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Small-Molecule Screening: It Takes a Village . . .

Successful implementation of a small-molecule screen can be a daunting task. As the old African proverb (and Hillary Clinton) says, "It takes a village" to do it well. In the case of a small-molecule screen, the "village" encompasses a wide range of multidisciplinary components: the libraries, the assay, the instrumentation, the data analysis, and the follow-up. If any of these components are lacking in quality or robustness, if any members of the village are off their game, the integrity of the entire screen is compromised.

The term "small-molecule screen" can include any screen performed in a high-throughput manner that explores the effects of small molecules on a biological system (*1, 2*). Small-molecule screening was once confined to big pharmaceutical companies with deep pockets, but a growing recognition of its power, combined with increased accessibility to resources that make it possible, have resulted in widespread implementation of small-molecule screening facilities throughout industrial, government, and academic institutions (see Table 1 for a list of academic institutions that have small-molecule screening facilities). In addition to drug discovery, small-molecule screening methods are finding applications in other areas, including target validation, assay development, secondary screening, pharmacological property assessment, and lead optimization. Accordingly, the characteristics of the screening components have evolved to accommodate the different screening formats and scales used. Fortunately, now many commercial and public resources are available, including products, services, and databases, to help plan, implement, and evaluate a wide variety of small-molecule screens.

Researchers considering embarking upon a small-molecule screen are wise to become familiar with the components of the screen, the resources available to facilitate its implementation, and the pitfalls to watch out for during its execution.

The Libraries. The libraries, or the collection of small molecules to be screened, are like the people of a village. Just as each person brings unique characteristics that shape the culture of the village, each compound brings structural characteristics that shape the content of the library. Some compounds will inevitably be more interesting than others, perhaps because they have higher activity or provide valuable structure–activity relationship information, whereas others may be totally inactive, promiscuously active, or toxic. But without the large numbers of compounds provided by the library, the interesting ones would be much more difficult to find.

Small-molecule libraries can be procured through several avenues. A wide variety of small-molecule screening libraries are now available from commercial vendors (Table 2). Libraries of natural products, U.S. Food and Drug Administration-approved drugs, compounds of known biological activity, compounds that target specific proteins, and various other collections with distinct characteristics can all be purchased, already formatted for screening.

As part of the National Institutes of Health (NIH) Roadmap for Medical Research Initiative, compound libraries are also available through the NIH Molecular Libraries Small

Jim Dandy, Stock Illustration, Getty Images

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TABLE 1. Academic institutions with facilities for screening small molecules

