

**PROCEEDINGS OF INTERNATIONAL SYMPOSIUM ON CHEMICAL  
BIOLOGY AND DRUG DISCOVERY**

**(ISCBDD-2016)**

**Jointly organized by:**

**National Institute of Pharmaceutical Education and Research (NIPER), Kolkata**

**Bose Institute, Kolkata**

**and**

**Chemical Biology Society (CBS), India**

**1-3 March, 2016**

**Venue: Taj Bengal, Kolkata**

## FOREWARD

A major challenge faced by chemical biologists is the capability to effectively identify and manipulate the molecular components of diverse biological systems. The ‘**ISCBDD 2016**’ presented a unique platform to discuss chemical biology and drug development research among international communities. The main goal of ‘**ISCBDD 2016**’ was to bring together scientists from across disciplines to explore new approaches and methodologies in molecular level understanding of biological systems and development of drug.

The symposium explored how effectively chemists and biologists are using the tools and philosophy of chemical biology to understand the molecular basis of diseases. The topics covered in the symposium included *Disease and Targets*, *Chemical Biology of Pathways*, *Natural Products and Drug Discovery* while keeping nanotechnology and medicinal chemistry perspective in mind.

*Prof. Siddhartha Roy, Professor & Dean*

*Bose Institute, Kolkata*

*Dr. V. Ravichandiran, Director*

*National Institute of Pharmaceutical Education and Research, Kolkata*

*Prof. P. Jaisankar, Senior Principal Scientist and Head*

*CSIR – Indian Institute of Chemical Biology, Kolkata*

## ACKNOWLEDGEMENTS

We deeply express our gratitude towards *Dr. V. K. Subburaj*, IAS (Secretary, DoP) Ministry of Chemicals and Fertilizers (Govt. of India) for giving his valuable time to by becoming the '*Chief Guest*' of '**ISCBDD 2016**' conference.

A special thanks goes to Prof. S. Chattapadhyay (IICB), Prof. S. Raha (Bose Institute), Prof. K. S. Rangappa (University of Mysore) and Prof. B. Suresh (JSS University).

We acknowledge everyone who assisted in conducting '**ISCBDD 2016**' with success. In particular we are indebted to our foreign delegates: Prof. Masatoshi Hagiwara from Kyoto University Graduate School of Medicine, Japan; Prof. Haiyan Fu from Emory University, USA; Prof. Ming-Wei Wang from Chinese Academy of Sciences; Dr. R. Chaguturu (Founder and CEO, iDDPartners, Princeton); Prof. Krishna Kumar (Tufts Medical Center, Boston, USA); Dr. Sourav Sarkar from Lehigh University; Prof. Anna Philpott from University of Cambridge; Dr. V. Nagarajan (Director, Vn Neuro Care Center); Prof. Hon Man Lee (National Changhua University of Education, Taiwan; Dr. Shrikanta Chattopadhyay, an Instructor in Medicine from Harvard Medical School, USA and Dr. Glenn Butterfoss (New York University) for their valuable time to participate in the conference by sharing their research findings.

Organizers are grateful to the scientists participants from India including Prof. Partha Majumder (NIBMG), Prof. G. Mugesh (Indian Institute of Science, Bangalore), Dr. V. Nagaraja (JNCASR), Prof. H. Thulasiram (CSIT-NCL), Prof. Tapas K. Kundu, Prof. Suresh Muthuvel, Dr. Souvik Maiti, Dr. Sri Prakash Pandey, Dr. Arindam Banerjee, Prof. Arabinda Chaudhuri (CSIR-IICT), Prof. M. Eshwaramoorthy, Dr. Surajit Ghosh, Dr. Apurba Sau, Dr. K. K. Datta, Dr Subrata Dey, Dr Netai Bhattacharya, Dr Santanu Tripathy and Dr R. N. Chaudhury for presenting their expert opinions in the field of Chemical Biology and Drug Discovery.

We express acknowledgements towards IICB-CSIR, Bose Institute, Chemical Biology Society of India and their support staff for making '**ISCBDD 2016**' very successful.

