Chemical biology in China takes on signal transduction

Hualiang Jiang, Jiarui Wu, Lihe Zhang, Wenping Liang, Feixue Gao, Canping Du, Xuelian Feng & Yongjun Chen

Funding support for chemical biology is essential for its growth around the world. A new funding initiative from the National Natural Science Foundation of China provides a model of a targeted funding program in the area of signal transduction.

Chemical biology has been appreciated by scientists in China since the subject emerged as an interdisciplinary field. In the late 1980s, the Ministry of Science and Technology of China initiated a basic research program, named the National Climbing Program, that was the precedent of the current major basic research project known as the National Basic Research (973) Program of China. This program funded a project entitled "Chemical Studies in Biological Processes," which can be considered the beginning of chemical biology research in China. Like their counterparts in other countries, scientists in China (mainly chemists) then tried to use chemical tools and principles to solve problems in biology. Since the 1990s, chemical biology has developed as an interdisciplinary field that has been widely applied in the biological and biomedical sciences[1]. During this period, scientists in China have appreciated the importance of chemical biology and expanded collaboration between chemists and biologists.

Scientists in China have also contributed much to chemical biology research, which frequently has been associated with the study of traditional Chinese medicine (TCM). One example is related to arsenic trioxide (As_2O_3), a widely used TCM. Arsenic may be the oldest drug in the world, and it was widely used in the early twentieth century to treat tuberculosis and syphilis[2]. In the late 1990s Chen *et al.* found that arsenic trioxide constitutes an effective therapy for acute promyelocytic leukemia (APL)[3] and has a synergistic effect with all-*trans*-retinoic acid (**1**, **Fig. 1**) for the treatment of people with APL[4,5]. The abundance of herbs native to China has led to the isolation of numerous bioactive natural products. Two famous examples are artemisinin (**2**), a lead compound for the potent antimalaria drug artemether[6], and huperzine A (**3**), a compound shown to be effective against Alzheimer's disease[7]. The mechanisms of action of most natural products are still unclear, and therefore represent an important research area for chemical biologists.

The National Natural Science Foundation of China (NSFC), the major funding organization supporting basic research in China, has supported hundreds of research projects related to chemical biology over the last decade. Funded projects covered almost all aspects of chemical biology, and the resulting achievements in recent years have argued convincingly for continued support of chemical biology research (**Fig. 2**). In addition, because chemists, not biologists, have traditionally driven chemical biology research, it was felt that ties between the chemistry and biology communities needed to be further strengthened to advance the field in China.

To build on this record of success, the NSFC organized and financially supported a series of symposiums, for example the Xiangshan Science Conference and the Shuang Qing Forum, to foster communication between scientists working at the interface between chemistry and biology. More recently, bilateral workshops on chemical biology, such as the Sino-German Symposia on Chemical Biology for Young Scientists (2004, 2006) and the China-USA Early Career Workshop on Chemical Biology (2007), were held to discuss how to best fund and perform chemical biology research in China.

To encourage efforts to overcome multidisciplinary challenges facing natural scientists, NSFC launched the Major Research Plan (MRP) in 2002 to (i) encourage scientists from different disciplines to cooperate collectively on the basis of common research interests, (ii) promote interdisciplinary research, (iii) strengthen focused basic research and some areas of applied research and (iv) enhance and develop the creative potential of science and technology in China. With input from many experts, chemical biology was selected as a multidisciplinary research priority area by NSFC at the end of 2005, which resulted in the launch of a new MRP on chemical biology named "Investigations on Signal Transduction Processes Utilizing Small Chemical Probes." The call for proposals was made in January 2007, and by the end of September 2007, the first 47 proposals were funded from a total of 242 applications (**Fig. 3**). This commentary addresses the objectives and strategies of the research and funding policies of the MRP project in chemical biology. We hope that this MRP may serve as a model for other national-level funding initiatives in chemical biology.

