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Chemical Biology in the USA

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Foreword

Chemical Biology is an interesting and important interdisciplinary scientific field that is likely to contribute strongly to many aspects of medical research.

The aim of this study has been to describe Chemical Biology-initiatives in the USA. The study is focused on what Chemical Biology is, the impact of the field, federal funding initiatives, examples of university initiatives and the industrial interest.

The project has been initiated and supported by VINNOVA and performed by Martin Wikström at ITPS, Washington D.C.

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Summary

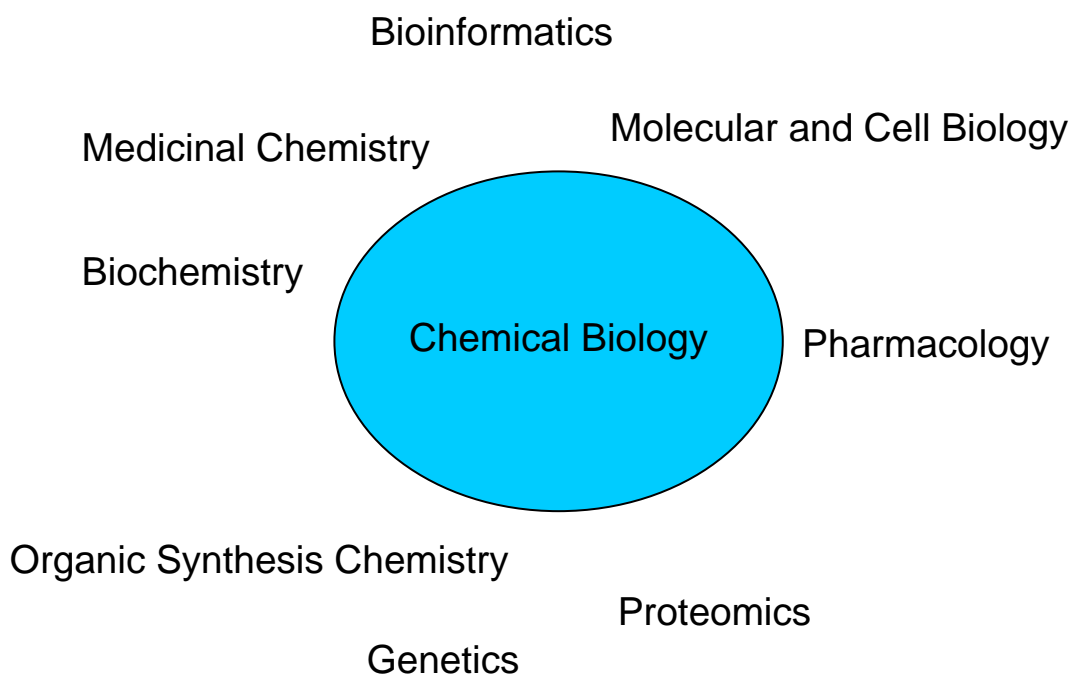
Although the origin of Chemical Biology can be traced to the 19th century it can be seen as a relatively new scientific area related to Molecular biology, Structural chemistry, Bioinformatics, Proteomics, Organic chemistry, Pharmacology, Medicinal chemistry and many others. The field is primarily concerned with research at the Chemistry-Biology interface but is in reality largely focused on small molecules as research tools and potential therapeutics. Synthesis of molecular compounds and screening of these with bioassays is a crucial part of the work in Chemical Biology. In contrast to many other scientific areas Chemical Biology often uses instrumentation normally associated with industrial Drug discovery. This includes efficient methods for the synthesis of large numbers of compounds and high-throughput screening in bioassays. The efforts made are likely to be of importance for disease areas such as Cancer, Neurodegenerative diseases, Inflammation and other. In the USA, the National Institutes of Health and other actors have recognized the need for national concerted efforts within the field and have therefore started National Screening Center networks, Libraries of compounds, Core facilities at some institutes and Databases in which researchers can search for specific molecules and associated data. Some of the databases are dedicated to a disease area (e.g. Cancer) while others are more general. The largest federal funder of Chemical Biology research and development are the National Institutes of Health. In addition, many universities and institutes in the USA have research and training programs in Chemical Biology. One of the most prominent is the Broad Institute (Cambridge, Massachusetts) which also organizes the ChemBank, a database of molecular compounds related to Cancer research.

The aim of this study has been to describe Chemical Biology-initiatives in the USA. The study is focused on what Chemical Biology is, the impact of the field, federal funding initiatives, examples of university initiatives and the industrial interest. The project has been performed by ITPS on initiative and with support from VINNOVA.

1 Introduction

Research at the Chemistry-Biology border is being done in many countries. However, the term “Chemical Biology” is not used everywhere. Although not uniformly used, it appears to be particularly common in the USA, UK, in Japan and in Canada. This does not infer that Chemical Biology research is not made in other countries but only that the *specific term* is not always used to describe it.