Facility	Location	Web site
Broad Institute Chemical Biology Program	Cambridge, MA	www.broad.harvard.edu/chembio/platform/screening/guidelines.htm
Chemical Genomics Core Facility of Indiana University School of Medicine	Indianapolis, IN	http://chemicalgenomics.iu.edu
Cleveland Clinic Lerner Research Institute Small Molecule Screening Core	Cleveland, OH	www.lerner.ccf.org/services/smsc
Columbia Genome Center[a]	New York, NY	www.genomecenter.columbia.edu
EMBL/DKFZ Chemical Biology Core Facility	Heidelberg, Germany	www.dkfz.de/en/abteilungen/v/screening_facility.html
Emory Chemistry Biology Center[a]	Atlanta, GA	http://sisyphus.emory.edu/lungcancer/emcbc.html
Gulf Coast Consortium for Chemical Genomics[a]	Houston, TX	http://cohesion.rice.edu/centersandinst/gcc/gccddr.cfm
Harvard Center for Neurodegeneration and Repair, Lab for Drug Discovery in Neurodegeneration	Boston, MA	www.hcnr.med.harvard.edu/programs/drugDisc.php
Hong Kong University of Science and Technology, Biotechnology Research Institute	Clear Water Bay, Kowloon, Hong Kong	www.ust.hk/~bri/index.shtml
ICCB–Longwood Screening Facility	Boston, MA	http://iccb.med.harvard.edu
Johns Hopkins University ChemCORE Facility	Baltimore, MD	www.hopkinschemcore.org
Keck–UWCCC Small Molecule Screening Facility	Madison, WI	http://hts.wisc.edu
Max Planck Institutes Chemical Genomics Centre	Dortmund, Germany	www.cgc.mpg.de
McMaster High Throughput Screening Laboratory	Hamilton, ON, Canada	http://hts.mcmaster.ca
Michigan High Throughput Screening Center	Kalamazoo, MI	http://mhtsc.kvcc.edu
Mount Sinai Hospital S.M.A.R.T. Facility	Toronto, ON, Canada	www.mshri.on.ca/robotics/index.html
National Screening Laboratory for the Regional Centers of Excellence in Biodefense and Emerging Infectious Disease	Boston, MA	www.rcebiodefense.org/rce_pub/rce6/core_screen.htm
New Mexico Molecular Libraries Screening Center[a]	Albuquerque, NM	http://nmmlsc.health.unm.edu
NIH Chemical Genomics Center[a]	Bethesda, MD	www.ncgc.nih.gov/index.html
NIMH Psychoactive Drug Screening Program	Chapel Hill, NC	http://pdsp.med.unc.edu/indexR.html
Penn Center for Molecular Discovery[a]	Philadelphia, PA	www.seas.upenn.edu/~pcmd
Pittsburgh Molecular Libraries Screening Center[a]	Pittsburgh, PA	http://pmisc.pitt.edu

TABLE 1. Academic institutions with facilities for screening small molecules, continued

Facility	Location	Web site
Rockefeller University High Throughput Screening Resource Center	New York, NY	www.rockefeller.edu/highthroughput/highthroughput.php
San Diego Center for Chemical Genomics[a]	La Jolla, CA	http://sdccg.burnham.org/metadot/index.pl?id=2207&isa=Category&op=show
Scripps Research Institute Molecular Screening Center[a]	La Jolla, CA/ Palm Beach County, FL	http://molscreen.florida.scripps.edu
Sloan Kettering Institute High-Throughput Drug Screening Facility	New York, NY	www.mskcc.org/mskcc/html/52147.cfm
Southern Research Institute[a]	Birmingham, AL	www.southernresearch.org/index.html
Stanford School of Medicine High-Throughput Bioscience Center	Stanford, CA	http://htbc.stanford.edu
University of Alabama, Center for Biophysical Sciences and Engineering	Birmingham, AL	www.cbse.uab.edu/biotechnology-pharmaceutical.shtml
University of California, Los Angeles, Molecular Screening Shared Resource	Los Angeles, CA	http://mssr.pharmacology.ucla.edu/index.html
University of Kansas High Throughput Screening Laboratory	Lawrence, KS	www.hts.ku.edu
University of Massachusetts Medical School Small Molecule Screening Facility	Worcester, MA	www.umassmed.edu/smsf
University of Michigan Center for Chemical Genomics High Throughput Screening Facility	Ann Arbor, MI	www.lifesciences.umich.edu/institute/labs/ccg/research.html
University of Minnesota High Throughput Biological Analysis Facility	St. Paul, MN	www.bti.umn.edu/htba
Vanderbilt Screening Center for GPCRs, Ion Channels, and Transporters[a]	Nashville, TN	www.vanderbilt.edu/MLSCN/Templates/index.htm
Yale University, Center for Genomics and Proteomics, Chemical Genomics Screening Facility	New Haven, CT	http://cgp.yale.edu/chemical/chem_info.html

[a]These institutions are members of the MLSCN.

Molecule Repository, which is distributed to the NIH Molecular Libraries Screening Center Network (MLSCN) (see Table 1 for laboratories in the MLSCN). In addition, a collection of synthetic and natural products that have potential anticancer and anti-HIV activity has been procured by the National Cancer Institute Developmental Therapeutics Program and is also available for screening.

