

Chemical Biology Research in India

B. Ruthrotha Selvi,[†] Siddhartha Roy,[‡] and Tapas K Kundu^{†,*}

[†]Transcription and Disease Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore 560 064, India

[‡]Division of Structural Biology and Bioinformatics, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata 700 032, India

Chemical biology, as the terminology suggests, is the intertwining of chemistry and biology. However, the exact definition of chemical biology has been constantly debated among the researchers working at the interface of chemistry and biology. One of the major differences between the closely related fields of biochemistry and chemical biology is that the former is more relevant to the actual physiological scenario, whereas the latter has a synthetic feel to it. Thus, exploring biology with the aid of chemical tools can be considered to be the main philosophy of chemical biology. The science of chemical biology in the present form is only about 2 decades old, and hence the successes and failures in this area are more in the limelight than many other fields of science. All over the world, there are active initiatives to merge this new area of research into the scientific mainstream. Universities such as MIT, Harvard, RIKEN, and McGill have full-fledged departments dedicated to chemical biology. Perhaps the earliest research institute in the world dedicated to chemical biology was the CSIR-Indian Institute of Chemical Biology in Kolkata, India. The 75-year-old research institute was reoriented and renamed in 1982 to its present form to explore the chemistry of life—with chemical and biochemical tools. In India, this exciting area of research has spread beyond this institute, and in this In Focus article we shall highlight the status of chemical biology research in India with respect to its past, present, and future. Although work at the interface of chemistry and biology is widespread in India, we will largely focus on institutions that use chemical tools to explore biology.

The Indian system of research and education is presently represented by three tiers of organizations: Universities, which include the Central, State, and Deemed Universities; research-based organizations; and institutions that, apart from carrying out research activities, are also academic centers. The famous Indian Institute of Science in Bangalore is a century-old institution that falls under the latter category. It has been and still continues to be one of the main research hubs of the nation. The research in these universities and institutes is largely supported by financial assistance from public funding agencies, which include the Council of Scientific and Industrial Research (CSIR), Department of Atomic Energy (DAE), Department of Biotechnology (DBT), Department of Science and Technology (DST), Indian Council of Agricultural Research (ICAR), and the Indian Council of Medical Research (ICMR) and Ministry of Human Resource Development (MHRD). Although the Indian efforts are gradually catching up with chemical biology based research initiatives internationally, the nation's tryst with this area of research is several years old.

In comparison with the international research, there are very few research initiatives in the country that involve chemical biology exclusively. However, the scientifically overlapping fields of peptide biology research, drug development, etc. have been shown to have elements of chemical biology research. Hence, we shall highlight the research activities in this country based on the areas of research that are both pure chemical biology based as well as those that have elements of chemical biology in them. Due to historical reasons, most of the research in chemical biology is confined to the research institutes, which receive the bulk of research funding. Hence, the article will focus mostly on the public funded research institutes.

■ AREAS OF RESEARCH

Despite having a very early presence in the field of chemical biology, the spread of this area is relatively limited in the country compared to established fields such as physics, chemistry, or biology. However, those institutions that do have this field of research as one of the major thrust areas have been performing well in the past decade, as represented in Figure 1. The following sections shall provide a brief overview of the main areas of chemical biology within which there are significant research activities being undertaken by Indian researchers.

Enzyme/Protein–Small Molecule Interactions. Although the field of enzymology is strictly a part of biochemistry, the studies involving interrogation of specific cellular properties with targeted small molecules against proteins or enzymes gets classified into the area of chemical genetics/biology. This happens to be one of the major subdivisions of chemical biology in which Indian researchers are actively involved. Starting from discovering different inhibitors for important enzymes, which are from both the natural sources as well as molecular modeling based organic synthesis, the effort extends to studying the effect of these inhibitors on cellular signaling and cellular physiology. Recently, there has also been increased interest toward exploring the scaffolds of different inhibitors of proteins and then thereby designing the best possible inhibitors or activators for these enzymes. Thus, this area by itself involves a combination of bioinformatic, synthetic, and cell biological based approaches. For example, there are certain enzymes that are characteristically involved in specific modifications, and simultaneously these modifications have also been identified as essential for certain