In principle Chemical Biology concerns research at the Biology-Chemistry border. Chemical Biology-related research is strongly interdisciplinary and contains elements from many scientific disciplines such as Medicinal chemistry, Molecular biology, Pharmacology, Biophysical chemistry, Biochemistry, Organic chemistry, Structural chemistry, Bioinformatics, Proteomics, Genetics and more. The definition of Chemical Biology is somewhat blurry and highly dependent on the person defining it. In principle Chemical Biology is defined as and contains both the *study of biological processes on the molecular level with a chemical (molecular) approach* and *the development of molecular tools inspired by biological processes*.



1.1 Origin of Chemical Biology

Although Chemical Biology is commonly described as an altogether new discipline, its origin can be traced (Morrison & Weiss, 2006) to the enormous scientific achievements in Chemistry and Biology during the 19th century. A typical example of a study that could be classified as being within Chemical Biology is Joseph Priestley's discovery of Nitric Oxide (NO) and subsequent testing of gases in mice *in vivo*. Many years later (1998) the Nobel Prize in Physiology or Medicine was given to Louis Ignarro, Ferid Murad and Robert Furchgott for the study of NO involvement in cell signaling. Another example in synthetic Organic chemistry is Wöhler's (Wöhler, 1828a; Wöhler, 1828b) demonstration that it is possible to synthesize biologically active compounds. In all, the development of synthetic Chemistry during the 19th century made an enormous impact and was crucial for the subsequent development of Chemical Biology. A third example is Ehrlich's development of methods for the visualization of cells in biological materials (e.g. Ehrlich, 1877). The examples above are only a few examples of what could be called very early "Chemical Biology".

1.2 Modern Chemical Biology

Modern Chemical Biology is driven by the fast expansion of scientific knowledge and methods that has occurred during the last decades in areas such as Molecular biology. Of special importance has been the recent mapping of the Human genome which has made it possible to open up the field of Proteomics. However, the fast development in other areas including Bioinformatics and Structural biology has also had a great impact. In addition, the technical development in for instance imaging, high-throughput screening (HTS) and Synthetic chemistry has been important.

Research in Chemical Biology is made in many ways and includes studies in for instance:

- Proteomics
- Glycobiology
- Receptorbiology
- Natural products chemistry
- Structural biology
- Synthetic chemistry
- Medical genetics
- Bioinformatics

Proteomics concerns investigations about the Proteome – the structures and functions of the vast number of proteins encoded by the Genome. Within Chemical Biology-related Proteomics, both the structure and function of the proteins are of importance as a protein may have fundamentally different functions dependent on its three dimensional structure. An example of when this can give clinical effects is the Mad Cow Disease (Bovine spongiform encephalopathy, BSE) which is caused by a specific type of misfolded protein called a prion.

One goal of Chemical Biology is to synthesize molecules that can be used as tools to selectively and reversibly modulate proteins. The synthesis of molecules to study extra- and intracellular signaling is another aim of Chemical Biology as well as some aspects of Glycobiology which is concerned with the study of different types of sugar molecules in the cell. In Chemical Biology studies, synthetic variations of sugar molecules can be used as tools for research. Another important branch of Chemical Biology uses endogenous biomolecules to develop chemical processes and/or materials.

Chemical Biology research is diverse and the above mentioned areas should only be seen as examples. Research in the field is often concerned with the understanding of biological functions in the healthy individual as well as of the pathological mechanisms related to disease conditions including cancer, neurodegenerative disorders, renal and pulmonary dysfunctions and metabolic disorders. The field is therefore important for the generation of knowledge and tools for basic science as well as for the study of disease mechanisms. For many diseases, it is also important for the production of countermeasures and preventive actions.

1.3 Impact of Chemical Biology

It is evident that Chemical Biology, that started to be a recognized term 10–15 years ago, is well established in the USA. A sign of how important the research community considers the field to be is the large number of international journals dedicated to it. Below some of the most important are listed (impact factor 2006 in parenthesis. NE = not yet established):

- ACS Chemical Biology (NE)
- Bioorganic & Medicinal Chemistry (2.624)
- BMC Chemical Biology (1.400, unofficial)
- ChemBioChem (4.100)
- Chemistry & Biology (NE)
- Current Opinion in Chemical Biology (8.320)
- Journal of the Royal Society Interface (2.984)
- Molecular BioSystems (2.450)
- Nature Chemical Biology (12.409)
- Chemical Biology and Drug Design (NE)

2 Small Molecule approach

In the USA and in other countries much of the Chemical Biology research is focused on the synthesis and development of small bioactive molecules (small is usually defined as <500 Da). These small molecules are synthesized using Combinatorial chemistry specifically for a target and are used for instance to selectively and reversibly modulate a protein, for instance an enzyme, in vitro or in vivo. In some cases the target molecule may also be manipulated. In the academic research environment, the objective is normally to produce research tools for the study of biological systems on the molecular level. However, the objective is also to contribute to Drug discovery that may lead to potential new therapeutic products.

