Chemical Genetics: Elucidating Biological Systems with Small-Molecule Compounds

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Chemical genetics employs diverse small-molecule compounds to elucidate biological processes in a manner analogous to the mutagenesis strategies at the core of classical genetics. Screening small-molecule libraries for compounds that induce a phenotype of interest represents the forward chemical genetic approach, whereas the reverse approach involves small molecules targeting a single protein. Here, we review key differences between the goals for small-molecule screening in industry *versus* academia, recent developments in high-throughput screening, and publicly available resources of compound collections, screening facilities, and databases. A particularly exciting outcome of a chemical genetic screen is the discovery of a previously unknown role for a protein in a pathway together with compounds that affect the function of that protein. In illustrative cases, such discoveries have led to progress toward therapeutic development and more commonly have increased the size of the small molecule "toolbox" available to the research community for the study of biological processes.

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Classical and chemical genetics

Over the past century, classical genetics has played a central role in elucidating biology by investigating the relationship between genes and phenotypes (Figure 1). Forward genetics identifies target genes and pathways via study of phenotypes induced by random mutagenesis. Reverse genetics begins with a particular gene of interest and then mutates the gene or alters expression of that gene product to identify the phenotype. The reverse genetic approach has become dominant over the past few decades owing

Editor's Note

Understanding the biological response to our environment including plants and chemicals has for centuries been a primary goal of science. The advancement of technology has allowed investigators to become increasingly specific in their investigation through purification of biologically active compounds, the isolation of individual cells for study and ultimately by the discovery of the human genome and the ability to explore biological responses by examining the function of individual genes. The unraveling of the mysteries of the genome has been approached for the most part by the classical genetic approaches of forward and reversed genetics, which utilizes mutations in genes to discover their functions. This pair of JID Perspectives describes a relatively new approach to understanding the functions of genes: chemical genetics. Kawasumi and Nghiem describe chemical genetics and its application in the discovery of the function of genes and new drug discovery. In a companion article, Komatsu and Orlow describe how, through the application of chemical genetics, novel molecules have been identified that can regulate pigmentation. Advancing biology ultimately requires looking ''backwards'': understanding begins with the study of the response of the entire animal, then moves to studies of a specific organ system, individual cells, and, most recently, studies of the function of genes and molecules within the cell. Chemical genetics represents an emerging powerful technology to aid scientists in the accomplishment of this goal and once again confirms the observations of Aldous Huxley: ''Technological progress has merely provided us with more efficient means for going backwards.''

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Abbreviations: SMM, small-molecule microarray; TNF-α, tumor necrosis factor-α

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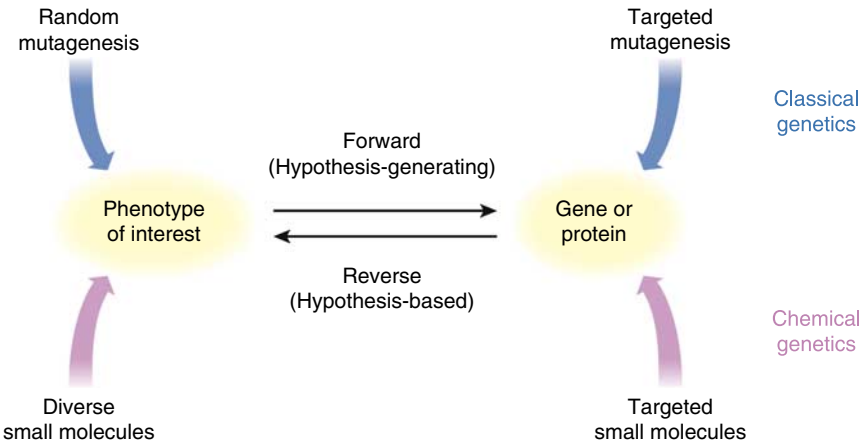

Figure 1. Classical and chemical genetic approaches. Classical genetics uses mutagenesis as a means of elucidating the relationship between genes and phenotypes, whereas chemical genetics employs small-molecule compounds to achieve the same general goals. A forward genetic study is a hypothesis-generating approach through which the gene responsible for the affected phenotype is identified. A reverse genetic study is a hypothesis-based approach in which genes or proteins are manipulated to characterize their role via identifying the resulting phenotype.