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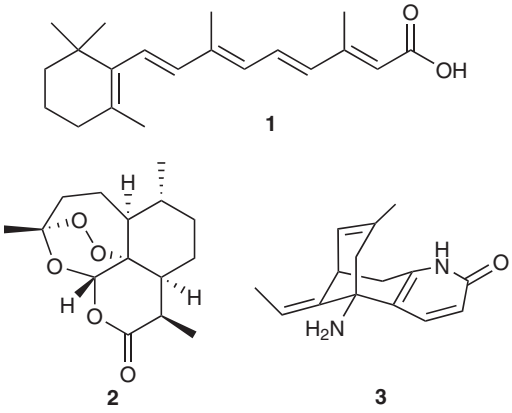

Figure 1 Chemical structures of three drugs discovered from natural and synthetic products by researchers in China.

Why signal transduction chemical biology?

Signal transduction refers to the transmission of signals from the outside to the inside of the cell, including very simple processes like signal propagation stimulated by binding of hormones and growth factors or by ion movements. These events cause alterations in cellular activity and changes in the program of gene expression (**Fig. 4**). Because signal transduction pathways represent the nexus through which nearly all biological information moves between and within cells and across organisms, manipulating these pathways is likely to be a powerful approach to effecting cellular responses.

Signal transduction is an outstanding system for investigation by chemical biology approaches. Chemical approaches, including synthetic and analytical methods, structure-function analysis and mechanistic investigations, are invaluable for identifying small molecules and tools to be used as probes in studying signal transduction networks and for providing lead compounds with potential therapeutic activity.

As a consequence, laboratories in academia as well as pharmaceutical and biotechnological industries are now emphasizing signal transduction. Numerous research groups have provided new insights into essential signal transduction processes induced by G protein–coupled receptors (GPCRs) and transforming growth factor-β (TGFβ) receptors, and into central signaling pathways involving Wnt and NFκB (refs. 8–20). In parallel, Chinese institutions such as the National Center for Drug Screening have established various high-throughput screening (HTS) and high-content screening (HCS) systems to target key proteins involved in disease-related signaling pathways, and have discovered numerous active compounds that target various signaling proteins (http://www.screen.org.cn,)[21,22]. These initiatives have increased collaboration between chemists and biologists in China who are working on signal transduction research and have produced promising results[15,16].