In contrast to what is common in many biomedical scientific disciplines, researchers working with small molecules as described above often use technical tools normally associated with industrial Drug discovery. Synthesis of large number of compounds is done with efficient large-scale technologies while bioassay testing of the molecules is done with high-throughput screening. In addition, large Cheminformatics databanks are being built up at a number of places across the United States to enable in particular researchers at universities and public institutions to access molecular structures and screening data. Typically such a database would contain:

- Small molecule data
- Results from Small molecule screening in assays
- Resources for studying data

A typical example of Chemical Biology research is the study of the different subtypes of Adenosine receptors (Jacobson & Gao, 2006; Jacobson et al., 2007) and their agonists and antagonists (activators and blockers). Adenosine receptors are known or suspected to be involved in multiple diseases and conditions including Inflammation, Endocrine disorders, Cancer, Vision disorders, Renal disorders, Pulmonary disorders, Dementia, Anxiety, Pain, Parkinson's disease, Sleep disorders and Ischaemia. It is therefore clear that molecular tools to reversibly and selectively manipulate the functions of different subtypes of receptors involved in the conditions may have the potential to become useful tools in the research and also in some cases useful therapeutics. It should be emphasized that some labs not only create molecules for the manipulation of receptors but also reengineer the binding sites on the receptors. These types of reengineered receptors are often called neoreceptors and may not be activated by their native agonist (e.g. Adenosine) but rather functions as a scaffold for the docking of novel small molecules, so called neoligands. This type of approach could lead to insights into the accuracy of G-protein coupled receptor modeling, signaling pathways, and not least, the design of small molecules to be able to rescue disease-related mutations and do small-molecule directed gene therapy. The combination of tailoring of small molecules and their protein targets is therefore of special interest.

In addition to the databases created, Chemical libraries of compounds are being built up at a number of locations in the USA. At these libraries researchers can get access to a large number of compounds that may be used as for instance research tools, a starting point for further drug development or alike. Many of the Cheminformatics databases are open to anyone. However, the policies of the Chemical libraries vary with some operating commercially while access to others may be restricted to for instance researchers at public institutions (including non-profit organizations such as private universities) or to the National Institutes of Health. It is however clear that the libraries and databases may also be of great value for the private for-profit sector including the pharmaceutical and biotechnological industry.

3 Federal initiatives and funding of Chemical Biology research in the USA

Chemical Biology research and funding programs are common in the United States. However, as noted earlier the term “Chemical Biology” is not always used to describe them. In reality, while many universities and research institutions use the term, few funding programs do. During this study, only two to three federal programs clearly stating that research should be done in “Chemical Biology” has been found. One of them is the National Institutes of Health’s (NIH) “Directors New Innovator Program” in which Chemical Biology is one out of ten named research areas. That many funding programs do not use the term does however not imply that Chemical Biology is little funded. Federal funding programs in many areas such as Cancer, Neurobiology, Renal diseases and General medical science are to a large degree directed to Chemical Biology research. The research funded may be concerned with for instance molecular studies, Informatics, Intracellular signaling, Organic or Structural chemistry, Proteomics or Genetics.

Many federal agencies support research and development in Chemical Biology. However, for the above mentioned reasons and as the definition of Chemical Biology is somewhat elusive it is difficult to do a complete survey of all initiatives directed to the field. Among the agencies that support some type of Chemical Biology are the:

- National Institutes of Health
- National Science Foundation (NSF)
- Department of Energy (DoE)

3.1 Federal initiatives

Most federal funding for Chemical Biology comes from NIH. The DoE-funded research is primarily concerned with new methods for energy production. In this study, we therefore focus on the NIH.

3.1.1 National Institutes of Health

NIH support Chemical Biology-related efforts from the synthesis of compounds all the way to animal tests (including toxicology) and clinical trials. The NIH budget doubled between 1998 and 2003 and in 2004 NIH launched the Roadmap in which it identified a number of key areas that were seen as crucial for the future of Medical research and in need of concerted national efforts. The roadmap is continuously updated and currently contains the following main initiatives:

- New Pathways to Discovery
 - Building Blocks, Biological Pathways and Networks
 - Molecular Libraries and Imaging
 - Structural Biology
 - Bioinformatics and Computational Biology
 - Nanomedicine

- Human Microbiome Project
- Epigenomics

- Research Teams of the Future
 - High-Risk Research
 - NIH Director’s Pioneer Award
 - NIH Director’s New Innovator Award
 - Interdisciplinary Research
 - Public-Private Partnerships

- Re-engineering the Clinical Research Enterprise
 - Reengineering the Clinical Research Enterprise Initiatives
 - Clinical Research Networks and NECTAR
 - Clinical Outcomes Assessment
 - Clinical Research Training
 - Clinical Research policy Analysis and Coordination
 - Translational Research

In particular, the “New Pathways to Discovery” program contains many Chemical Biology-related initiatives. Some important examples are listed below.