Table 1. Advantages and disadvantages of major technologies that perturb functions of genes or proteins

	Advantages	Disadvantages
Conditional knockout animals	Tissue-, time-, and gene-specific	Labor-intensive Lose all functions of deleted gene product
RNA interference	Gene-specific Easy to apply siRNA to cells Easy to synthesize siRNA	Limited *in vivo* applications Off-target effects
Small molecules	Work rapidly, often reversibly Can perturb one function of a multifunctional protein Can disrupt protein-protein interactions Usually function across cell types and species Potential for therapeutic development	Variable specificity Limited to available and characterized compounds

to the development of powerful and familiar techniques: mutagenesis, transgenic, knockout/knock-in animals, and RNA interference technologies that are now the basis of much of modern biology.

Chemical genetics has emerged in the past 5–10 years as a complementary approach to illuminate biological function through systematic, increasingly available screens of diverse small-molecule compounds. ''Small molecules'' are defined as carbon-based compounds whose molecular weight is usually under 500 and always less than that of macromolecules such as DNA, RNA, and proteins.

The similar logic of classical and chemical genetic approaches is shown in Figure 1. Through phenotype-based (forward) screening of small molecules, compounds that induce a phenotype of interest can be selected, followed by identifying the target of the compound. Target identification leads to an understanding of novel functions of genes or proteins, but remains a significant challenge in many cases (Burdine and Kodadek, 2004). Although the number of small-molecule compounds that alter the function of particular proteins has been increasing, there are still very few compared with the number of possible targets. A central goal of chemical genetics is to increase the number of pathways and proteins for which a small molecule modulator exists.

Small molecules to probe biology

Small-molecule compounds that intervene in biological systems have been sought as tools to perturb enzymes and signaling pathways and of course as therapeutic agents for disease. Widely used genetic technologies, to perturb the function of genes, are conditional knockout and RNA interference. Their advantages and disadvantages are summarized in Table 1. In contrast to these genetic approaches to study biology, small molecules are easy to apply to cells and work rapidly and often reversibly. In some cases, small molecules that allow highly selective inhibition of only certain isoforms of an enzyme have been developed. For example, several small-molecule inhibitors of phosphoinositide 3-kinases were recently profiled for their ability to inhibit specific kinase isoforms and then used to elucidate the respective roles of these isoforms in insulin signaling (Knight *et al.*, 2006).

Another advantage of small molecules over genetics is that chemical compounds can be used to disrupt a single function of a multifunctional enzyme. Several kinases have been

Table 2. Small-molecule screening in industry and academia

	Industry	Academia
Central goal	Drug development	Biological pathway characterization and manipulation
Typical assay target	Therapeutically ''validated'' enzyme	Pathway involved in a phenotype
Number of compounds screened	$\sim 10^6$	$\sim 10^4$
Compound source	Proprietary, in-house collection	Public repositories, diversity-oriented synthetic compounds, known bioactive compounds
Interest in known bioactive compounds?	No	Yes
Diseases of interest	Major diseases (>$1 billion market)	Rare, orphan diseases as well as major

identified that have distinct functions mediated by their enzymatic activity and by their protein scaffold activity. Because kinase inhibitors selectively block the phosphotransferase activity, but not the protein scaffold function of such proteins, they allow separation of distinct functions that would both be lost by deletion of the gene product (Knight and Shokat, 2007). Tubacin is an example of a small molecule that can inhibit one function (tubulin deacetylase activity) of the multifunctional protein histone deacetylase 6, while not disturbing its histone deacetylase activity (Haggarty *et al.*, 2003). Tubacin accomplishes this by binding to one of two catalytic domains, inhibiting only the domain that possesses tubulin deacetylase activity. Tubacin is an excellent example of a small molecule probe as it has been used in seven subsequent studies by multiple groups to separate the histone *versus* tubulin deacetylase activities of this enzyme in mediating cell motility and protein degradation (Hideshima *et al.*, 2005).