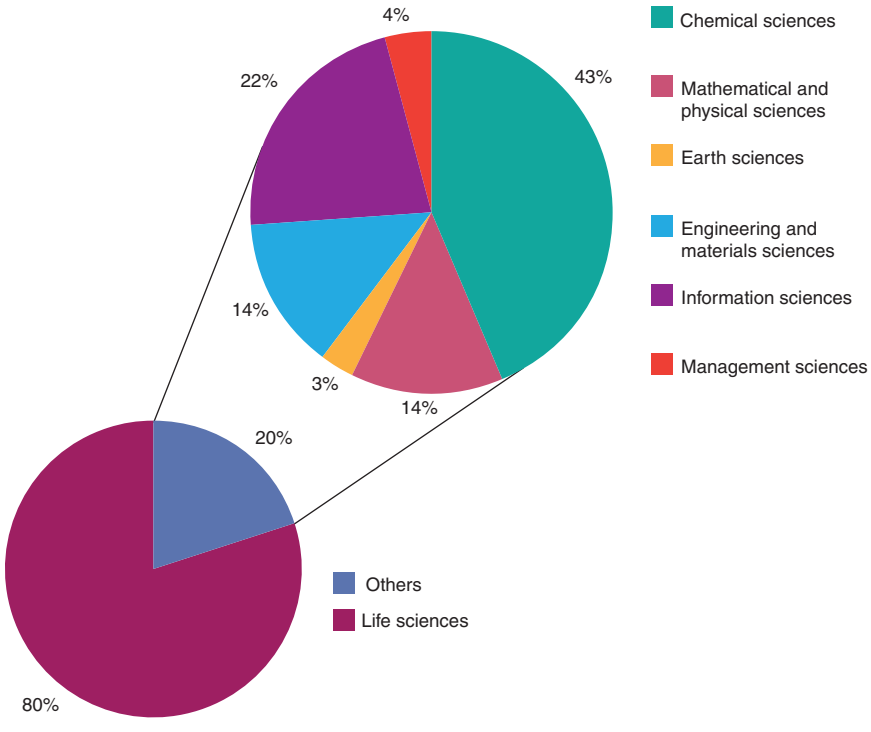

Figure 2 NSFC budget distribution for health sciences, 2004–2008. Total NSFC budget for health sciences over this period is 500 million RMB.

NSFC Major Research Plan on chemical biology

The major objectives of the MRP are to bridge the traditional disciplines of chemistry and biology and to aid the development of biomedicine. To achieve these goals, the MRP includes initiatives to develop new methods and technologies, apply small molecules as probes of important molecular events in signal transduction processes, uncover the mechanisms regulating cell signaling and provide clues for the discovery of new biomarkers, new drug leads and targets. In a broader sense, the initiative seeks to promote a broader chemical biology infrastructure in China by promoting seamless collaboration between chemistry and biology laboratories and by preparing multidisciplinary research teams for future research at this interface. The research portfolio of the MRP includes the following specific themes.

Generation of chemical probes for studying signal transduction. This theme addresses the need to advance our understanding of the daunting complexity of signal transduction processes and to produce small-molecule compounds as drug leads. Although China has established a solid foundation for chemical synthesis and natural products chemistry, these strengths have not translated into enhanced chemical probe discovery owing to the traditional lack of collaboration between chemistry and biology departments in China. The MRP will develop new methods and tech-

nologies to obtain active probes. At the same time, it will establish a public library of chemical probes that any researcher can access for his or her own academic work. The four sections that will be funded in this theme include discovering synthetic probes that induce physiological changes in cells, discovering chemical probes from medicinal herbs by isolation and structural modification, designing labeling probes for signaling pathway investigation and public library construction. To achieve these aims, the MRP will take full advantage of the existing facilities dispersed in the universities and research institutions in China, such as the screening systems and the compound library of the National Center for Drug Screening.

Development of new techniques and methods for detecting the information of signaling processes. Signaling processes are informational exchanges between the exterior and interior of cells that are mediated by a series of molecular binding events, including protein-protein, protein–nucleic acid and macromolecule–small-molecule ligand interactions. These intermolecular contacts form complex biological networks, and understanding these networks is a pivotal step towards elucidating the diverse biological actions of signal transduction processes. Projects funded under this theme will emphasize new techniques for analyzing information flow encoded in biomolecular networks, including technologies for detecting molecular interactions involved in signaling within cells, new algorithms for integrating the information of biological pathways and networks and systems for modeling these pathways and networks.

Signaling mechanisms of cellular functions based on chemical small molecules. Cells use a large number of distinct signaling pathways to regulate physiological and pathological activities. These signaling pathways involve transferring the information generated by external stimuli at the cell surface to intracellular effector systems such as nuclei. The informational processing of these signaling pathways is usually based on protein-protein interactions, which are reversible and transient. Small molecules are useful tools for the analysis of signaling mechanisms because they act on protein targets quickly and can be applied in a reversible manner. This theme, which focuses on identifying and applying these small molecules to signaling pathways, is the core of the MRP. The major topics to be funded are as follows: (i) establishing screening systems to identify specific small chemical probes for important signaling pathways; (ii) elucidating the structure, function and mechanisms of important signaling pathways using chemical probes, including the