3.1.2 Chemical Biology initiatives in the NIH Roadmap

National Technology Centers for Networks and Pathways

This initiative aims to develop highly sensitive tools to enable quantitative measurements of activity, translocation, and interactions of intracellular protein molecules. The centers will cooperate in a network to develop new technologies directed at gathering information at the level needed to characterize sub-cellular processes. In addition, the methods will be aimed at defining the dynamics of complex intracellular systems.

Metabolomics Technology Development

The field of Metabolomics is concerned with small molecules found within cells and tissues. There is currently no single technology that can effectively and accurately measure the diverse range of metabolites and dynamic fluctuations within cells. The initiative therefore encourages the development of innovative and sensitive tools to identify and quantify these. The technologies developed will be major contributions to research on the chemical and molecular pathways in cells involved in development, normal function, aging, and disease.

Molecular Libraries & Molecular Imaging

The Molecular Libraries are aimed at providing public sector researchers with access to small organic molecules that may be used as chemical probes to study the functions of genes, cells, and biochemical pathways in health and disease. It will also, most likely, facilitate the development of new drugs by providing early stage chemical compounds to researchers so that they will be able to find successful matches between chemicals and targets.

Molecular imaging is an emerging research field aiming to visualize biochemical and physiological processes on different levels. The initiative enhances the discovery and availability of technologies to image molecules and molecular events within single cells and whole organisms. The long-term goal is to enable a detailed molecular understanding of cell and tissue functions in normal and disease states.

NIH Small Molecule Repository

The NIH Small Molecule Repository acquires, maintains, and distributes up to 500,000 compounds obtained from commercial and academic sources. The molecules have diverse chemical structures and known or unknown biological activities. The repository provides compounds to the NIH Molecular Libraries Screening Centers Network (MLSCN, see below) for use in high-throughput screening (HTS) with diverse set of biological assays.

NIH Molecular Libraries Screening Centers Network

The Molecular Libraries Screening Centers Network (MLSCN) is a national resource to enable scientists to explore the importance of small molecules in biological systems with HTS assays. Screening "hits" will most likely be further developed and in some cases used by the scientific community as bioactive probes to study molecular targets and cellular pathways. They may also be used as starting points for therapeutics development. Chemical structures of the molecules and screening data obtained from the MLSCN, will be available through PubChem (<http://pubchem.ncbi.nlm.nih.gov>). Molecules are kept in a central repository (see above).

Molecular Libraries Screening Instrumentation

The Molecular Libraries Screening Instrumentation (MLSI) initiative is intended to develop new instrumentation for high-throughput screening (HTS) systems in order to identify small molecules that are important in biological mechanisms within living cells. The initiative seeks to develop faster, more accurate and more efficient HTS instrumentation than currently available systems.

High-Throughput Molecular Screening Assay Development

The initiative aims to increase the number of research application of HTS. Its goal is to create new biological assays that can be used for automated screening at the NIH Molecular Libraries Screening Centers. New assays providing additional insights into cellular and/or molecular targets that have not been the focus of previous HTS approaches are emphasized.

Molecular Imaging Probes

Molecular imaging may display biochemical and physiological abnormalities that underlie diseases. The initiative encourages the development of new more sensitive and selective probes that will improve the ability to detect and image specific molecular events *in vivo* and *in vitro*. The new probes developed may become important for clinical applications.

Structural Biology

The initiative aims to study the molecular shapes of proteins in the body and is designed to enhance our understanding of how proteins function. This requires the development of new methods to produce protein samples. The aim is also to find ways to discern structures of protein biomolecular assemblies—sets of proteins that act together to carry out essential cellular functions.

Nanomedicine

One goal of this initiative is to create materials and devices at the level of molecules, to cure disease or repair damaged tissues. The initiative contains a process to develop a network of **Nanomedicine Development Centers**. In the centers, teams of scientists from different disciplines, including Cell biology, Biochemistry, Mathematics, Physics and Engineering, work together to develop new technologies that will enable a better understanding of molecular interactions within living cells and the physical and chemical properties of molecular structures. This knowledge will lead to a deeper understanding of biological principles, which later may permit scientists to engineer/repair molecular structures in order to treat diseases or damaged cells and tissues.

3.1.3 Roadmap budget for Chemical Biology

The NIH roadmap is a very important initiative to address urgent scientific needs that benefit from an approach on the national level in the USA. As the Roadmap is very well known by the research community both inside and outside the United States it may come as a surprise that it actually amounts to a relatively small part of the NIH budget. The Roadmap only corresponds to 1–2 per cent of the NIH budget as most of it is reserved for various purposes including ongoing projects. However, it should be noted that many of the NIH-funded Chemical Biology activities are funded via other sources than the Roadmap. The NIH support both extramural and intramural research and the support occurs in many forms such as through research awards, young investigator awards, network support, training grants and support for large scale efforts and programs.