Another unique mechanism of action of small-molecule inhibitors is the disruption of protein–protein interactions, although achieving this goal has often proved challenging. A recent example in which a protein–protein interaction was intentionally blocked, occurred in the development of a small molecule inhibitor of the proinflammatory peptide tumor necrosis factor-α (TNF-α). Up to now, the therapeutic inhibition of TNF-α has been limited to expensive fusion proteins or modified antibodies that must be delivered parenterally. By screening for small molecules that bind subunits of TNF-α *in vitro*, an inhibitor was developed that could potently interact with the biologically active TNF-α trimer, displace a subunit of the trimer, and lead to the rapid inactivation of TNF-α (He *et al.*, 2005). Further development of such an agent may lead to an orally bioavailable TNF-α inhibitor for psoriasis or rheumatoid arthritis.

Although small-molecule compounds may have advantages such as the inhibition of one function of a multifunctional protein and the disruption of protein–protein interactions, target specificity can vary greatly. Many small-molecule compounds may have a target beyond the protein of interest including other proteins, DNA, RNA, lipids, or saccharides. Target identification is often difficult. One solution to the problem of target identification is to use tagged small-molecule libraries, which are designed for both screening and rapid subsequent target identification, as employed in Dr Seth Orlow's pigmentation research (Snyder *et al.*, 2005). In this approach, an internal linker is included in each small-molecule compound in a library. This linker can then be used to attach the selected compound to an affinity matrix directly allowing the cellular target of the compound to be identified by affinity chromatography.

Currently, the major limitation regarding the use of small-molecule inhibitors is that in most cases none have been identified that are capable of inhibiting a protein of interest with high or even moderate specificity. This limitation is the major motivation for chemical genetics that aims to expand the ''toolbox'' for biologists by synthesizing and collecting compounds and by improving access to screening facilities.

Small-molecule screening in industry and academia

Small-molecule screening has long been a component of drug discovery in industry and thought by many not to be a viable aspect of research in an academic setting. Several factors have conspired to change that assumption in recent years and small-molecule screening in academia is now a much more common practice than in the past. This is because of the availability of public repositories of small molecules, commercial small-molecule libraries, and multiple economical screening approaches amenable to an academic setting. Despite the fact that screening is now common in both settings, small-molecule screening in an academic center typically differs in many regards from that in industry (Table 2).

For industry, the research and development costs of new drugs have significantly increased with the average cost per new drug a few years ago in excess of $802 million (DiMasi *et al.*, 2003). Therefore, drug targets are limited to major diseases that have large potential markets and typically to a single enzyme that has already been well characterized as a potential therapeutic target. Because chemical genetic screens can be carried out economically, this approach can be used in academia to study orphan diseases and pathways that are unlikely to yield blockbuster drugs. Indeed, the goal of chemical genetics is to characterize a pathway and provide chemical tools to modulate its function.

Biological insight, publications, and novel probes are typically the end result rather than a therapeutic lead. Chemical genetic screens within academia are likely to involve far fewer compounds and to use compounds that are not proprietary. In particular, so-called ''known bioactive compounds'' (FDA-approved drugs and other small molecules with known biological activity) have been of particular interest in academic chemical genetic studies. If a positive is found among the bioactives, something may already be known about its targets, toxicity, and most likely more compound can be readily purchased without a requirement for chemical synthesis. Academic chemical genetic screens are also more likely to target an entire biological pathway, perhaps in intact cells, than to involve a single purified enzyme. The goals of small-molecule screening in academia *versus* industry are thus distinct and complementary.

