobiology of these disorders. Recent genetic studies have indeed suggested new targets, but the identification of specific genetic risk factors remains elusive. The genetic results are themselves variable, often have small effect sizes and need independent replication. Although many psychiatric disorders are strongly heritable, the statistical evidence for the involvement of any one gene or genomic hotspot is difficult to obtain. Unraveling the mechanisms mediating psychiatric symptoms is also tricky in the absence of established animal models and in face of the phenotypic heterogeneity of these disorders. As the new ideas emerging from genetic studies remain unproven, the PsychHTS initiative has an air of audacity about it. Chances are that this program will deliver useful probes for basic neuroscience, but whether it also can prime the drug pipeline with promising leads and new types of targets remains to be seen. Nevertheless, bridging the translational gap between basic science and commercial development is critical, and we're keeping our fingers crossed for the success of this ambitious venture. ■