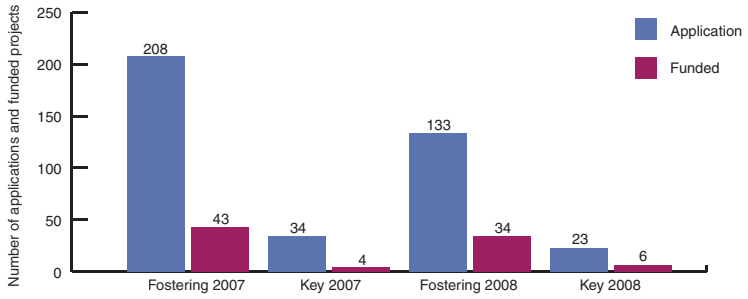

Figure 3 MRP funding statistics, 2007–2008.

interaction of signaling molecules and cross-talk between signaling networks, and (iii) mapping the mechanisms of signaling pathways to key biological processes, including the regulation of cell proliferation, apoptosis, differentiation and migration.

Biomarker, target and lead discovery based on signal transduction processes. This theme aims to discover biomarkers, drug targets and leads based on results from the other themes. One central section of this theme is to further validate the biological functions of the discovered networks and pathways related to signal transductions and to construct stable screening models for biomarker and lead discovery. In addition, research related to this theme may also provide effective probes to facilitate the comprehensive study of biological pathways and networks. Researchers will also focus on the development of new technologies for compound screening, lead discovery and optimization targeting the functionally verified proteins involved in special signaling pathways.

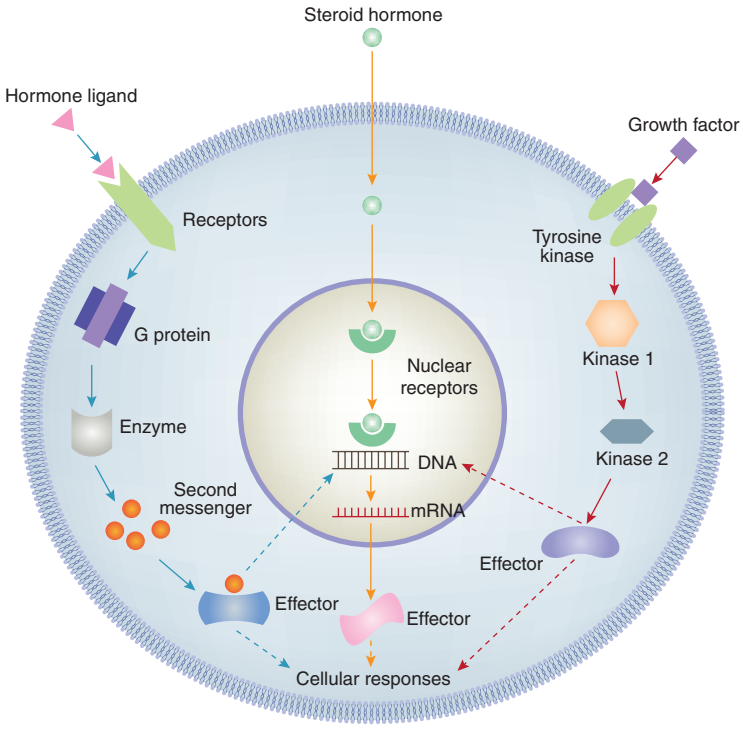

Figure 4 Major types of signaling transductions in cells. Three typical signaling pathways are used in eukaryotic cells: (i) signaling based on first and second messengers, in which first messengers such as hormones bind to a membrane receptor (for example, a GPCR) and then induce second messenger signals (for example, cAMP) that activate the downstream cellular responses; (ii) signaling based on steroid hormones, in which these lipophilic hormones can penetrate the nucleus and regulate gene expression by DNA binding; (iii) signaling based on growth factors, in which growth factors (for example, EGF and PDGF) activate tyrosine kinases at the plasma membrane and produce a downstream kinase cascade.