Illustrative screens yielding biological insight as well as novel probes

One example of successful pathway-based screening in academia is that carried out by Dr Seth Orlow's group on pigmentation. By screening for small molecules capable of rescuing defective pigmentation in albino melanocytes, a small molecule ''melanogenin'' was discovered that could induce pigmentation. Using an elegant linker system to immobilize the small molecule to a matrix, the target of melanogenin was readily identified as prohibitin, a scaffold protein involved in transcriptional regulation and possibly chaperone function (Snyder *et al.*, 2005). This example is illustrative because through this pathway-based screen of 1,170 compounds, a new inducer of pigmentation was discovered and a novel role for prohibitin in pigmentation was elucidated. Remarkably, melanogenin appears to act as a protein–protein disrupter for this scaffold protein rather than as an enzymatic inhibitor as no enzyme activity has been ascribed to prohibitin. If the traditional approach to ''drug discovery'' had been used, melanogenin could not have been discovered because prohibitin's role in pigmentation had not been documented and prohibitin has no known enzymatic activity that could be screened for in a traditional assay.

An early example of the power of the chemical genetic approach was the identification of a small molecule that acted as a mitotic inhibitor through a novel pathway, distinct from that of taxol and other microtubule polymerization inhibitors (Mayer *et al.*, 1999). A high throughput primary screen for small molecules that arrested cells in mitosis was followed by a biochemical screen (microtubule polymerization) and a microscopic screen (mitotic spindle structure) to identify a compound with the desired properties. This compound, monastrol, was subsequently found to inhibit a mitotic motor protein (kinesin or Eg5). This 1999 observation has led to 62 publications by numerous groups and development of a new class of potential cancer therapeutic agents, the kinesin inhibitors, currently under development at several pharmaceutical companies. In this example, although kinesin was known to be involved in mitosis, no inhibitors existed. The discovery of monastrol proved that a kinesin could be pharmacologically inhibited and that this would block mitosis through a novel mechanism entirely independent from that of taxol.

Small-molecule screening methods and small-molecule libraries

It has been estimated that the number of potential unique carbon-scaffold small-molecule compounds that could be generated is approximately 10^{60}. Such a number is roughly equivalent to the number of molecules in the universe and is an unimaginable and unattainable number. How then, can scientists attempt to create and test this vast potential chemical space for a desired bioactivity? Clearly, this requires the generation of diverse small molecules that has been a central problem for chemists in academia and industry for years. One approach taken predominantly in academia is diversity-oriented synthesis in which various scaffolds are used and highly diverse functional groups are attached to them (Schreiber, 2000; Tan, 2005). Diversity-oriented synthesis is aimed at creating libraries of compounds with structural complexity and diversity, rather than compounds biased toward one particular enzyme target. It aims to do this through exploring untapped or under-represented regions of chemical structure space. Various chemical compound libraries are now available through commercial and public resources that include known bioactive compounds, therapeutic agents, diversity-oriented synthesis compounds, natural products, and their derivatives.

Recent progress in developing both high-throughput screening methods and diverse small-molecule libraries has facilitated the chemical genetic approach to dissecting biological systems. One frequently used screening assay is based on small molecule-mediated alteration of expression of a reporter construct (often luciferase) under control of a promoter of interest, a routine tool in biological study. Below, we compare three relatively recently developed powerful high-throughput methods ideal for small-molecule screening in different circumstances.

Small-molecule microarray

A high-density microarray of approximately 10,000 covalently bound diverse small-molecule compounds, called a small-molecule microarray (SMM), can be used in a high-throughput protein-binding assay to detect which small molecules will bind and recruit a protein of interest from solution as shown in Figure 2a (MacBeath *et al.*, 1999). This approach was used successfully to identify a small molecule that affected the function of a yeast transcriptional regulator, Ure2p. Binding of soluble recombinant epitope-tagged Ure2p to compounds on a glass slide was detected by fluorescent antibody. This revealed a small molecule later called uretupamine that could bind Ure2p (Kuruvilla *et al.*, 2002). Indeed, uretupamine was then identified as an activator of a glucose-sensitive transcriptional pathway downstream of Ure2p. Thus, uretupamine both bound and inhibited the transcriptional repressor function of Ure2p.

