NIH FORMS NETWORK OF MOLECULAR SCREENING CENTERS TO IDENTIFY NOVEL CHEMICAL PROBES FOR LIFE-SCIENCE RESEARCH

BY MICHELE ARDUENGO, PH.D., PROMEGA CORPORATION

A Roadmap for 21st-Century Life-Science Research

At age seven, Jim Inglese took his new Gilbert Chemistry Set and set up his first laboratory in the basement of his childhood home. Now, Jim Inglese, Ph.D., is helping to set up another laboratory, the NIH Chemical Genomics Center (NCGC; www.NCGC.nih.gov), this time combining state-of-the-art technology with the efforts of some of the best scientific minds in academia, government and industry. NCGC is one of ten national screening centers created as part of the Molecular Libraries Initiative of the NIH Roadmap (1).

The NIH Roadmap is a trans-institute plan outlined by NIH leadership to help the NIH maintain excellence and responsiveness in an environment of sweeping change and progress in the biological sciences (2). The NIH Roadmap identifies three major themes around which initiatives and projects are organized. The *New Pathways to Discovery* theme focuses on generating an improved set of research tools for understanding complex biological questions; *Research Teams for the Future* reflects the increasing need for highly interdisciplinary and creative research efforts, and *Re-engineering the Clinical Research Enterprise* strives to make clinical research more efficient and better integrated with basic science research (2).

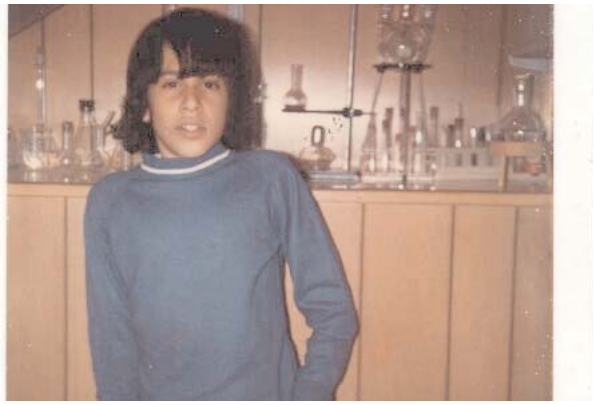

Figure 1. Jim Inglese, age 11, showing off his basement chemistry lab. Dr. Inglese is Deputy Director of the NCGC. He credits his parents, a couple of inspiring high school teachers, and Alfred Carlton Gilbert, creator of the Gilbert Chemistry Set, for nurturing his interest in chemistry. Dr. Inglese received his B.S. in Chemistry from Rensselaer Polytechnic Institute (Troy, NY) in 1984 and a Ph.D. in organic chemistry from the Pennsylvania State University in 1989. He worked on GPCR biology as a postdoc in the laboratory of Bob Leftowitz at Duke University. He later moved to Pharmacopeia, a combinatorial chemistry company, and then Merck, where he directed HTS programs and evaluated technologies for robotic screening and high-content imaging.

This paradigm shift reflects NCGC's interest in chemical genomics, where the aim is to define a high-resolution map of the landscape formed by the intersection of chemical space and biological activity.

New Tools for Groundbreaking Research

Created in July 2004, the NCGC is the first component of the Molecular Libraries Screening Center Network (MLSCN), which is a national network of ten screening centers created to discover small molecules or chemical "tools" for investigating fundamental biological questions and validating drug targets. Because of its mission of creating new tools, the MLSCN falls under the *New Pathways to Discovery* theme of the NIH Roadmap. According to Jim Inglese, Deputy Director of the NCGC, the MLSCN will help realize the promise of the Human Genome Project. The Human Genome Project identified the approximately 25,000 genes of the human genome, a landmark achievement in science representing international-level collaboration and significant technology development. The goal of the MLSCN is to build on that work by identifying small molecules that probe the functions of the >100,000 proteins encoded by the genome.

The work of the MLSCN will complement the ongoing screening programs of drug discovery and pharmaceutical companies. The goal of MLSCN is not to discover new blockbuster drugs, but rather to identify compounds that can be used to validate new drug targets or provide information about complex biological pathways. "While pharmaceutical companies are searching for the next Lipitor®, MLSCN is looking for the next cycloheximide," explains Dr. Inglese. Cycloheximide is a protein-synthesis inhibitor that is widely used by biologists to investigate a variety of biological questions; more than 20,000 peer-reviewed articles have been published in which cycloheximide was used as an investigative tool (3). The MLSCN seeks to uncover more tools like cycloheximide for the life-science researcher.