Finally, gratitude is also due to the officials, faculty and the students of NIPER–Kolkata for their hard work during the last several months for making the conference successful.

*Prof. Siddhartha Roy, Professor & Dean  
Bose Institute, Kolkata*

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**International Symposium on Chemical Biology And Drug Discovery  
(ISCBDD-2016)**

**Schedule**

<b>Time (h)</b>	<b>Day 1: Tuesday, 1 March 2016 Taj Bengal</b>	
9:30-10:30	<b>Registration/Tea</b>	
10:30-11:00	<b>Inauguration</b>	
	<b>Session 1: Disease and Targets</b>	
<b>11:00-11:35</b>	<b>Special Lecture: Prof. Masatoshi Hagiwara, Japan</b>	Chairs: Prof. Siddhartha Roy/ Prof. Dhruvajyoti Chattopadhyay
<b>11:35-12:10</b>	<b>Lecture 1: Prof. Haiyan Fu, USA</b>	
<b>12.10-12.45</b>	<b>Lecture 2: Prof. Ming-wei Wang, China</b>	
<b>12.45-13.20</b>	<b>Lecture 3: Prof. Krishna Kumar, USA</b>	
13.20-14.20	<b>Lunch</b>	
	<b>Session 2: Chemical Biology of Pathways</b>	
<b>14:20-14:50</b>	<b>Lecture 4: Prof. Partha Majumder, India</b>	Chair: Prof. Saumitra Das
<b>14.50-15.20</b>	<b>Lecture 5: Prof. G. Mugesh, India</b>	
<b>15:20-15:50</b>	<b>Lecture 6: Dr. Sourav Sarkar, USA</b>	
<b>15.50-17.30</b>	<b>Poster Session I + Tea</b>	Evaluators: Prof. Anna Philpot, Dr. Glenn Butterfoss, Dr. P Shanmugam, Dr. K. T. Manisenthilkumar, Dr. Arindam Talukdar, Dr. R. Natarajan

<b>Time (h)</b>	<b>Day 2: Wednesday, 2 March 2016 Taj Bengal, Kolkata</b>	
	<b>Session 4: Natural Products and Drug Discovery</b>	
<b>09.30-10.05</b>	<b>Lecture 9: Prof. Rathnam Chhaguturu, USA</b>	Chair: Prof. K. S. Rangappa, Vice Chancellor, MU
<b>10.05-10.35</b>	<b>Lecture 10: Prof. V.Nagaraja, India</b>	
<b>10.35-11.05</b>	<b>Lecture 11: Prof. H. Thulasiram, India</b>	
<b>11.05-11.30</b>	<b>Tea Break</b>	
	<b>Session 5: CNS and Drug discovery</b>	
<b>11.30-12.00</b>	<b>Lecture 12: Dr. Anna Philpott, UK</b>	Chairs: Prof. Hemanta Majumdar/ Dr. Snehasikta Swarnakar
<b>12.00-12.30</b>	<b>Lecture 13: Prof. V. Nagarajan</b>	
<b>12.30-13.00</b>	<b>Lecture 14: Prof. Tapas Kundu, India</b>	
<b>13.00-14.00</b>	<b>Lunch</b>	
<b>14.00-15.00</b>	<b>Session 6: Panel Discussion on Rare diseases</b> <b>Panelists:</b> <ul style="list-style-type: none"> <li>➤ <b>Dr K. K. Datta, India</b></li> <li>➤ <b>Dr Subrata Dey, India</b></li> <li>➤ <b>Dr Netai Bhattacharya, India</b></li> <li>➤ <b>Dr Santanu Tripathy, India</b></li> <li>➤ <b>Dr Shrikanta Chattopadhyay, USA</b></li> </ul>	Chair: Prof. B. Suresh, Vice Chancellor, JSS University President- PCI
	<b>Session 7: Drug Discovery</b>	
<b>15.00-15.30</b>	<b>Lecture 15 : Prof. Hon Man Lee, Taiwan</b>	Chairs: Dr. Arun Bandopadhyay / Prof. Prasanta Kumar Das
<b>15.30-16.00</b>	<b>Lecture 16: Prof. Suresh Muthuvel, India</b>	
<b>16.00-16.30</b>	<b>Lecture 17: : Dr. Shrikanta Chattopadhyay, USA</b>	
<b>16.30-16.45</b>	<b>Tea</b>	
	<b>Session 8: RNA</b>	
<b>16.45-17.15</b>	<b>Lecture 7: Dr. Souvik Maiti, India</b>	Chair: Prof. Syamal Roy
<b>17.15-17.45</b>	<b>Lecture 8: Dr. Sri Prakash Pandey, India</b>	
<b>17.45-19.00</b>	<b>Poster Session - II EC meeting of CBS+AGM</b>	
	Evaluators: Prof. Anna Philpot, Dr. Glenn Butterfoss, Dr. P Shanmugam, Dr. K. T. Manisenthikumar, Dr. R. Natarajan, Dr. Arindam Talukdar	

