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International Symposium on Challenges in Chemical Biology: Toward the Formation of Chemical Biology Society of India

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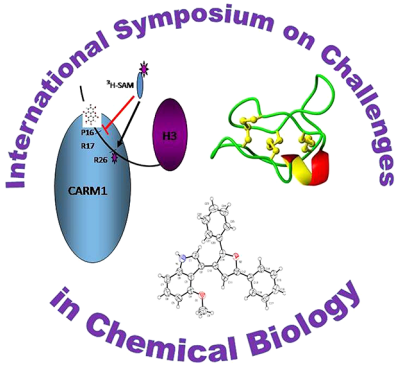
Research on understanding biological phenomena using chemical tools, known as chemical biology today, has a long history in India. Even before the term "chemical biology" was popularly coined for this approach, the Indian Institute of Chemical Biology was established by Prof. B. K. Bachhawat in 1982 by reorientation of an already established research institute. Since then, with the advancement of our understanding of biology, especially in the post-genomic era, it is becoming clear that the use of chemical tools to study complex biological networks will be an essential component of modern chemical and biological research. In the backdrop of escalating advances in chemical biology, the Indian chemical biology community was gearing up to assemble and discuss the status of chemical biology research in the country, when a boost came in the form of an offer from *ACS Chemical Biology* to review the status of chemical biology research in India.[1] Soon after the article was published, enormous feedback was received. Based on these comments, it was realized that a platform should be created to bring Indian scientists from different disciplines together. An international meeting was thus planned to initiate this activity. In this context, the "International Symposium on Challenges in Chemical Biology (ISCCB)" was held at the Indian Institute of Chemical Biology, Kolkata during January 27–29, 2013.



PEPTIDES, PEPTIDOMICS, AND CYCLOTIDES

The origin of modern chemical biology probably lies in using small molecules to study biology from an integrative point of view. However, recent advances in peptide therapeutics have raised the hope that peptides can be used very effectively as a tool for studying biology. The meeting started with an introductory lecture by P. Balaram, a well-known chemical biologist and peptide chemist from the Indian Institute of Science, Bangalore. He elegantly introduced the diversity of peptides using unnatural amino acids as a model to understand protein folding. His presentation on the characterization of these peptides by both NMR and X-ray crystallography underlined the importance of unnatural amino acid substituted peptides for chemical and structural biology. This lecture was followed by the presentation of Vadim Tikhanovich Ivanov from the Russian Academy of Sciences on peptidomics. Apart from importance of peptidomics of different animal and plant sources, his work mainly focused on the development of molecular diagnostics based on the detection of peptide markers in clinical samples.[2] His work on the use of liquor peptide in the understanding of Guillain–Barre syndrome was interesting. The next presentation continued in the area of peptide biology, but this time it was on cyclotides (cyclic peptides), by David J. Craik from the Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia. The broad introduction he provided regarding the 300 different cyclic peptides from diverse plant sources was very useful for scientists outside the field of peptide research. His presentation indicated that these cyclotides can really fill the gap between small molecules and biologicals as far as therapeutics are concerned[3] and are applicable for a range of diseases, including cancer (antiangiogenics), foot and mouth disease, obesity (melanocortin receptor agonist), *etc.* The next talk of the day presented by Paramjit Arora from New York University was about targeting protein–protein interactions by α-helix mimetics. His novel approach involved the use of hydrogen bond surrogates as helix stabilizers.[4] He showed that such stabilized helices can block important therapeutic pathways, such as the signaling pathway mediated by *Ras*.[5] In the same area, on the second day of the meeting, Krishna N. Ganesh of IISER, Pune, India, gave a talk on the importance of 4-hydroxy proline (Hyp) in collagen. His group has examined the crucial structural role of Hyp by replacing the hydroxyl group with an amino group to obtain 4(R/S)-amino proline collagens, which exhibited superior triplexing properties. The 4(R/S)-guanidinoproline collagen peptide was shown to be a good DNA transfecting agent. Their work on modified collagen peptides has therapeutic implications such as tissue engineering and ligament therapy, by designing new collagen-based materials. Rituparna Sinha Roy from IISER, Kolkata, presented her work on peptide- and protein-based biomolecules with tailored functionality and structure to develop next-generation therapeutics. [6]

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SYNTHETIC TRANSCRIPTION FACTORS