Box 1 Chemical biology graduate training programs in China

Universities
Peking University
Wuhan University
Nankai University
Sichuan University
Fudan University
Southwest University
Huazhong Normal University
Beijing Normal University
East China University of Science and Technology
Capital Medical University
Tsinghua University
Zhejiang University
Hunan University
Lanzhou University
Nanjing University
Xiamen University

Research institutes
Shanghai Institutes for Biological Sciences, CAS
Shanghai Institute of Organic Chemistry, CAS
Institute of Chemistry, CAS
Kunming Institute of Botany, CAS
Fujian Institute of Research on the Structure of Matter, CAS
Lanzhou Institute of Chemical Physics, CAS

Funding strategy and guidelines

Over the last ten years, NSFC has been the major driving force in promoting chemical biology research in China, and it established a chemical biology division within the Department of Chemical Sciences in 2002. At the same time, some universities and research institutes established chemical biology departments, research centers or research laboratories, most of which have graduate training programs that will educate the next generation of chemical biologists (**Box 1**). The budget for chemical biology research in general has been increased by about 20% annually over the last five fiscal years.

Because signal transduction is a vast research area, an MRP over an extended period that is supported with relatively large sums of funding (150 million RMB) is necessary to make major advances. In this regard, the MRP has divided the funded projects into two categories. The first group, called 'key projects', are granted to applications with sound scientific foundations and preliminary data that describe clear key aims requiring in-depth and systematic studies. Key projects receive, on average, 2.5 million RMB per project for four years. The second group, called 'fostering projects', are granted to creative applications that will require exploratory study and development and are typically funded at a level of approximately 500,000 RMB per project over three years. The combination of research teams in chemistry and in biological and related disciplines is valued and must be reflected in the application.

The MRP is administered by a seven-member team of scientists with expertise ranging from chemistry (synthetic, analytical and medicinal) and cell biology to biochemistry. This panel defines the objectives and guidelines for the program and identifies specific research priorities related to the MRP and monitors the progress of funded projects. A 17-member panel consisting of experts from all disciplines related to the MRP has been enlisted to select the proposals to be funded. One third of the panelists are from institutions in the United States and Canada.

Because chemical biology is expanding around the globe, NSFC attaches great importance to international cooperation and exchange in the development of the field. The guide to programs of the MRP has stressed that excellent Chinese scientists are encouraged to collaborate with scientists in other countries to enhance chemical biology research in China. NSFC has also incorporated the Major International Joint Research Project (MJRP) into the MRP. Over the last five years, NSFC has supported more than five MJRPs (100 million RMB each) on chemical biology associated with foreign research institutes, including Harvard University, the Weizmann Institute of Science, École Normale Supérieure de Paris and Hamburg University. To further these efforts, additional funds to support international joint research projects are likely to be allocated in the future.

Chemical biology in China

The current MRP aims to develop new methods and technologies using small molecules as probes to understand and interfere with signal transduction processes in living systems. We hope these efforts will reveal the controlling factors of signal transduction processes by taking full advantage of the benefits of interdisciplinary research. In addition, an emphasis on signal transduction chemical biology lays the foundation for the identification of new drug targets, pharmaceuticals and biomarkers for the benefit of human health. Finally, the integration across chemical and biological sciences provides an important training ground for the next generation of chemical biologists, who will lead new initiatives at the interface of chemistry and biology.

Recent achievements in stem cell research have opened several avenues of research at this interface. Like other areas of the biological sciences, chemistry will be a major player in understanding and advancing stem cell biology[23,24]. Therefore, it is likely that future chemical biology research funding initiatives in China will include studies at the intersection of stem cell biology and chemistry. In particular, to build on efforts for public library construction, the MRP will support studies focused on identifying small molecules that may regulate stem cell differentiation or promote induced pluripotent stem cell formation.

Yiyu Chen, the president of NSFC, stated at its 20th anniversary celebration that "natural science is developing in the directions of both differentiation and integration"[25]. New disciplines such as chemical biology are being created at the same time that the borders of traditional disciplines are being blurred. The NSFC is deeply committed to interdisciplinary research in general, and in particular to chemical biology research, which will help the NSFC to achieve its broader goals of enhancing the capability of Chinese scientists and fostering original research and innovation. We hope that these funding initiatives in signal transduction will further encourage innovative chemical biology research in China.

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