Finally, libraries can purposefully be created from scratch by individual laboratories for screening purposes. The tremendous progress in combinatorial synthesis methods has enabled many laboratories to design and synthesize their own libraries, creating new molecules containing whatever structural features happen to tickle their imagination (*3*). In addition, in accord with another adage, "One man's trash is another man's treasure", some laboratories are organizing screening collections from compounds that have already been synthesized and are sitting in the freezers in their own or neighboring groups (*4*).

Regardless of the source, it is important to ensure that the library being screened is of high quality. Compound purity, accuracy of compound concentration, sufficient solubility, and lack of notoriously toxic or promiscuous molecules are all factors that should be carefully considered before screening begins (*5*).

Finally, if known positive or negative control compounds exist for a specific assay of interest, it is worthwhile to incorporate them into the screen as part of the library.

TABLE 2. Vendors that sell small-molecule libraries, provide assay reagents, or perform small-molecule screens

Company	Libraries	Reagents	Screening	Web site
AbCam		X		www.abcam.com
Abgent		X		www.abgent.com
Albany Molecular Research	X	X	X	www.albmolecular.com
AnalytiCon Discovery GmbH	X			www.ac-discovery.com
Applied Biosystems		X		www2.appliedbiosystems.com
Asinex Corp.	X		X	www.asinex.com
ATCC		X		www.atcc.com
BD Biosciences		X		www.bdbiosciences.com
BioImage		X	X	www.bioimage.com
BioMol	X	X	X	www.biomol.com
Cell Signaling Technology		X		www.cellsignal.com
Cerep	X		X	www.cerep.fr
Chembridge	X			www.chembridge.com
Chemical Diversity Laboratories	X			www.chemdiv.com
DiscoveRx		X		www.discoverx.com
EMD Biosciences		X		www.emdbiosciences.com
Enamine	X	X		www.enamine.net
Evotec	X		X	www.evotec.com
GE Healthcare (Amersham Biosciences)		X		www.gehealthcare.com
Hybrigenics			X	www.hybrigenics.com
Invitrogen		X		www.invitrogen.com
Key Organics	X	X		www.keyorganics.ltd.uk
Maybridge	X	X		www.maybridge.com
MicroSource Discovery Systems, Inc.	X			www.msdiscovery.com
New England Biolabs		X		www.neb.com
Peakdale	X	X		www.peakdale.co.uk
Pierce		X		www.piercenet.com
Prestwick Chemical Company	X			www.prestwickchemical.com
Promega		X		www.promega.com
Sigma-Aldrich	X	X		www.sigmaaldrich.com
Timtec	X			www.timtec.net
Tripos	X		X	www.tripos.com

Databases such as SciFinder (www.cas.org/SCIFINDER) or MDL Isis/Base (www.mdli.com/products/framework/isis_base/index.jsp) enable structure-based searches that provide commercial sources for compounds of interest. Alternatively, the web sites of companies can be searched directly for product availability. In the event that a desired compound is not commercially available, several of the companies listed in Table 2 also custom-synthesize small molecules.

The Assay. If the libraries are the people of the village, then the assay is the village social scene. It is where all the action happens, where the compounds take action provided that they are structurally competent. Myriad assay formats can be employed to explore interactions or processes of interest in a high-throughput fashion (*2*). Critical factors to consider when developing an assay for a small-molecule screen include the type of assay (phenotypic or target-based, biochemical or cellular, microarray,