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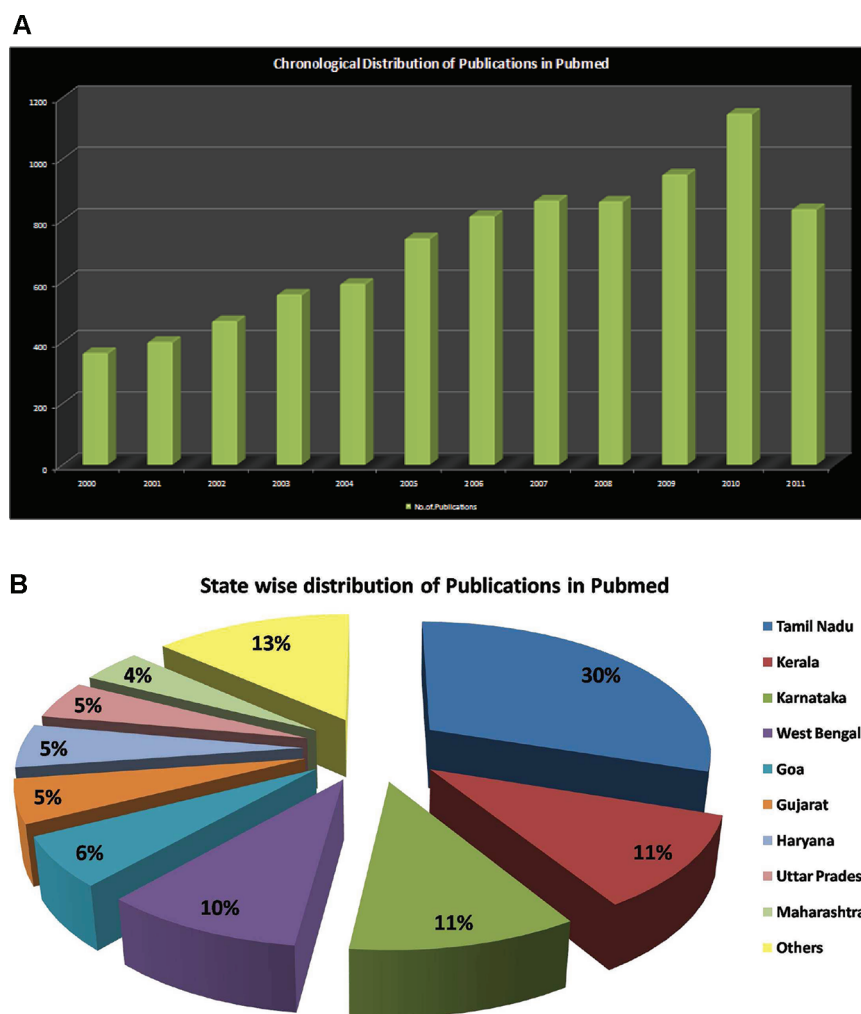


Figure 1. (A) Chronological distribution of publications related to the area of chemical biology in India. Publications pertaining to the area of chemical biology were retrieved from Pubmed in the subareas of peptide biology, nucleotide biology, synthetic biology, nanoparticle mediated drug delivery, antibiotic research, small molecules and drug delivery. The publications were considered from the year 2000 to the year 2011. A general increase in the trend in the area of chemical biology research is observed. (B) Statewise distribution of chemical biology based research in India: The publication lists from panel A were categorized based on the state from which the work was carried out and this has been represented in this pie chart.

physiological processes. Specific inhibitors for each of these enzymes may help in understanding any tissue-specific or event-specific processes. [At JNCASR, Bangalore, active research in this aspect of chemical biology is being pursued. One of the inhibitors identified from a natural source was subjected to chemical modifications to obtain a p300 acetyltransferase specific inhibitor, which induced a global alteration in the gene expression profile. It is important to note here that p300 is a transcriptional coactivator and its specific inhibition also led to an upregulation of expression of a certain class of genes.¹¹ Thus, a small molecule inhibitor could greatly help in identifying the physiological role of the enzyme.] This area of research is a multidisciplinary initiative, and it is mostly prevalent in the institutions mentioned in Table 1. Another important aspect of research that falls in this class of research area is anticancer compound characterization with respect to its effects on signaling pathways, which is a major component of research being pursued in almost all of the institutions and organizations involved directly or indirectly with chemical biology research in the country.

