



# NIH BACKGROUND

National Institutes of Health

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## Molecular Libraries and Imaging

A class of organic chemicals, commonly referred to as "small molecules," has proven to be extremely important to researchers exploring cellular functions at the molecular level. Such molecules have also been valuable for treating diseases. Most medicines marketed today are small molecules.

It remains difficult to predict which small molecules will be most effective at modulating a given biological process or disease state. Therefore, researchers must systematically screen tens or hundreds of thousands of small molecules to find a successful match between a chemical and its target. The capacity for such screening has been built within the pharmaceutical and biotechnology sectors for the purposes of drug development over the last ten years, but similar resources have not existed in the public sector.

The Molecular Libraries Roadmap will offer public sector biomedical researchers access to small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways. It will provide new ways to explore the functions of major components of cells in health and disease.

NIH anticipates that these projects will also facilitate the development of new drugs, by providing early stage chemical compounds that will enable researchers in the public and private sectors to validate new drug targets, which could then move into the drug-development pipeline. This is particularly true for rare diseases, which may not be attractive for development by the private sector.

Three key technological advances drive NIH's effort to build small molecule libraries. First, the successful completion of the Human Genome Project has provided an enormous cache of human biology to be studied and potential drug targets to be discovered. Second, developments in chemistry have given researchers in the public sector the ability to synthesize large numbers of related molecules, a capability previously available only to researchers in pharmaceutical and biotechnology companies. Third, advances in robotic technology and informatics now allow scientists to screen hundreds of thousands of compounds in a single day, an orders of magnitude greater capacity than was available a decade ago.

The Molecular Libraries Roadmap has three components:

1. **Molecular Libraries Screening Center Network (MLSCN).** In June 2004, NIH established the NIH Chemical Genomics Center, the first component of a nationwide consortium of chemical genomics screening centers that will produce innovative chemical tools for use in biological research and drug development. The MLSCN will

accept assays adapted to high-throughput screening (HTS) from the research community, screen a large number of molecules maintained in a central molecule repository, and perform the optimization chemistry required to produce useful *in vitro* chemical probes of the targets or phenotypes studied in the assays. The MLSCN will initially establish a collection of 500,000 chemically diverse small molecules of both known and unknown activities. Over time, this collection will be expanded and modified to provide a working set of molecules that will target larger domains of "biological space," which represents all of the biomolecular surface domains that can potentially interact with a small molecule. All results will be placed into a new public database, and probe compounds will be made available to all researchers, in both public and private sectors, for their use in studying biology and disease.

2. **Cheminformatics.** A new and comprehensive database of chemical structures and their biological activities is being developed by the National Center for Biotechnology Information at NIH. The database, called PubChem, will house both compound information from the scientific literature as well as screening and probe data from the MLSCN. This effort will also fund grants to develop and test new algorithms for computational chemistry and virtual screening.
3. **Technology Development.** As was the case with the Human Genome Project at its inception, the ultimate goal of the Molecular Libraries Roadmap--a comprehensive set of small molecule modulators of a majority of the genes and functions of humans and other organisms--is unachievable with current technologies. Therefore, 30 percent of the Molecular Libraries Roadmap budget is devoted to technology development in the following four areas:
  - **Chemical Diversity.** This area will support the development of new synthetic methods; new and diverse chemical libraries for screening in the MLSCN centers; new methods for isolating and characterizing natural products; and the computational and experimental characterization of diversity space.
  - **Assay diversity.** This area will support the development of assays for novel types of proteins and biological phenomena.
  - **Instrumentation.** This area will support the development of new methods for high-throughput measurement of novel biological assays.
  - **Predictive ADME/Toxicology.** This area will support the development of data sets and analysis methods to allow better prediction of ADME (absorption, distribution, metabolism, and excretion) and toxic properties of novel molecules. The goal is to help obviate the trial-and-error testing that accounts for a large proportion of the time, expense, and failure in the use of small molecules as *in vivo* research tools and drugs.

The Molecular Libraries and Imaging Roadmap will also enhance the discovery and availability of small molecules for molecular imaging. This includes imaging of molecules or molecular events in biological systems that span the scale from single cells to whole organisms. Ultimately, it is hoped that this effort will enable personalized profiles of cell and tissue function, which may lead to more individualized approaches to diagnosing and treating disease. By significantly enhancing the support of this emerging field, NIH will ensure that molecular imaging will become a powerful tool for biomedical research and will be a synergistic component of research in molecular medicine that promises landmark improvements in clinical care.

The Molecular Imaging Roadmap has three components:

1. **High-specificity/high-sensitivity molecular imaging probes.** The goal of this initiative is to improve probe detection sensitivity 10- to 100-fold within 5 years.
2. **Imaging Probe Database.** A specialized portion of the PubChem database will catalog imaging probe information, describing the specificities, activities, and applications of imaging probes for a wide range of diseases and biological functions.
3. **Imaging Probe Development Center.** This center will produce known imaging probes for the research community in cases where there is no viable commercial supplier, as well as generate novel imaging probes for biomedical research and clinical applications.

The URL for the NIH Roadmap web site is [nihroadmap.nih.gov](http://nihroadmap.nih.gov). For more information on the Molecular Libraries portion of the Molecular Libraries and Imaging initiatives, contact Geoff Spencer, Communications Specialist, National Human Genome Research Institute, (301) 402-0911, [spencerg@mail.nih.gov](mailto:spencerg@mail.nih.gov). For more information on the Molecular Imaging portion of the Molecular Libraries and Imaging initiatives, contact Colleen Guay-Broder, National Institute for Biomedical Imaging and Bioengineering, (301) 451-4246, [broderc@mail.nih.gov](mailto:broderc@mail.nih.gov). Further information about NIH can be found at its Web site: [www.nih.gov](http://www.nih.gov).