The total Roadmap budget and the “New Pathways to Discovery” initiative budget can be seen in table 1. According to NIH representatives Chemical Biology research has suffered relatively little from recent cuts in the NIH budget.

Table 1 Roadmap budget, in Million of US Dollars.

| Year | New Pathways to Discovery | Total Roadmap Budget |
|------------------------|----------------------------------|-----------------------------|
| 2006 | 171 | 332 |
| 2005 (estimate) | 181 | 483 |
| 2008 (budget) | 208 | 486 |

Source: NIH budget justification, AAAS R&D FY 2008

3.1.4 Examples of specific NIH Chemical Biology initiatives

Small Molecule Center Network

NIH supports a network of Small Molecule Screening Centers. In 2005 these were located at:

- Columbia University Medical Center, New York
- Emory University, Atlanta, Georgia
- Southern Research Institute, Birmingham, Alabama
- The Burnham Institute, La Jolla, California
- The Scripps Research Institute, La Jolla, California
- University of New Mexico Albuquerque, New Mexico
- University of Pennsylvania, Philadelphia, Pennsylvania
- University of Pittsburgh, Pennsylvania
- Vanderbilt University, Nashville, Tennessee

In addition the following institutions are associated with the effort:

- NIH Chemical Genomics Center (NCGC)
- Molecular Libraries Small Molecule Repository, San Francisco

NIH consists of 27 institutes concerned with research in particular areas. Most Chemical Biology initiatives are taken on the institute level. Below, a few prominent examples of initiatives are described.

National Cancer Institute (NCI)

At the NCI, a new Chemical Biology program has recently been suggested. The program is focused on the development of new therapeutics/diagnostics, new technologies, prevention of Cancer and AIDS and training. The training part concerns in particular the training of Chemists in methods and technologies at the Chemistry/ Biology border.

Furthermore, intramurally at NCI, it has been suggested that the

- connections and communication within and between the Chemical and Structural biology faculties as well as with other relevant groups (e.g. Nanobiology) should be improved.
- that a stronger working relationship with Molecular target and Developmental therapeutic faculties should be developed.
- that a focus on Chemistry should be emphasized.
- support for a multi-tiered model for providing compounds to the NCI should be developed.
- that the integration of Chemical toxicology and Natural products sciences with Synthetic chemistry and Biochemistry should be strengthened.

NCI Initiative for Chemical Genetics (ICG)

The aim of this initiative is to enable public research using small molecules to accelerate the discovery of Cancer-relevant small-molecular probes. A systematic approach to develop screening tools and compounds and to accelerate the development of new strategies and therapies for Cancer is used. The focus is on biological assays, chemical libraries, a repository of chemical probes, and a scientific database. Through efforts in Synthetic chemistry, the ICG has so far synthesized more than 10,000 new compounds. All data is deposited in **ChemBank**, an online database (handled by the Broad Institute, see below) that currently includes chemical data on 700,000 small molecules of which some have also been characterized further using assays. ChemBank is intended to guide chemists synthesizing novel compounds or libraries, to assist biologists searching for small molecules that perturb specific biological pathways, and to catalyze the process by which drug developers discover new and effective medicines. Investigators can use ChemBank's tools to query and analyze available data and export raw information for subsequent analysis. The ICG initiative includes:

- The creation of tightly integrated teams of Synthetic and Analytical chemists, Assay developers, High-throughput screening and automation engineers, Computational scientists, and Software developers.
- 76 Biology laboratories from 39 institutions (2006).
- That all Chemistry and Screening data are deposited into the ChemBank web site.

National Institute of Diabetes and Kidney Diseases (NIDDK)

NIDDK Chemical Biology Core Facility

In order to facilitate the discovery of new medicinal agents with therapeutic potential a Chemical Biology core facility has been developed at the NIDDK. The facility consists of a multidisciplinary team of researchers who are experts in Organic synthesis and Pharmacological analysis. The main aim is to promote and advance collaboration within NIDDK chemical and biological laboratories. Most importantly, the facility assembles Chemical libraries and numerous Biological assays.