In this meeting, understanding of transcription regulation by artificial transcription factors or synthetic gene switches was discussed at length. The lecture presented by Aseem Z. Ansari [University of Wisconsin; after his brief advertisement of Khorana and Bose fellowships (http://www.biochem.wisc.edu/faculty/ansari/khorana_program/)] was enlightening. The identification of DNA binding cognate sites by employing synthetic molecules as described by him could be highly useful in mapping genome-wide binding landscapes (Genomescapes).[7] His data really justifies his statement "The resulting insights promise to accelerate the creation of precision-tailored nucleic acid targeted therapeutics and uncover principles that govern sequence specificity of DNA and RNA binding molecules". Another talk in this area was presented by Siddhartha Roy (CSIR-IICB), who described the use of bivalent α-aminoisobutyric acid substituted peptides as transcription factor mimics.[8] The synthetic transcription factor repressed gene expression specifically, albeit less efficiently than the natural transcription factor inside a bacterium.[9] He also described the attachment of the same transcription factor to an activating peptide leading to targeted gene activation. The penultimate talk of the meeting, by Chinmay Majmudar from Anna Mapp's group at University of Michigan, was also in a similar line of thought. He presented their recent work on targeting the GACKIX domain of the global transcriptional coactivator CBP/p300 using small molecules to probe the cellular importance of transcriptional activation domain−GACKIX interactions.[10] Impressively, one of the compounds, sekikaic acid, identified by high-throughput screening of a large number of natural products, was highly selective for GACKIX over other similar motifs. Another set of compounds identified using disulfide tethering enabled determination of the first crystal structure of the GACKIX domain and provided an additional level of site-specific inhibitors.[11]

TARGETING miRNA

Our understanding of different biological phenomena has received a new dimension through the window of noncoding RNA-mediated regulation. It is quite evident now that one of the key regulators of gene expression and genome organization are the underlying small noncoding RNAs (miRNAs). Intervention of this miRNA function by using different chemical probes not only promises more understanding in these biological functions but also possesses therapeutic promise. The work presented by Kazuhiko Nakatni (Osaka University) on miRNA and riboswitches dealt with the discovery of several small molecules that bind to different species of noncoding RNA and can switch the expression of downstream genes On/Off. Among these, naphthyridine carbamide dimer (NCD)/NCT6 seemed to be highly promising.[12] Following this excellent talk, Souvik Maiti from CSIR-Institute of Genomics and Integrative Biology, New Delhi presented his recent work on novel ways to silence microRNA. In the beginning of his talk, he presented a study on antagomirzymes, nucleic acid based enzymes to silence miroRNAs.[13] Then he presented the data on the abilities of small molecules in antagonism of miRNA.[14] Further he presented a high-throughput in vitro screening assay to identify small molecule inhibitors of miRNA maturation and as proof of principle found five potential inhibitors of model oncomir miR-27a.[15]

CHEMICAL BIOLOGY AND EPIGENETICS

Epigenetics has occupied the center stage in present day research and in the understanding of biological phenomena. A chemical biology approach to epigenetics is essential to gain precise insight into several physiological and pathophysiological events. After briefly explaining the concept of epigenetics, Tapas K. Kundu (JNCASR, Bangalore) presented his group's work on a specific small molecule inhibitor of arginine methyltransferase, CARM1, and its use as a potential anticancer therapeutic as well as to elucidate the role of the arginine methyltransferase in differentiation.[16] He also described some recent discovery on carbon nanosphere (CSP) conjugated small molecule mediated activation of CBP/p300 acetyltransferase activity in mice brain and its possible implications in spatial and temporal memory formation.[17] G. V. Shivashankar (NUS, Singapore) described their ongoing work that provides links between epigenetics, nuclear mechanics, chromosome organization, and genome regulation for which they employ multidisciplinary approaches.[18] Although Hiroshi Sugiyama's (Kyoto University) presentation could be mentioned in two sections of this report, namely, epigenetics and nanostructures,[19] we prefer to mention it in this section. He elegantly presented his work on the epigenetic regulation of gene expression using designed molecules and elucidation of this mechanism using single molecule imaging.[20]

DNA TOPOLOGY AND NANOSTRUCTURES

Shantanu Bhattacharya from the Indian Institute of Science (IISc) described efforts in his laboratory in strategizing the formation and stabilization of intra- and intermolecular G-quadruplexes by designed synthetic molecules, which favors the association of such molecules to the face or grooves of the G-quartet as opposed to the overwhelming population of Watson−Crick DNA duplexes.[21] He also explained the importance of these studies in the development of anticancer drugs.[22] V. Nagaraja from the same institute (IISc) described their effort to target DNA gyrase and Topoisomerase I of mycobacteria. He also presented their work on gyrase interacting proteins that inhibit the enzyme *in vitro* and specific inhibitors of DNA topoisomerase I and nucleoid associated protein (e.g., HU) from *Mycobacterium tuberculosis*. Yamuna Krishnan, of the National Centre for Biological Sciences, TIFR, Bangalore described two DNA-based molecular devices, a DNA polyhedron and a synthetic nano-pH sensor created by her group, exploiting the ability of DNA to self-assemble by specific base pairing, which are being used to interrogate living systems.[23]

CHEMICAL GENOMICS AND DISCOVERY OF NEW DRUGS

Dulal Panda from the Indian Institute of Technology Bombay explained the role of microtubule dynamics in many cellular functions including chromosome segregation during mitosis. He discussed their present understanding of the development of resistance to microtubule-targeted anticancer drugs and the role of microtubule plus end binding proteins in cell motility. His work emphasized the importance of tubulin acetylation in cell migration.[24,25] Uday Bandyopadhyay and his group (from CSIR-IICB, Kolkata) have designed a small molecule tryptamine−gallic acid hybrid (SEGA), which enters the mitochondria and prevents nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy. Mechanistically, SEGA offers