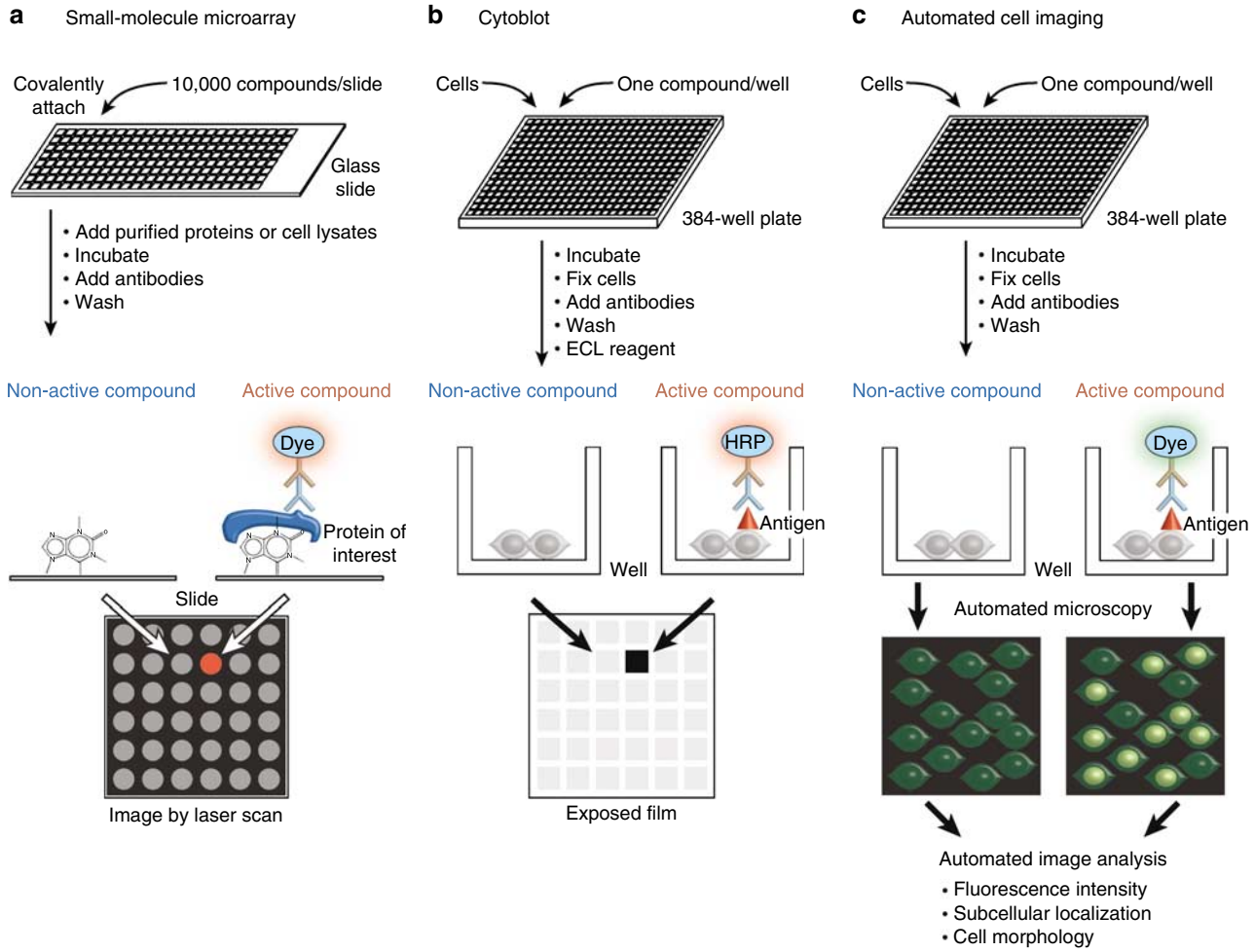

Figure 2. Small-molecule screening methods that were recently developed. (**a**) Small-molecule microarrays allow screening for compounds that bind a protein of interest. Small-molecule compounds are covalently attached onto a glass slide in high density. The microarray is incubated with purified proteins or cell lysates. A primary antibody against a protein of interest and a secondary antibody conjugated with a fluorescent dye are then added. The binding of proteins to specific small-molecule compounds can be detected by a laser scan of the entire slide (a representative region of 36 spots is shown at the bottom). (**b**) Cytoblot assays allow screening for desired post-translational changes in a cell-based assay. Cells are seeded onto a 384-well plate and a single compound is added to each well. After incubation, cells are fixed and a primary antibody of desired specificity is added. Detection is as in Western blotting with a secondary antibody conjugated with horseradish peroxidase (HRP) and enhanced chemiluminescence (ECL) reagent. Light emission is visualized by exposing to autoradiography film or by using a chemiluminescence plate reader. (**c**) Automated cell imaging allows screening for cell morphology, antigen expression, or antigen location within cells. Cells are seeded onto a 384-well plate and a single compound is added to each well. After incubation, cells are fixed and appropriate primary and secondary antibodies are added. Fluorescence images of cells in each well are acquired by an automated fluorescence microscope. The acquired images are analyzed to quantitate physiological change at the single-cell level.

As originally developed, SMMs required purified proteins to identify protein–small molecule interactions. Because not all proteins are readily purified in an active state, SMM has recently been improved to be more versatile. Bradner *et al.* (2006) modified the covalent capture chemistry to accommodate a greater variety of functional groups allowing more diverse compounds to be printed on a given slide. They also modified the SMM approach enabling detection of binding of an epitope-tagged protein of interest directly from cell lysates (Bradner *et al.