Pharmaceutical companies concentrate on what they describe as the "druggable" genome, those biological targets

Figure 2. "While pharmaceutical companies are searching for the next Lipitor®, MLSCN is looking for the next cycloheximide," explains Dr. Inglese. The Kalypsys suite of ultrahigh-throughput screening technologies, being installed at NCGC, can evaluate the biological activity of more than 1 million chemical compounds per day. Shown here, the system's robotic arm assembly in the midst of system installation. The compound archive and assay incubator carousels, cmpound and reagent dispensers and multiple detectors will be located around the robotic arms.

that lead to the development of commercially viable therapeutics. For instance, according to Dr. Inglese, G-protein coupled receptors (GPCRs), which are targets for 50% of marketed drugs, account for less than 2–3% of the genome. The MLSCN will focus on "nontraditional" targets, ones that are not studied by pharmaceutical companies because they are not perceived as commercially interesting. The chemical probes identified can be used by public-sector researchers to interrogate the basic biological pathways that interest them, and thus will drive progress on complex biological questions.

The Molecular Libraries Screening Center Network

The MLSCN consists of ten high-throughput screening centers around the nation, each with a specific focus or expertise. Each center will be responsible for optimizing assays for high-throughput operations, screening the compound library using these optimized assays, managing data, and even developing technologies, such as label-free detection systems, to support the network's activities. Discovery Partners International, a pharmaceutical chemistry firm, will maintain the repository of chemical compounds and distribute them to the screening centers (4). In addition, a new and comprehensive database of chemical structures and their biological activities has been developed by the National Center for Biotechnology Information at NIH. The PubChem™ database (http://pubchem.ncbi.nlm.nih.gov) will house both compound information from the scientific literature as well as screening and probe data from MLSCN.

The NCGC will perform screening assays that can be optimized for 1536-well screening formats. The center will be responsible for assay optimization, screening, parallel medicinal chemistry probe optimization and informatics. According to Dr. Inglese, for molecules that have interesting effects on biological systems and that are chemically tractable (analogs easily synthesized), the center will develop analogs with the goal of making small, targeted libraries of potent probes with excellent aqueous solubility. For phenotypic assays where the molecular target is frequently unknown, compounds with interesting screening profiles may be linked to an imaging moiety, biotinylated or photoactivated to create tools for more extensive investigation.

The NCGC moved into its laboratory space in February 2005 and installed its Kalypsys automated high-throughput screening system in July. Since February, NCGC has developed several unconventional and exciting test assays in collaboration with NIH scientists using offline detectors and liquid handling systems. In the last two months, NCGC scientists have screened several targets in a 1536-well format, generating 500,000 data points and creating about 50,000 dose-response curves in their primary screens (3). This is a huge achievement, particularly considering that dose-response curves, such as EC_{50} values, are usually generated only in secondary screening efforts. This paradigm shift in part reflects NCGC's interest in chemical genomics, where the aim is to define a high-resolution map of the landscape formed by the intersection of chemical space and biological activity.

While the NCGC is focused on ultrahigh-throughput screening and generation of targeted probe libraries, other centers in the network will have different capabilities. For instance, the MLSCN Center at Columbia University will have the capability to perform high-speed microscopy screens using a state-of-the-art, high-throughput confocal cell imaging system (5). The University of Pittsburgh Molecular Laboratories Screening Center will have the capability to perform model organism-based assays in *Drosophila* and zebrafish (6). The other centers forming the MLSCN are: the Emory Chemistry-Biology Center in the MLSCN at Emory University in Atlanta, GA; the Southern Research Molecular Libraries Screening Center in Birmingham, AL; the San Diego Chemical Library Screening Center in La Jolla, CA; the Scripps Research Institute Molecular Screening Center in La Jolla, CA; the New Mexico Molecular Libraries Screening Center in Albuquerque, NM; the Penn Center for Molecular Discovery at the University of Pennsylvania in Philadelphia, PA; and the Vanderbilt Screening Center for GPCRs, Ion Channels, and Transporters in Nashville, TN (http://nihroadmap.nih.gov/molecularlibraries/fundedresearch.asp).

Getting the Tools and Information to Public-Sector Researchers

Academic researchers will be able to avail themselves of the MLSCN resources and should view the MLSCN as a "collaborative extension of their laboratory" according to Dr. Inglese. For instance, a researcher studying a particular pathway may have developed a novel assay that could be run against the MLSCN library of compounds. That researcher can submit the assay to the MLSCN program. Proposed assays must be compatible with HTS platforms and address novel biological questions. Guidance for researchers on submitting assays is provided in the Molecular Library Initiative Program Announcement (http://grants.nih.gov/grants/guide/pa-files/PAR-05-060.html) on the NIH Roadmap Web site, and assay applications are accepted three times a year. Proposed assays undergo peer review, and accepted assays are assigned to one of the various MLSCN centers based on the particular expertise of the center. Researchers can access all of the data generated from MLSCN through the PubChem™ database to identify compounds that might be useful in their research projects.