<b>Time (h)</b>		<b>Day 3: Thursday, 3 March 2016 Taj Bengal, Kolkata</b>	
<b>Session 9: Peptides</b>			
<b>9.30-10.00</b>	<b>Lecture 18: Dr. Ranjan Chakrabarti, USP</b>	Chairs: Gautam Basu/ Dr. Sibsankar Roy	
<b>10.00-10.30</b>	<b>Lecture 19: Dr. Glenn Butterfoss, Abu Dhabi</b>		
<b>10.30-11.00</b>	<b>Lecture 20: Prof. Arindam Banerjee, India</b>		
<b>11.00 – 11.30</b>	<b>Tea Break</b>		
<b>Session 10: Drug Delivery</b>			
<b>11.30-12.00</b>	<b>Lecture 21: Prof. Arabinda Chaudhuri, India</b>	Chairs: Prof. Pinakpani Chakrabarti / Dr. Rajkumar Banerjee	
<b>12.00-12.30</b>	<b>Lecture 22: Prof. M. Eshwaramoorthy, India</b>		
<b>12.30-13.00</b>	<b>Lecture 23: Dr. Surajit Ghosh, India</b>		
<b>13.00-14.00</b>	<b>Lunch</b>		
<b>Session 11: Drug Targets</b>			
<b>14.00-14.30</b>	<b>Lecture 24: Dr. Apurba Sau, India</b>	Chair: Dr. S. N. Kabir	
<b>14.30-15.00</b>	<b>Lecture 25: Dr. Chetna Sachidanandan, India</b>		
<b>15.00-15.30</b>	<b>Tea Break</b>		
<b>15:30-16.00</b>	<b>Dr. Rathnam Chaguturu: Special lecture on Scientific Ethics</b>		
<b>Session 12: Valedictory Session</b>			
<b>16.00-17.00</b>	<b>Valedictory Session: Presentation of Poster Awards and Concluding session</b>	Chief Guest: Dr. M Ariz Ahammed, IAS, Joint Secretary, Ministry of Chemicals and Fertilizers, Govt. of India Dr. V. Ravichandiran	

## EXECUTIVE SUMMARY

Recently, NIPER Kolkata in collaboration with Bose Institute and Indian Institute of Chemical Biology had jointly organized a symposium entitled '**International Symposium on Chemical Biology and Drug Discovery**' (ISCBDD-2016) which was held from March 1-3, 2016 at Taj Bengal, Kolkata. Scientists from all over the world consisting of nearly 200 delegates from various research disciplines gathered at **ISCBDD-2016** to discuss the understanding of biological systems and drug development at molecular level. Among many dignitaries **Dr. V. K. Subburaj, IAS** (Secretary, DoP) Ministry of Chemicals and Fertilizers (Govt. of India), was present as the '*Chief Guest*'. Other dignitaries included, Prof. S. Chattopadhyay (IICB), Prof. S. Raha (Bose Institute), Prof. K. S. Rangappa (University of Mysore) and Prof. B. Suresh (JSS University).