TABLE 3. Small-molecule screening instrumentation and data analysis companies

Company	Instrumentation	Data analysis	Web site
Affymetrix	X	X	www.affymetrix.com
Agilent	X	X	www.home.agilent.com
Applied Biosystems	X	X	www2.appliedbiosystems.com
Beckman Coulter	X	X	www.beckman.com
Biacore	X	X	www.biacore.com
Biotek	X	X	www.biotek.com
Caliper Life Sciences	X	X	www.caliperls.com
Cellomics	X	X	www.cellomics.com
Dynex Technologies	X	X	www.dynextechnologies.com
GE Healthcare	X	X	www.gehealthcare.com
ID Business Solutions		X	www.idbs.com
Innovadyne	X		www.innovadyne.com
MDL Information Systems		X	www.mdli.com
Molecular Devices	X	X	www.moleculardevices.com
PerkinElmer	X	X	www.perkinelmer.com
Photometrics	X	X	www.photomet.com
Tecan	X	X	www.tecan.com

etc.), the detection technology employed (fluorescence, luminescence, radioactive, label free, *etc.*), and the reagents required (cell lines, antibodies, purified proteins, enzyme substrates, positive and negative controls, detection reagents, *etc.*).

Assays for exploring the effects of small molecules on biological systems come in many shapes and sizes, but for simplicity, they can be divided into three categories: high-throughput screens (HTS), high-content screens (HCS), and small-molecule microarrays (SMM).

HTS Assays. These come in many formats and can be divided into several subcategories. HTS assays can be target- or process-based, biochemical or cell-based, or homogeneous or separation-based. In other words, HTS assays can be set up to find small-molecule modulators of the activity of a specific protein, such as a G-protein-coupled receptor or a kinase, or of a specific cellular event, such as apoptosis. Purified proteins, protein mixtures, or live cells can be used to conduct HTS assays (not to be confused with phenotypic assays, which are also performed in live cells but use image-based detection to evaluate a phenotypic change). And, HTS assays can be developed as homogeneous assays that do not require separation of the assay components before the detection step or as separation-based assays in which the reaction product is detected after its removal from the starting material. In addition, the detection technology employed in HTS assays, such as fluorescence, luminescence, radioactivity, or UV absorption, also varies depending on the assay design. Homogeneous assays often use innovative fluorescence-based technologies, such as fluorescence polarization, homogeneous time-resolved fluorescence, or FRET; luminescence-based technologies, such as the Alpha screen; or radioactive-based technologies, such as scintillation proximity assays. Many other HTS assay formats, such as the separation-based biochemical assays like enzyme-linked immunosorbent assays, affinity chromatography, or filter-binding assays, generally employ more straightforward applications of fluorescent, luminescent, radioactive, or UV absorption detection methods. The numerous assay formats and detection technologies available for HTS assays provide many options for designing an assay that effectively evaluates the activity of a specific protein, a particular biological pathway, or a cellular event (*5*).

HCS Assays. HCS, synonymous with phenotypic screening or screening by imaging, relies on imaging of cells or organisms that have been treated with small molecules (or other agents) *via* fluorescent detection reagents and automated microscopy (*6, 7*). HCS assays are designed to find small-molecule modulators of a specific process that cause an altered phenotype. The hits identified in HCS assays are already active in a cellular context and are likely relatively specific, a big advantage over hits from biochemical assay formats that may possess undesired properties upon examination in cells. Technological advances in image analysis and automated microscopy have also revolutionized the applications of this powerful technology. However, significant challenges come along with this assay format, including the complex image analysis and the need for target identification of the hits, which can be quite a labor-intensive and experimentally elusive process. Inclusion of compounds with known mechanisms of action as additional positive controls can provide clues about how hits from the screen may be working. Also, if the structure of the hit permits, synthesis of deriva-

tives tagged with affinity or detection reagents can greatly facilitate the deciphering of the mechanism of action and the target identification process.