Peptide Biology. The research activities pertaining to the area of peptide biology involve both the physiologically relevant peptides as well as the biophysical characterizations of the peptide–protein interactions. [In IISC, Bangalore, one of the pioneer research team in the area of peptide biology have identified a peptide from a poisonous marine snail with modulatory effects on the sodium channel.⁴] The information obtained from these small peptide interactions are then used in designing important molecules that can perturb these interactions and thus be relevant in a biomedical scenario. For example, the interaction surface of the tumor suppressor p53 has been mapped by several researchers with respect to its different interacting partners including mdm2. The information gained from these studies has then been used to design small molecules as well as small peptides capable of disrupting the interactions. [At CSIR-IICB, Kolkata, researchers have been working on the interactions of p53 with other proteins to design interaction-disrupting peptides and as a proof of concept have recently shown that indeed this is possible for p53 and positive cofactor, PC4, wherein initial NMR-based studies led to the identification

Table 1. Institutes/Universities Where Chemical Biology Based Research Is Being Pursued in India and Research Areas Considered when Compiling the Table^a

institute/department	research area
CDFD: Centre for DNA Fingerprinting and Diagnostics (Cell Signaling Laboratory)	inositol pyrophosphates in physiology and metabolism, molecular targets of anticancer agents
IISc: Indian Institute of Science (Biochemistry dept, Chemistry dept, Molecular Reproduction and Developmental Genetics, Molecular Biophysics Unit)	secondary metabolite characterizations, pathway modulation to enhance secondary metabolites, ³ cyclic nucleotide mediated signaling events, gene regulation by hormones and their modulators, ¹⁰ natural peptide products and their functions, ^{4,14} molecular mechanism of DNA–drug interaction
IICB: Indian Institute of Chemical Biology	therapeutic agents targeted against DNA topoisomerases, molecular targets of chlorogenic acid, ⁶ peptidomimetics against protein–protein interactions, ^{8,23} glycosylation of biomolecules in pathophysiological states
IIT: Indian Institute of Technology	microtubule dynamics modulators, anticancer compounds and signaling pathways
IISER: Indian Institute of Science Education and Research	anticancer compounds and signaling pathways
CSIR-IGIB: Institute of Genomics and Integrative Biology	chemical biology for pathway identification, ¹⁵ zebrafish chemical genetics, novel chemistry for biochip development, pharmacogenomic investigations of antidepressant, antipsychotic drugs to identify signaling events, peptidomimetics as antihypertensive drugs ¹³ host–pathogen interactions to identify novel therapeutic targets
ICGEB: International Centre for Genetic and Engineering and Genome Biology	
JNCASR: Jawaharlal Nehru Centre For Advanced Scientific Research (Molecular Biology and Genetics Unit, Chemistry and Physics of Materials Unit, New Chemistry Unit)	small molecule modulators of chromatin-modifying enzymes and their role in elucidating aspects of gene expression, ^{11,16,19} targeted delivery mechanisms, modulators of parasite metabolic pathways, ⁷ biosensor applications ²⁴
JNU: Jawaharlal Nehru University (School of LifeSciences, Special Centre for Molecular Medicine)	iron homeostasis, neuropeptides characterization, biochemical and molecular characterization of events associated with green tea administration, mechanism based nontoxic anticancer agent development, protein glycosylation in pathophysiology, effect of drugs and hormones in the animal brain ²¹
NBRC: National Brain Research Centre	role of natural toxins or environmental pollutants in neuroinflammation, therapeutic strategies against neural inflammation, ¹⁸ new intervention methods against signal transduction in glioma, epigenetic changes during memory formation ²²
NII: National Institute of Immunology	therapeutic implications of folded proteins and their alterations, ²⁰ receptor-mediated endocytosis as a therapeutic drug delivery system, ¹ chemistry and biology of the GPI-cell surface molecules, ⁹ chemoenzymatic studies toward protein engineering ¹²
SINP: Saha Institute of Nuclear Physics	DNA-anti cancer drug interactions, ² study of effect of natural products in biological systems
TIFR: Tata Institute of Fundamental Research/ NCBS: National Centre for Biological Sciences	functional characterization of enzymes, metabolism by biophysical methods, molecular motors, nucleotide nanomachines ¹⁷
University of Hyderabad (School of Chemistry), CSIR-CCMB: Centre for Cellular and Molecular Biology, CSIR-IICT: Indian Institute of Chemical Technology	development of inhibitors for biological functions, peptide biology ⁵

