Editor's LETTER

ACS chemical biology

Screening for Success

For almost two decades, the pharmaceutical and biotech industries have been using high-throughput screening (HTS) to obtain small-molecule hits against validated biological targets. Although these industries have amassed a wealth of data and experience on target selection, technology development, and hit validation, resources for HTS have not always been readily available to researchers in academia and in government institutions. But times are changing, thanks in part to the advent of the National Institutes of Health (NIH) Molecular Libraries Roadmap. This endeavor—consisting of a network of small-molecule screening centers, the PubChem database for small-molecule and screening data, and resources for technology development—has helped researchers outside of industry utilize HTS to identify chemical compounds that modulate the activities of biological targets (*1*).

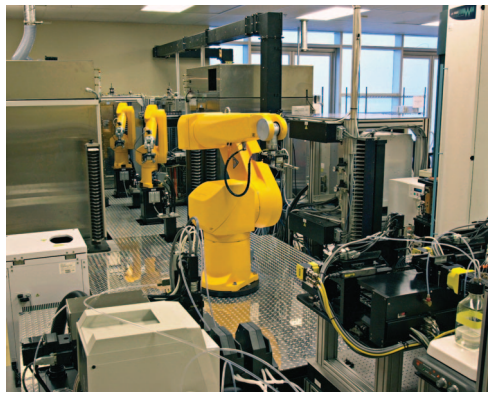

Image courtesy of J. Malmquist. http://genome.gov/pressDisplay.cfm?photoID=79. Accessed on August 1, 2008.

This is an important advance for the field of chemical biology. HTS in an academic environment is expanding the diversity of both chemical compounds and biological targets beyond those pursued in industrial drug discovery, where the goal is to identify drug leads for targets associated with human diseases. It is encouraging to note that more and more academic researchers are utilizing HTS to identify small molecules that modulate biological processes in their favorite organisms. HTS is also a key component in large public projects. For example, the NIH Chemical Genomics Center, the Environmental Protection Agency, and the National Toxicology Program are currently collaborating on the development of an HTS resource with biochemical and cell-based assays to assess the toxicity of chemical compounds (*2*). As the goal of this project is to use HTS quantitatively to generate data on toxicity, the composition of the compound library naturally varies from that used in drug discovery programs (*2*).

Notwithstanding the enthusiasm for this powerful technology, significant challenges remain with using HTS for hit identification. Particularly vexing is that a large number of hits identified in HTS assays are found to be assay-format-dependent false leads when examined further. Studies have demonstrated that small molecules form colloidal aggregates in aqueous solution that nonspecifically inhibit enzyme activity, which may explain why testing for inhibition is particularly troublesome (*3*). As an example, in a recent HTS analysis, 95% of the hits resulted from compound aggregation concomitant with enzyme inhibition (*4*). Aggregation, however, is not the only cause of artifacts. On page 463 in this issue of *ACS Chemical Biology,* Auld *et al.* (*5*) provide evidence that false leads may be derived from HTS platforms using luciferase reporter-gene assays where the activity arises not from the target but from the stabilization of the luciferase enzyme. As one can envisage similar arti-

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facts due to stabilization in other reporter-gene assays, caution should be taken while interpreting results solely on the basis of screens. Ultimately, all promising compounds identified by HTS must be subjected to further experimentation to identify genuine hits. Studies such as these are a timely warning that as HTS gains popularity, focus must remain on the assiduous examination of the assay system, the chemical properties of the hits, and the biological relevance of the interaction with the target.

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