The MLSCN of the Molecular Libraries Initiative is one of many ways the NIH Roadmap plans to lead biological research through the new millennium, capitalizing on the wealth of information and successful model of collaboration provided by the Human Genome Project. It will create valuable new tools for life science researchers in a variety of settings, encourage truly creative and groundbreaking research collaborations between disciplines, and drive technology development. ■

References

1. Austin, C.P. *et al.* (2004) *Science* **306**, 1138–9.
2. Zerhouni, E. (2003) *Science* **302**, 63–72.
3. Inglese, J. (2005) Personal communication: interview July 7.
4. McCody, M. (2004) *Chem. Eng. News* **82**, 8.
5. Rothman, J.E. (2005) Abstract for MLSCN Center at Columbia University. *CRISP* (http://crisp.cit.nih.gov/crisp/CRISP_LIB.getdoc?textkey=6950639&p_grant_num=1U54HG003914-01&p_query=&ticket=15762064&p_audit_session_id=73965193&p_keywords=, accessed July 11, 2005).
6. Lazo, J.S. (2005) Abstract for Pittsburgh Molecular Libraries Screening Center. *CRISP* (http://crisp.cit.nih.gov/crisp/CRISP_LIB.getdoc?textkey=6950645&p_grant_num=1U54MH074411-01&p_query=&ticket=15761987&p_audit_session_id=73965193&p_keywords=, accessed July 11, 2005).

Lipitor is a registered trademark of Pfizer. PubChem is a trademark of The National Library of Medicine.

Promega Corporation
2800 Woods Hollow Road
Madison, WI 53711-5399 *USA*
Tel: 608-274-4330
Fax: 608-277-2516
Toll-Free: 800-356-9526
Toll-Free Fax: 800-356-1970
Internet: www.promega.com

Promega Biosciences, Inc.
A Division of Promega Corporation
San Luis Obispo, California

***Australia,* Sydney**
Tel: 02 9565 1100
Fax: 02 9550 4454
Freecall: 1800 225 123
Freefax: 1800 626 017
E-mail: aus_custserv@au.promega.com

***China,* Beijing**
Tel: 10 6849 8287
Fax: 10 6849 8390
E-mail: promega@promega.com.cn

***France,* Lyon**
Tel: 04 37 22 50 00
Fax: 04 37 22 50 10
Numero Vert: 0 800 48 79 99
E-mail: fr_custserv@fr.promega.com

***Germany/Austria,* Mannheim**
Tel: (+49) (0) 621 8501 0
Fax: (+49) (0) 621 8501 222
Free Phone: 00800 77663422
Free Fax 00800 77663423
E-mail: de_custserv@de.promega.com

***Italy,* Milan**
Tel: 02 54 05 01 94
Fax: 02 55 18 56 64
Numero Verde: 800 69 18 18
E-mail: it_custserv@it.promega.com

***Japan,* Tokyo**
Tel: 03 3669 7981
Fax: 03 3669 7982
E-mail: jptechserv@jp.promega.com

***Belgium/Luxembourg/ The Netherlands,* Leiden**
Tel: (+31) (0) 71 5324244
Fax: (+31) (0) 71 5324907
Free Tel BE: 0800 18098
Free Fax BE: 0800 16971
Free Tel NL: 0800 0221910
Free Fax NL: 0800 0226545
E-mail: bnl_custserv@nl.promega.com

***Latin America Region,* Brazil**
Tel: (55 31) 3262 2915
Fax: (55 31) 9235 2085
E-mail: latinoam@promega.com

***Pacific Asia Region,* Singapore**
Tel: 65 6725 9915
Fax: 65 6725 9889
E-mail: sg_custserv@promega.com

***Spain,* Barcelona**
Tel: 902 538 200
Fax: 902 538 300
E-mail: esp_custserv@promega.com

***Switzerland,* Wallisellen**
Tel: 044 878 90 00
Fax: 044 878 90 10
Technical Service: 044 878 90 20
E-mail: catalys_custserv@promega.com

***United Kingdom,* Southampton**
Tel: 023 8076 0225
Fax: 023 8076 7014
Free Phone: 0800 378994
Free Fax: 0800 181037
E-mail: ukcustserve@promega.com