^aThis table is not an exhaustive list of all research organizations in the country. It is representative of the few places where chemical biology based research is being done.

of specific interacting residues that were later used for synthesizing peptides capable of disrupting their functional cooperation in the cellular system.²³] The final aim of this is to utilize these against diseases such as cancer. Also, since neurodegenerative disorders such as Alzheimer's disease are also mainly caused by the aggregation of polypeptides, such strategies of disrupting the peptide interactions are also being tested. The actual contributions toward the peptide biology based research in the country are highlighted in Table 1.

Drug Delivery Systems. One of the main aspects of the chemical biology research includes utilizing chemical synthesis

both to probe biological functions as well as to utilize it as therapeutic strategies. Apart from developing molecules that can target important enzymes or proteins or disrupt vital interactions, an equally important feature is to design efficient drug delivery mechanisms. It is here that the field of biotechnology and chemical biology overlap significantly. Identifying specific drug delivery mechanisms such as by using peptides for facilitating cell permeability or efficient action [at IGIB in Delhi researchers have been testing the peptides as improved analgesics¹³] and nanomaterial-based specific targeting of the active agents are the thrust areas that fall under the category of drug delivery systems.

[At NBRC based in Manesar, an active area of research is to investigate such approaches for therapeutic interventions against neuroinflammatory disorders.¹⁸] The actual research being carried out is detailed in Table 1.

Antibiotic Research Based on Novel Pathways. The pure chemical biology aspects are those that are highlighted above. The following areas have an applied component of chemical biology research. Here again, the facet of structure-based compound design is involved, which primarily needs information from genetic studies to identify potential therapeutic targets as well as any known chemical agent that can perturb these aforementioned targets. This area of research is an actively worked upon field in the country. [At CSIR-IGIB, Delhi, researchers have been actively involved in the elucidation of pathways in pathogenic organisms such as *Mycobacterium tuberculosis*,¹⁵ which are being characterized for their novelty so as to serve as potential therapeutic targets in the long run.] This initiative is also supported by the vast natural resources that exist in the country as well as the backing of active chemists involved in the synthesis and modification of the existing scaffolds as depicted in Table 1. This is one of the major thrust research areas in the universities in the country.

Synthetic Biology. The area of synthetic biology is a new area of research that has gained attention even in the international scenario very recently. The area represents where chemical biology and synthetic biology overlap, including the engineering of complex metabolic pathways in bacteria or yeast. The major focus has been on antibiotic pathways or certain metabolic pathways both for commercial exploitation as well as for gaining knowledge. The Indian Institute of Technology and several universities in the country are pursuing research pertaining to this category. Council of Scientific and Industrial Research has taken a major initiative in this regard and initiated a major program on metabolic engineering of pathways of some Indian plants. Other efforts in this field are represented in Table 1.