*, 2006). SMM is thus an extremely miniaturized high-throughput binding assay. Using cell lysates, virtually any protein of interest can be tested for its ability to bind to any of >10,000 diverse small molecules. At this time, this platform is not commercially available, however, a cancer-relevant assay can be set up on a collaborative basis through a National Cancer Institute-funded program at the Broad Institute (http://www.broad.harvard.edu/chembio/).

Cytoblot

Any post-translational modification for which a good antibody exists can be the basis for a cytoblot assay to detect altered phosphorylation, protein expression, etc, following treatment with a small molecule as shown in Figure 2b. In this high-throughput cell-based approach, cells are plated in a 384-well format, a small molecule is delivered to each well, and after incubation, ''Western blotting'' is essentially carried out in each well to reveal the extent of binding of a specific antibody to the

cells in that well (Stockwell *et al.*, 1999). Unlike SMM, the effects of small-molecule compounds on cell physiology can be detected in the miniaturized cell-based assay. The cytoblot assay was the key approach used in the discoveries of monastrol (unique mitotic inhibitor) (Mayer *et al.*, 1999) and tubacin (tubulin deacetylase-selective inhibitor) (Haggarty *et al.*, 2003).

Recently, a two-color fluorescent cytoblot has been developed as a means of normalizing for well-to-well variations (Chen *et al.*, 2005). Cells were simultaneously stained with two primary antibodies and fluorescent signals from the two antibodies were captured by a microplate scanner with two lasers. A combination of phospho-specific and pan antibodies allowed detection of the effects of small-molecule compounds on protein phosphorylation more precisely. Because the cytoblot readout is per well and not per cell, this assay cannot detect intracellular localization of signals or cell-to-cell signal differences. Unlike Western blotting, cytoblot cannot distinguish the protein of interest by size, making antibody specificity critical for this approach.