SMM Assays. Application of the throughput capabilities of the microarray format to screening small molecules has become a powerful complement, or even alternative, to other small-molecule screening technologies (*8*). In SMM, small molecules are typically covalently attached to a microarray surface (usually a glass microscope slide) and exposed to a target of interest. Fluorescence is then used to detect resulting binding events. In addition to the throughput capabilities and the relative simplicity of the process, SMM assays are attractive because they enable access to screening of targets that may be difficult to evaluate by other methods. Many exciting new formats of SMM are rapidly emerging that facilitate the screening of complex mixtures or even cells against small molecules, expanding the utility of this screening method (*9*). One challenge of the SMM format is the development of a reliable, efficient method to attach the small molecules to the microarray surface. In addition, because most applications of this technology search for small molecules that bind to targets of interest, it is important to have appropriate follow-up assays in place to further characterize the biological activity of the hits.

Emerging Assay Formats. Some technologies that have not traditionally been used in a high-throughput setting are now finding applications in small-molecule screening, either as a complement or in some cases as a replacement for common assay formats. Technical advances in NMR, which provides an exceptional amount of structural information in addition to data about the affinity and the binding location of potential lead compounds, has enabled much increased sample throughput (*10*). In addition, the development of sample-handling devices for microwell plates and other automated accessories for technologies such as flow cytometry (*11, 12*) and surface plasmon resonance (*13*) has increased the sample capacity of these powerful technologies, opening the door for their use in small-molecule screening as well.

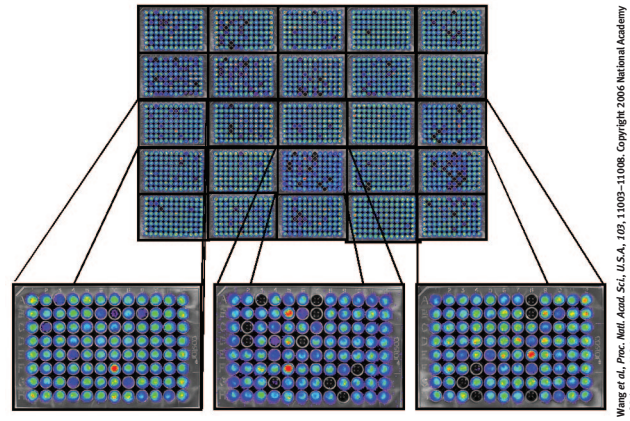
Assay Design. Regardless of the assay format chosen, it is worth the time to investigate available resources that could facilitate running the screen. Many companies supply reagents useful for screens, including kits for assay development, purified proteins, biologically active small molecules, detection reagents, antibodies, and cell lines (see Table 2). Again, databases such as SciFinder or Isis/Base can also help determine whether certain compounds can be purchased and, if so, from where. In addition, many companies provide custom services, such as compound synthesis or antibody or cell line generation, if such reagents are desired.

Although determination of the *Z′* factor, which is a measure of the quality of the assay, may cause some researchers to yearn for a few extra Zzzz's, it is important to ensure that the assay has sufficient dynamic range and manageable margins of error before time and resources are invested into a small-molecule screen.

Several companies will optimize assays and even run entire small-molecule screens (see Table 2). These companies can be a tremendous help if the time or resources are not available to develop or run the desired screen.

The Instrumentation. The instrumentation is like the village infrastructure—the shops, the restaurants, the post office—everything that the villagers need in their daily lives. Likewise, it is critical to have instrumentation that fulfills the needs of the screen. As the desire for higher throughput in small-molecule screens has increased, high-throughput instrumentation has fortunately followed suit. For HTS and HCS, automated microwell plate readers, washers, incubators, and liquid-handling devices have been developed to accommodate 96-, 384-, and even 1536-well microwell plates. For SMM, automated microarray printers, incubation chambers, washers, dryers, and scanners have also greatly facilitated screen implementation.

Companies that specialize in instrumentation for small-molecule screening generally have specialists that can help researchers determine which instrumentation is most appropriate for their screen and can train them on how to use it. Table 3 lists some of the principal vendors that have developed instrumentation for small-molecule screening.