DNA, Nucleotide Structures. The understanding with respect to the organization of DNA has also been considered as a contribution of chemical biology. There are presently several young researchers in the country who have turned their attention toward exploring the organizational aspects associated with chromatin and DNA, as well as toward understanding the intricate connections that these organizational aspects have with the actual functioning of the system. While presently the scientific community around the world has been concentrating on introducing mutant histones in the chromatin and studying their alterations in the structure as well as the function, the Indian scientific community has also started research in these areas of introducing unusual DNA structures and studying their effects. [At NCBS: National Centre for Biological Sciences, Bangalore, one of the research group is presently testing DNA based nanomachines for various applications.¹⁷] Also elaborate studies are presently being carried out not just in the country but also internationally to elucidate DNA binding molecules and their effect on the overall chromatin. [Such research pursuits are done by groups in SINP, Kolkata.^{2,16}] Such initiatives are presently helping in understanding the mechanistic details of the different anticancer compounds. These efforts have been highlighted in Table 1.

■ FUNDING FOR CHEMICAL BIOLOGY RESEARCH IN INDIA

As indicated above, the major funding for research initiatives in the country is supported by the funding organizations, of

which most of the chemical biology based research is supported by the Council of Scientific and Industrial Research (CSIR), the Department of Science and Technology (DST), the Department of Biotechnology (DBT) and partly by the Department of Atomic Energy (DAE). To date, in India there are no graduate programs providing a degree in chemical biology. The main contribution toward the field of chemical biology in terms of the work force is from Ph.D. students and postdoctoral researchers as well as the research assistants who work with the scientists involved in the chemical biology research area. There is hope that soon there will be a larger work force due to the recent initiatives by the government, which is discussed further below.

■ INTERNATIONAL STATUS (A BRIEF OVERVIEW)

The international scientific community has awakened to the need for chemical biology research much earlier and hence their efforts have also been greater in comparison to India's contribution. MIT and Harvard University have come up with a unique chemical biology program, which looks at small molecules in context of biological systems and encompasses both physiological and pathophysiological states. The forerunner in this area of research, The Scripps Research Institute, started in 1996 an entire center, The Skaggs Institute for Chemical Biology, which has been working extensively in the area of chemical biology research since its inception. The Rockefeller University also has a dedicated group working in chemical biology, as does the Johns Hopkins Medical Institute. Several universities such as the Max Planck and McGill Universities have now started graduate programs in the area of chemical biology to train young researchers in the field from an early time point. Hopefully, the new initiatives by the Indian government would also see such early training prospects for the young Indian researchers too.

■ FUTURE OF CHEMICAL BIOLOGY RESEARCH IN INDIA

The government of India has recently identified areas of research to be focused on in the coming decade, and one such identified area is chemical biology. The Department of Biotechnology (DBT) has initiated a UNESCO-supported initiative for research areas under which chemical biology is also included. Apart from that there is increasing awareness among the young researchers in the country regarding the potential of chemical biology based research. This is truly reflected in the newly opened IISERs in the country that have dedicated laboratories pursuing research in the area of chemical biology. The premier research institute of the nation, IISc, has also recently launched a chemical biology program for graduates. One of the major aims of CSIR-IICB is to isolate novel molecules, particularly from indigenous natural resources, and explore the effects on living organisms, in both natural and pathophysiological states. This effort is going to be expanded in the next few years, including a systems biology approach to study the effect of natural molecules on living organisms. Presently at JNCASR, the researchers have been adopting the small molecule approach to understand the role of the chromatin modifying enzymes in the stem cell differentiation process.

The few aspects that might play a role in deciding the future of chemical biology research in India include a more interdisciplinary collaboration especially between chemists and biologists. Some of the unconventional chemical biology areas such as metals in physiology and medicine need to be explored. Understanding of

stem cell biology and its further application in regenerative medicine could also be included within the circumference of chemical biology. Nanomaterials and chemical sensors need to be utilized more in the context of biological systems. Finally, the Indian traditional medicinal system (Ayurvedic medicine system) and its potential to be linked with chemical biology need to be further explored.

AUTHOR INFORMATION

Corresponding Author

*E-mail: tapas@jncasr.ac.in.

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