Automated cell imaging

Recent technical innovations in automated microscopy allow image-based small-molecule screening in a high-throughput manner as shown in Figure 2c. Such an assay is often referred to as ''high-content'' screening, because highly detailed images of cells are acquired and analyzed for various measurements. The actual imaging of a 384-well plate requires approximately 60 minutes. A major challenge with this approach is the difficulty of manipulating the large data files generated because each 384-well plate converts to nearly 1,000 MB of image data. Acquired cell images can then be analyzed by automated image analysis software to quantitate physiological changes at the single-cell level. For example, fluorescence signal intensity derived from a particular antigen within the nucleus can be measured if DNA staining was carried out simultaneously. Such localization-specific detection helps to improve the signal to noise ratio. Also, signal intensity can readily be normalized to the number of cells, diminishing the effects of well-to-well variance in cell number. Furthermore, per-cell readouts allow analysis of the physiological state of single cells including morphological changes and cell toxicity.

Automated microscopy has also been used for phenotype-based screens of small molecules. To identify small-molecule modulators of cell migration, Yarrow *et al.* (2003, 2004) adopted a commonly used wound-healing assay. They observed the effects of compounds on cell migration after mechanically scratching a cell monolayer in 384-well plates by imaging migrating cells from the borders of ''healing wounds'' with an automated microscope. A small-molecule compound, Rockout, was identified as a cell migration inhibitor and submitted to secondary assays that revealed its ability to inhibit Rho kinase (Yarrow *et al.*, 2005). Rho kinase is probably the relevant target of Rockout for cell migration because Rho kinase is known to be involved in cell blebbing.

A microscopy-based screen was used to identify small molecules that may have therapeutic value in a rare lethal genetic lipid storage disease. Niemann–Pick disease type C is an autosomal-recessive genetic disorder characterized by abnormal cholesterol accumulation. These patients develop neurologic abnormalities mostly in early childhood and the disease is usually fatal by the teen years as no effective therapy exists. To discover small-molecule compounds that reverse excessive intracellular cholesterol accumulation, Pipalia *et al.* (2006) screened small-molecule libraries in Niemann–Pick cells, using filipin, a fluorescent detergent that binds to free cholesterol. They found compounds that reduced filipin intensity in lysosomes, suggesting blockage of pathologic cholesterol accumulation by these small molecules. Second-generation compounds demonstrated greater potency and less toxicity although nothing is known currently about the molecular mechanism of these compounds.

National screening resources for academia

Small-molecule screening is typically performed for drug development in pharmaceutical companies using their large proprietary chemical compound libraries. The accessibility to such extensive compound collections and the availability of high-throughput screening methods were, however, essentially not available in academia. With the increasing evidence of success of the chemical genetic approach in academia, the National Institutes of Health (NIH) moved to support these efforts through several approaches including the Roadmap Initiative. One of the earliest publicly accessible screening facilities was funded by the National Cancer Institute as the Initiative for Chemical Genetics (ICG) (Tolliday *et al.*, 2006). The ICG aims to facilitate the discovery of biologically active small-molecule compounds, particularly focusing on cancer. Screening data are deposited into a readily searchable public database, ChemBank. The ICG is based at the Broad Institute (Cambridge, MA) and researchers focused on cancer-relevant biology can make screening proposals (http://www.broad.harvard.edu/chembio/), which, if accepted, allow access to the small molecule repository and screening facilities of the ICG.

The Molecular Libraries Screening Centers Network (http://mli.nih.gov/) was launched in 2005 as part of the NIH Roadmap to aid academic researchers in chemical genetic studies related to all types of biological processes (Austin *et al.*, 2004). The network is a nationwide consortium of 10 high-throughput screening centers and is providing researchers in academia with access to approximately 100,000 chemical compounds. These compounds are contained in the Molecular Libraries Small-Molecule Repository and accessed through the individual screening centers that also develop high-throughput screening methods. The repository includes natural products, known bioactive compounds, and diverse compounds that were synthesized and deposited by chemists in academia. The repository is continuously expanding and is expected to

exceed 500,000 compounds in the near future. The data from high-throughput screening assays performed in the network are deposited after data verification into a database, PubChem, as described below.