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The Data Analysis. Just as a good village newspaper provides a comprehensive review of what happens in the village, the data analysis process provides a comprehensive review of what happened in the screen. Software programs and new data-mining techniques designed to facilitate data analysis are available for most screening formats (*14*). However, with the immense amount of information produced by the screen and the increasing complexity of

the data, it is useful to have researchers skilled in information technology to help manage and analyze the data. Often, some customization may be necessary to help with organization or interpretation of the data.

Several vendors provide data analysis packages for small-molecule screens (see Table 3). Often, software for data analysis comes with the instrumentation used in the screen, but some data-mining companies also have specialized programs for small-molecule screening data.

The Follow-Up. A thriving village needs a good plan for its future; likewise, a successful screen needs a good plan for following up on the hits. Hit validation, structure–activity studies, target selectivity, determination of the mechanism of action, and target identification are all important follow-up steps to consider.

Validation of the hits facilitates assessment of the competency of the screen, confirmation that the molecules identified indeed possess the desired biological activity, and evaluation of the propensity for obtaining false positive results. It is important to evaluate and attempt to understand the causes of false positives in the primary screen, but the design of the follow-up assay should also be considered to avoid a high rate of false negatives, which could complicate evaluation of the true activity of the hits. If the target is known, secondary assays that provide selectivity and kinetic or mechanistic information will help determine which molecules warrant further study.

If the target is unknown, as is often the case in HCS, target identification is an important next step. Several genetic and chemical methods can help identify the targets of hits from phenotypic screens, including affinity chromatography, RNA interference, gene knockouts, and candidate testing (*15*).

Databases such as SciFinder, Isis/Base, or PubChem (http://pubchem.ncbi.nlm.nih.gov) (which is a component of the NIH Molecular Libraries Roadmap Initiative) are extremely useful resources that provide chemical and biological information about small molecules. The databases can be searched to determine what, if any, additional biological activity the hits may possess. If a compound of interest is not present in the database, it could still be useful to search for structurally related compounds that may provide hints about the mechanism of action of the compound or the identity of the target.

Pitfalls. As most seasoned screeners know, running an assay is not always as straightforward as it appears on paper. Pesky details can get in the way at any step of the process and cause a multitude of unexpected problems. Careful planning will help sidestep some pitfalls, but sometimes it will be necessary to come up with creative solutions in a pinch, and the more tools and resources at one's disposal, the easier it will be to deal with the problems that arise.

Many issues can surface when an assay is adapted from the development stage to an HTS that can ruin the integrity of the screen or cause increased errors. On the one hand, careful calculations must be made to ensure that enough materials and reagents are available for the entire screen. At the same time, adjustments must be made to accommodate for differences in assay environment. For example, the sheer numbers of plates being handled add a significant amount of processing time to any step of the assay, which could be a source of error if every plate is not exposed to the same conditions (temperature, humidity, amount of light, *etc.*) for the appropriate amount of time. In addition, the volume of liquid in a microwell plate may be quite a bit smaller than that used during the assay development process, and issues that were not previously a concern, such as evaporation, may complicate the logistics of running the screen. Automation can help eliminate some of these complications, but it is important to be aware of how all of the differences between running the assay on a small scale and in high throughput may affect the screening process.

Another factor to pay close attention to is the rate-limiting step of the screen. Careful consideration should be given to the "slow step" of the screen, because that is the step that is going to hold up the process, whether it is data analysis, protein production, or an incubation step. Ideally, the slow step should be the minimum time it takes to run the assay itself. If that is not the case, measures should be taken to make the slow step more efficient if possible.

The criteria used to define a "hit" should also be contemplated seriously. The difference in signal between the compound and the negative control, the number and consistency of replicates, and the throughput of follow-up assays can help set appropriate guidelines for defining hit rates.