National Institute of General Medical Sciences (NIGMS)

In contrast to most other NIH institutes, NIGMS funds only extramural research. NIGMS is one of the largest funders of Chemical Biology research which is present in many programs. The most common form of funding is the normal research award. Approximately 60 per cent of the NIGMS budget of 1.94 billion USD concerns such grants and of this 1/3 has a significant chemical component. NIGMS also supports chemical methods and libraries network with four centers as well as a research training program in Chemical Biology. Some examples of programs with a Chemical Biology content that are funded by NIGMS are:

- Metals in Medicine
- Chemical Methodologies and Library Development (CMLD)
- Consortium on Functional glycomics
- Lipid metabolites and Pathways consortium
- Support for Chemistry – Biology interface PhD-training program (1993–)

4 University/Institute initiatives

A relatively large number of universities in the USA have formal “Chemical Biology” initiatives. However, as the term is not always used, it is difficult to assess exactly how many they are. Among universities (or similar) with high profile Chemical Biology research are:

- The Broad Institute (MIT, Harvard, MA)
- Scripps Institute (CA & FA)
- Yale (CT)
- University of California San Francisco (CA)
- University of Pittsburgh (PA)
- NIH (Intramural, MD)
- University of Wisconsin - Madison (WI)
- University of Texas Southwest (TX)
- Cornell (NY)
- Rockefeller (NY)
- Columbia (NY)
- Salk Institute (CA)
- Stanford (CA)

4.1 Education initiatives

Many universities have training programs in Chemical Biology. Among those with formal programs are:

- University of Michigan (MI)
- University of Wisconsin – Madison (WI)
- University of California – Berkeley (CA)
- Penn State (PA)
- Scripps (CA)
- Harvard & Massachusetts Institute of Technology (MIT, MA)
- Columbia University (NY)

4.2 The Broad Institute

Research at the Broad institute is focused on the molecular basis of diseases and Genomic medicine. In addition, the institute handles the ChemBank database (ICG, funded by the NCI, See above) which is a national resource. The institute is a joint effort between MIT and Harvard University and is located in Cambridge (MA). It was founded in 2003 and is largely based on an original donation of 100 million USD made by Eli and Edythe Broad (The Broads have since then made a second donation of 100 million USD to the institute). The Whitehead Institute/MIT Center for Genome Research (WICGR) founded in 1990 and the Institute of Chemistry and Cell Biology (ICCB) founded in 1998 were predecessors of the institute and are now part of it. The institute has 6 core members that have their research labs on the premises and 108 associate members. The core members are:

- Eric Lander, Director
- Stuart Schreiber, Director, Chemical Biology
- David Altschuler, Director, Medical & Population Genetics
- Todd Golub, Director, Cancer program
- Deborah Hung, Ass Prof, Chemical Biology
- Aviv Regev, Ass Prof, Computational Biology

The institute has a special organization based on **scientific platforms** and **programs**.

The platforms are:

- Biological Samples
- Chemical Biology
- Genomic Sequencing
- Genetic Analysis
- Imaging
- Proteomics
- RNAi

The Chemical Biology platform consists of the following elements:

Chemistry

Use of an advanced technical platform enables the synthesis of large collections of natural-product like molecules and small molecules based on core structures that may be modified for use in experiment. Efficient synthetic pathways result in collections of small molecules having skeletal, stereochemical, and appendage diversity.

Informatics

The informatics platform manages data collection and integration from chemical synthesis to screening and data analysis. In principle all material is computerized (including lab book notes). The automated lab management system enables high-throughput operation and improved data quality.

Screening

A number of advanced automation systems for compound management and screening are used in the screening facility. According to the institute, new systems are being put in place that will enable storage and handling of up to 500,000 compounds and the use of a large number of assays. Novel screening approaches with relevance to many diseases are used.

The scientific programs are:

- Cancer program
- Genome Biology & Cell Circuit program
- Program in Medical & Population Genetics
- Chemical Biology program
- Metabolic Diseases initiative
- Infectious Disease initiative
- Psychiatric Diseases initiative
- Computational Biology and Bioinformatics

Chemical Biology program

Although research of a number of different types is represented much of it concerns small molecules. In line with this the program is focused on small molecules as tools to dissect gene functions and interactions. New small molecules are synthesized to find new tools for the modulation of biological processes and for non-invasive imaging. New high-throughput screening methods are developed as well as computational tools to analyze data.

The Director of the Chemical Biology program is Prof. Stuart Schreiber. In addition, there are seven associate faculties, seven research fellows and in total approximately 150 in total staff.

The **ChemBank** is a public, web-based informatics environment funded in large part by the NCI Initiative for Chemical Genetics (ICG) and located at the Broad institute. It is described above.

5 Industrial interest in Chemical Biology

The interest in Chemical Biology from the industry is much dependent on the possibility that the efforts in the field will result in an accelerated drug discovery, an increased understanding of disease mechanisms as well as a work force skilled in the whole process of drug discovery from the synthesis of compounds to testing of these in biological assays. Of interest to companies is also access to the molecular libraries and databases created. Many collaborative efforts between industry and academic institutions including the NIH occur and industry may be involved in any stage in the scientific processes. Formally seen many NIH funding schemes are open to investigators from industry. It is however rare that industrial researchers apply for these. Typical companies that are likely to benefit from Chemical Biology efforts are big pharmaceutical companies such as AstraZeneca, Pfizer, Merck, GlaxoSmithKline and Abbott. However, it is clear that also medium-sized and small companies involved in drug discovery and design may benefit. A company that is involved in Chemical Biology and was founded partly by Stuart Schreiber, director of the Broad institutes Chemical biology program, is ARIAD Pharmaceuticals Inc. (www.ariad.com). The company is based in Cambridge (MA) and is involved in the discovery of novel medicines to treat cancer by regulating cell signaling with small molecules.