The NIH aims to facilitate individual academic investigators in their appropriate use of chemical genetics through an integrated program. To give opportunities for researchers to access the network, the resource access award (X01) mechanism is used. Applicants for this mechanism propose well-developed assays adaptable to high-throughput screening. With the approval of the application, the network offers free screening with staff expertise for identifying small-molecule compounds that modulate biological functions.

Both of the two main chemical–biological databases, PubChem and ChemBank, provide publicly accessible information on chemical structures and biological activities of small-molecule compounds. Although it requires some practice for the uninitiated, strength of both platforms is their capacity to perform comparisons of compounds across multiple parameters of interest (e.g., bioactivity in selected assays, hydrophobicity, molecular weight, etc) with readouts in customized displays. Using either platform, researchers can easily find how active a compound was in assays of interest performed by other screeners. These two databases are, however, different in terms of visualization, types of information links, analysis tools provided, and data source. ChemBank (http://chembank.broad.harvard.edu/) contains compound data from assays that have been performed in the Initiative for Chemical Genetics, whereas PubChem (http://pubchem.ncbi.nlm.nih.gov/) has been collecting small molecule information from assays performed at the 10 NIH Roadmap-sponsored screening centers. As of early 2007, PubChem contains more than 10 million unique compound structures and more than 400 bioassays. Researchers at any institution can deposit their chemical structure and/or assay data into PubChem regardless of where the assay was performed. ChemBank data is restricted to assays performed in the Initiative for Chemical Genetics and undergoes a more extensive standardized statistical analysis that details the reproducibility and validity of the bioassay. Screening at any of these publicly funded facilities requires that the raw screening data be deposited into the affiliated database (PubChem or ChemBank) by a specified number of months after the assay is carried out to improve the breadth and depth of the database.

Public databases in which screening data have been deposited have great potential to facilitate target identification and drug discovery. By comparing and clustering the cytological profiles composed of many measurements from many small molecules, Perlman *et al.* (2004) succeeded in grouping compounds by mechanism. They also demonstrated that ''blinded'' compounds of known mechanism clustered with similar compounds based on their cytological profiles. Thus, by comparing new data from an unknown compound with cytological profiles of already characterized compounds, it will be possible to predict the cellular effects, mechanism of action, and cellular target of novel small-molecule compounds whose mechanism of action is unknown (Perlman *et al.*, 2004; Mitchison, 2005). In this manner, intelligently interpreting patterns from compiled screening data in the databases will be an increasingly powerful and accessible tool to promote drug development.

Chemical genetics in cutaneous biology and the future

The application of chemical genetics to the understanding of pathophysiological phenomena in skin has been expanding. This approach has recently been applied to pigmentation research as described above and in the accompanying Perspective review article. Regarding skin cancer, Williams *et al.* (2003) identified a novel synthetic small-molecule inhibitor of the Hedgehog pathway whose aberrant activation is associated with basal cell carcinoma. The Hedgehog inhibitor induced regression of basal cell carcinoma-like lesions in a newly developed *in vitro* basal cell carcinoma model, whereas it had no effect on normal skin cells.

As it has in other fields, the chemical genetic approach will increasingly impact cutaneous biology as it becomes more routinely used owing to NIH-supported screening centers, databases, and small-molecule repositories. Like the classical genetic approach, it can provide important new insight into biological processes. A uniquely exciting aspect of chemical genetics is that it can also yield small-molecule tools that can later facilitate the work of scientists studying other processes and even validate targets and pathways that can lead to therapeutic development.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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