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gastroprotective effect by scavenging mitochondrial superoxide anion and intramitochondrial free iron released by NSAIDs as a result of mitochondrial oxidative stress.[26] The work described by Rajesh Gokhale, from IGIB, New Delhi was mainly focused on understanding biology of unusual metabolites, complex lipids and melanins, both of which have significance in distinct pathological diseases, tuberculosis and vitiligo. He also discussed how temporal expression of lipid remodeling may be important in providing selective advantage to the bacteria. Ettore Appella, of the National Cancer Institute, USA, presented recent work characterizing the homologous metal-binding sites of PP2C-alpha phosphatase (PPM1A), a known tumor suppressor, and Wip1 phosphatase (PPM1D), a negative regulator of tumor suppressors. The findings further elucidate the catalytic mechanism of these enzymes and present new possibilities for the development of specific inhibitors.[27,28] Thomas Surrey, from London Research Institute, provided mechanistic details of the dynamic behavior of the microtubule cytoskeleton, plus-end tracking proteins, and the establishment of antiparallel microtubule overlaps in the spindle during cell division using *in vitro* reconstitution assays and surface chemistry.[29] Tarun Kapoor from the Rockefeller University gave an impressive talk on identifying and validating chemical inhibitors that could be developed into new drugs. In his presentation, he described pyrimidine and indole analogues as potent kinase-5 inhibitors. In the same context, he presented their recent discovery of the first selective inhibitor of dynein, a microtubule-based motor protein.[30] He also discussed another elegant work from the group, in the area of mechanism of drug action in human cells, in which they have isolated multiple-drug-resistant clones and analyzed the transcriptome to find mutations in each clone, using the cytotoxic anticancer drugs BI 2536 and bortezomib.[31] Shiladitya Sengupta from Harvard Medical School spoke about mechanistically inspired cancer chemotherapy. In his presentation he explained major drawbacks of the anticancer drug cisplatin. To overcome the side effects associated with cisplatin, his group has been involved in synthesis of cisplatin analogues that have better bioavailability and fewer side effects. He also showed that when a PI3kinase inhibitor and a cholesterol derivative are administrated together the bioavailability is dramatically improved.[32]

NANOMATERIALS AND DRUG DISCOVERY

Sandeep Verma, of the Indian Institute of Technology Kanpur, described solution morphologies of peptide superstructures and the possibility of machining soft materials with the help of focused ion/electron beam for the development of malaria specific peptide containers.[33] Prasanta Kumar Das from Indian Association for the Cultivation of Science, Kolkata, presented the importance and possibility of using carbon nanotube included self-assembled nanocomposites in biomedical applications. He explained the role of pseudo-one-dimensional allotrope of carbon in therapeutic and diagnostic fields including the development of drug delivery vehicle.[34] Arabinda Chaudhuri of CSIR-Indian Institute of Chemical Technology, Hyderabad described their research on amphipilic lipopeptides containing the RGDK- and RGDGWK- peptide sequences in their headgroup regions that could selectively target genes to tumor vasculature presumably via the proangiogenic $\alpha5\beta1$ integrin receptors. They have developed mannose receptor selective liposomal DNA vaccine carriers that are capable of inducing long-lasting immune response.[35] Trevor Douglas, from Montana State University, USA gave an interesting talk on the encapsulation of multiple enzymes into supramolecular protein cage structures *in vitro* and their ability to function as native biological entities in the cellular microenvironment. His team co-encapsulated three enzymes, namely, β-glucosidase, glucokinase, and galactokinase, from *Pyrococcus furiosus*.[36]

There were 45 posters presented by students and postdoctoral fellows from different Indian institutes/universities in India. A wide area of chemical biology was covered by these posters: unusual aminoacid-containing peptides; anti-Leishmania, anticancer, antimicrobial synthetic as well as natural small molecule compounds; a new type of cell-penetrating morpholinos; small molecule modulators of miRNA expression and epigenetic enzymes; and radiopharmaceuticals for tumor imaging. Among these posters, two posters entitled, "3-Furanyl-Indole Derivatives Induce Apoptosis in U937 Cells via Oxidative Stress and Mitochondrial Dysfunction" by Madhumita Mandal (CSIR-IICB, Kolkata) and "SERS Based Investigation as a Drug Discovery: A Case Study on Aurora A Kinase Specific Inhibitor" by D. Karthigeyan (JNCASR, Bangalore) were selected for *ACS Chemical Biology* poster awards.

CONCLUSION

The meeting was successfully concluded with the unanimous acceptance of the formation of a Chemical Biology Society in India by the participants. The next meeting, which will be the first formal meeting of the new society, will be held at the CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad, India, and Arabinda Chaudhuri from the same institute will be the convener.

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