Many chemical libraries are commercially and internationally available. However NIH Roadmap compounds are not freely distributed and are normally only available to NIH-supported screening centers. Access to the NIGMS Centers for Chemical Methodology and Library Development is granted to collaborators by the centers depending on their objectives. There is no principle prohibition against collaborations with industry. Databases such as PubChem and ChemBank are available to anyone.

5.1 Patents and Spin-off companies

Patents as a result of Chemical Biology research will in most cases relate to drug entities (as tools or therapeutics), new bioassays, screening and imaging technologies. However patents relating to the above may also be the result of other scientific approaches.

Many researchers at US universities have companies and collaborations with industry. However, at NIH, spin-off companies are not allowed although licensing of drugs is.

6 Conclusions

Chemical Biology is a relatively new research field at the Chemistry-Biology border area. However, the origin of the field can be traced to the 19th century. Chemical Biology is clearly interdisciplinary and has to a large extent been driven by the fast development in Molecular biology during the last decades. It is clearly related to Proteomics and in particular the mapping of the Human genome has been exceedingly important. It is clear that the field is well established in the American research community and at least 10 international scientific journals (including *Nature Chemical Biology*) are largely dedicated to the field. The definition “Chemical Biology” is not always used in the USA and it is therefore difficult to find all initiatives. The reason for this is that Chemical Biology to some extent may be characterized as an “approach to science” and not a research field in the classical sense (such as for instance Neuroscience, Anatomy, Structural Chemistry or Immunology). The definition of Chemical Biology is somewhat fluent and may be defined as the study of biology with molecular methods and the production of molecular tools with inspiration from biology. However, much of the research in the USA concerns the production of small molecules as research tools and potential therapeutics. A typical molecular research tool can be a molecule that when directed to a protein target reversibly and selectively changes the function of the protein. It can also be a molecular tool for imaging of cellular processes. Some types of Chemical Biology are also concerned with the modification of biological targets for small molecules. Chemical biologists often have a relatively wide skill-set and are familiar with for instance both Organic synthesis chemistry and Receptor biology. In contrast to many other research fields, Chemical Biologists use more industrial-scale equipment for synthesis of compounds, and screening.

Federal funding for Chemical Biology in the USA mostly comes from the NIH although other agencies such as NSF contributes as well. While much of the funding arises from the 27 NIH institutes that focus on different aspects of medical research (often disease-related), a significant part comes from the strategic NIH Roadmap initiatives. In the Roadmap, NIH has defined a number of areas that are crucial for the future of American medical research and that need concerted national efforts. Among these are the building of Networks of Screening Centers, Technical Development Centers, Compound Libraries and online Databases of compound structures and results from screenings. Many American universities and institutes such as for instance the Broad institute, the University of Wisconsin-Madison and Yale have research and training programs in Chemical Biology. In addition, there is a clear interest from industry relating not least to the libraries and databases that are being built as well as a workforce trained in many aspects of Drug discovery. It should also be noted that Chemical Biology initiatives exist in many other countries including Canada, Japan, Germany, France and the United Kingdom as well.

In all, Chemical Biology is an interesting and important interdisciplinary scientific field that is likely to contribute strongly too many aspects of Medical research. The approach that Chemical Biology represents should be of interest to Sweden and the European Union not least because it appears to be an efficient way to create molecular research tools and speed up the drug discovery process. In addition, compound libraries and chemical databases can be of great use both for academic researchers and industry.