Just as every good village needs a sheriff to protect the quality of life of its citizens, every good screen should have a quality control system in place to protect the integrity of the data. Whenever possible, positive and negative controls should be included in every plate or glass slide to ensure that the screen is working properly. If budget and availability of materials allow, running the compounds in duplicate or even triplicate can help eliminate false positives and verify real hits. If possible, the hits should also be retested in an independent run in the same format to confirm the results.

One method that may help prevent some of these pitfalls is to recruit experienced screeners to help plan and perform the screen. Many academic institutions (Table 1) now have the capability and even trained personnel who can help interested researchers to conduct small-molecule screens. Many companies will run established small-molecule screens for a fee (Table 2), and some will even develop or optimize new screens as a part of their service.

Conclusion. When properly planned and judiciously executed, small-molecule screens are an invaluable method for identi-

fying powerful biological tools and potential new medicines. The emergence of various academic, government, and industrial institutions that routinely run small-molecule screens and the resources that they provide benefit the community immensely. For biological and medicinal discovery, small-molecule screening is definitely a village worth living in!

—Eva J. Gordon, Ph.D., Science Writer

REFERENCES

1. Fox, S., Farr-Jones, S., Sopchak, L., Boggs, A., Nicely, H. W., Khoury, R., and Biros, M. (2006) High-throughput screening: update on practices and success, *J. Biomol. Screening 11*, 864–869.
2. Liu, B., Li, S., and Hu, J. (2004) Technological advances in high-throughput screening, *Am. J. PharmacoGenomics 4*, 263–276.
3. Dolle, R. E., Le Bourdonnec, B., Morales, G. A., Moriarty, K. J., and Salvino, J. M. (2006) Comprehensive survey of combinatorial library synthesis: 2005, *J. Comb. Chem. 8*, 597–635.
4. Hergenrother, P. J. (2006) Obtaining and screening compound collections: a user's guide and a call to chemists, *Curr. Opin. Chem. Biol. 10*, 213–218.
5. Walters, W. P., and Namchuk, M. (2003) Designing screens: how to make your hits a hit, *Nat. Rev. Drug Discovery 2*, 259–266.
6. Clemons, P. A. (2004) Complex phenotypic assays in high-throughput screening, *Curr. Opin. Chem. Biol. 8*, 334–338.
7. Eggert, U. S., and Mitchison, T. J. (2006) Small molecule screening by imaging, *Curr. Opin. Chem. Biol. 10*, 232–237.
8. Uttamchandani, M., Walsh, D. P., Yao, S. Q., and Chang, Y. T. (2005) Small molecule microarrays: recent advances and applications, *Curr. Opin. Chem. Biol. 9*, 4–13.
9. Chiosis, G., and Brodsky, J. L. (2005) Small molecule microarrays: from proteins to mammalian cells—are we there yet? *Trends Biotechnol. 23*, 271–274.
10. Hajduk, P. J., and Burns, D. J. (2002) Integration of NMR and high-throughput screening, *Comb. Chem. High Throughput Screening 5*, 613–621.
11. Krutzik, P. O., and Nolan, G. P. (2006) Fluorescent cell barcoding in flow cytometry allows high-throughput drug screening and signaling profiling, *Nat. Methods 3*, 361–368.
12. Edwards, B. S., Oprea, T., Prossnitz, E. R., and Sklar, L. A. (2004) Flow cytometry for high-throughput, high-content screening, *Curr. Opin. Chem. Biol. 8*, 392–398.
13. Jung, S. O., Ro, H. S., Kho, B. H., Shin, Y. B., Kim, M. G., and Chung, B. H. (2005) Surface plasmon resonance imaging-based protein arrays for high-throughput screening of protein-protein interaction inhibitors, *Proteomics 5*, 4427–4431.
14. Harper, G., and Pickett, S. D. (2006) Methods for mining HTS data, *Drug Discovery Today 11*, 694–699.
15. Burdine, L., and Kodadek, T. (2004) Target identification in chemical genetics: the (often) missing link, *Chem. Biol. 11*, 593–597.