References

Articles

- Berg, J.M. Opportunities for Chemical Biologists: A View from the National Institute of Health. *ACS Chem. Biol.* 1(9): 547–548 (2006).
- Buchholz, T.J., Palfey, B., Mapp, A.K., Glick, G.K. Graduate Education in Chemical Biology at the University of Michigan. *ACS Chem. Biol.* 1(8): 487–488 (2006).
- Couzin, J. NIH Divests into drug Discovery. *Science* 302: 218–221 (2003).
- Ehrlich, P. *Mikr. Anat.* 13, 263–277 (1877).
- Gerlt, J.A., Marletta, M.A. Mechanisms. Research highlights at the chemistry/biology interface. *Curr. Opin. ChemBiol.* 2: 605–606 (1998).
- Gray, N.S. Drug discovery through industry-academic partnerships. *Nature Chem. Biol.* 2(12) 649–653 (2006).
- Jacobson, K.A., Gao, Z-G. Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov.* 5(3):247–264 (2006).
- Jacobson, K.A., Gao, Z-G, Liang, B.T. Neoeptors: reengineering GPCRs to recognize tailored ligands. *Trends Pharmacol. Sci.* 28(3) 111–116 (2007).
- Kohler, J.J. A century at the chemistry-biology interface. *Nat. Chem. Biol.* 2(6) 288–292 (2006).
- Kotz, Chemical biology at the Broad Institute. *Nat. Chem. Biol.* 3(4) 199 (2007).
- Macasco, C.A. Chemical Biology: Adventure Awaits. *ACS Chemical & Engineering News.* 84(16) 47–49 (2006).
- Moro S, Gao Z-G, Jacobson K.A., Spalluto G. Progress in the pursuit of therapeutic adenosine receptor antagonists. *Med Res Rev.* 26(2):131–59 (2006).
- Morrison, K.L., and Weiss, G.A. The origins of Chemical Biology. *Nat Chem Biol.* 2, 3–6 (2006).
- Sawyer, T.K. Chemical Biology & Drug Design: First Anniversary-2007. *Chem Biol. Drug Des.* 69:1–2 (2007).
- Schreiber, S.L. Small molecules: the missing link in the central dogma. *Nature Chem Biol.* 1(2) 64–66 (2005).
- Silvius, J. Strength in diversity: a cross-disciplinary approach to graduate training in chemical biology. *Nat. Chem. Biol.* 2(9) 445–448 (2006).
- Tan, D.S. Diversity-oriented synthesis: exploring the intersections between chemistry and biology. *Nature Chem. Biol.* 1(29) 74–84 (2005).
- Thomas, P. The Chemical biologists. Small molecules and “systematic serendipity” yield big ideas in life-sciences and biomedical research. *Harvard Magazine.* March-April 38–47.
- Wöhler, F. *Poggendorff's Ann.* 12, 253–256 (1828a).
- Wöhler, F. *Ann. Chim. Phys.* 37, 330–333 (1828b).

Editorials in Nature Chem. Biol.

An emerging role for chemical biology 1(3): 121 (2005).

Meetings of the Minds 1(5): 235 (2005).

Nature Chemical Biology features 1(2): 63 (2005).

Vision Statement for a New Chemical Biology Program at the CCR, National Cancer Institute (Internal document)

Web sites

ACS Chemical Biology <http://pubs.acs.org/journals/acbcct/index.html>

American Association for the Advancement of Science www.aaas.gov

American Chemical Society www.acs.org

Ariad Pharmaceuticals Inc. www.ariad.gov

AstraZeneca www.astrazeneca.com

Blackwell publishing <http://www.blackwell-synergy.com>

Broad Institute www.broad.mit.edu

Current Opinion in Chemical Biology

http://www.elsevier.com/wps/find/journaldescription.cws_home/601299/description#description

Department of Energy www.doe.gov

Department of Health and Human Services www.hhs.gov

GlaxoSmithKline www.gsk.com

Health Canada <http://www.hc-sc.gc.ca/>

National Institute of Health www.nih.gov

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Pharmaceutical Research and Manufacturers of America (PhRMA) www.phrma.org

Royal Chemical Society (UK) <http://www.rsc.org>

Science www.science.com

The Scripps Institute www.scripps.edu

Web of Science www.isiknowledge.com

White House www.whitehouse.gov

Yale University (Chemical Biology conference) <http://www.yale.edu/chemicalbiology/>

Other university web sites

Methods

This study has been made using literature studies including web-searches, interviews and analysis of the collected material. The individuals that have been interviewed are:

Interviews

Tim Corless, Director of Business Development, Columbia University Science and Technology Ventures

Kenneth A. Jacobson, Chief, Molecular Recognition Section

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health

Beth Kauderer, Senior Associate Director Columbia University Science and Technology Ventures

Michael E. Rogers, Director, Pharmacology, Physiology, and Biological Chemistry Division, National Institute of General Medical Sciences, National Institutes of Health

Stuart Schreiber, Director Chemical Biology program, Broad Institute

Lana Skirboll, Director, Office of Science Policy, National Institutes of Health (NIH)

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The Swedish Institute for Growth Policy Studies (ITPS) is a Government Agency responsible for providing policy intelligence to strengthen growth policy in Sweden. ITPS primarily provides the Government Offices, Members of the Swedish Parliament, other state authorities and agencies with briefings based on statistical material, policy papers and key analyses. Business policy and regional development policy are areas given high priority.

Changes in policy should be based on:

- Statistic data and analyses of the structure and dynamics of industry – to obtain an up-to-date view of future challenges and opportunities.
- Evaluation of results and effects of policy measures and programmes – to provide benchmarks and learn from measures implemented earlier.
- Policy intelligence in order to look outwards and ahead – what issues are likely to come on the growth policy agenda in the future?

These represent the principal missions of ITPS.

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