The three-day symposium included the following themes including Chemical Biology, Molecular drug design, Pharmaceutical formulations, Drug development, understanding of dynamic genome organization, nanotechnology aspect of Chemical Biology and few other topics related to Chemical Biology. Prof. Siddhartha Roy (Bose Institute) welcomed the conference attendees, following the address of Prof Tapas Kundu (President, Chemical Biology Society of India) and Prof. V. Ravichandiran (Director, NIPER Kolkata).

The subjects were covered through the following sessions: Disease and Targets, Chemical Biology of Pathways, Natural Products and Drug Discovery, CNS and Drug discovery, Rare diseases, Drug discovery, RNA, peptides, drug delivery and drug targets and scientific ethics. Several poster sessions also contributed immensely to the understanding of the theme of the conference.

Renowned international scientists including Dr. Masatoshi Hagiwara from Kyoto University Graduate School of Medicine, Japan, Dr. Glenn Butterfoss (New York University of Abu Dhabi), Prof. Haiyan Fu (Emory University, USA), Prof. Anna Philpott from University of Cambridge were among the large pool of speakers from abroad. Prof. Arabinda Chaudhuri (CSIR-IICT, Hyderabad), Prof. Arindam Banerjee (IACS, Kolkata), Prof. Prakash Pandey (IISER, Kolkata) among several eminent scientists from India who delivered their interesting research findings.

The three-day symposium concluded with valedictory session with presentation of poster awards following concluding remarks given by Dr. V. Ravichandiran and vote of thanks given by Prof. P. Jaisankar (CSIR-IICB).

## OVERVIEW

**Day 1: March 1, 2016**

### Session 1: Disease and Targets

*Chairs: Prof. Siddhartha Roy, Prof. Dhrubajyoti Chattopadhyay*

**Dr. Masatoshi Hagiwara** from Kyoto University Graduate School of Medicine, Kyoto, Japan presented about the development of new chemical therapeutics of genetic diseases by manipulating transcriptome elements of peptoid structure. Patients of congenital diseases have abnormalities in their chromosomes and/or genes. Therefore, it has been considered that drug treatments can serve to do little for these patients more than to patch over each symptom temporarily when it arises. Although we cannot normalize their chromosomes and genes with chemical drugs, we may be able to manipulate the amounts and patterns of mRNAs transcribed from patients DNAs with small chemicals. Based on this simple idea, we have looked for chemical compounds which can be applicable for congenital diseases and found INDY, TG003, and SRPIN340 are promising as clinical drugs for Down syndrome, Duchenne muscular dystrophy and Denys Drash Syndrome, respectively.

**Dr. Haian Fu** from Emory University, USA discussed about interrogating protein-protein interactions in cancer. Protein-protein interactions have emerged as a promising class of molecular targets for therapeutic interventions. This presentation will briefly summarize our recent study on cancer genomics-based protein-protein interaction network mapping for informing potential therapeutic strategies.

G protein-coupled receptor GPR160 is associated with apoptosis and cell cycle arrest of prostate cancer cells. **Dr. Ming-Wei Wang** from Chinese Academy of Sciences, China presented this important aspect of research. G protein-coupled receptors (GPCRs) represent the largest membrane protein family implicated in the therapeutic intervention of a variety of diseases including cancer. Exploration of biological actions of orphan GPCRs may lead to the identification of new targets for drug discovery. This study investigates potential roles of GPR160, an orphan GPCR, in the pathogenesis of prostate cancer. The transcription levels of GPR160 in the prostate cancer tissue samples and cell lines, such as PC-3, LNCaP, DU145 and 22Rv1 cells, were significantly higher than that seen in normal prostate tissue and cells. Knockdown of GPR160 by lentivirus-mediated short hairpin RNA construct targeting human GPR160 gene (ShGPR160) resulted in prostate cancer cell apoptosis and growth arrest both *in vitro* and in athymic mice. Differential gene expression patterns in PC-3 cells infected with ShGPR160 or scramble lentivirus showed that 815 genes were activated and 1193 repressed. Functional annotation of differentially expressed genes (DEGs) revealed that microtubule cytoskeleton, cytokine activity, cell cycle phase and mitosis are the most evident functions enriched by the repressed genes, while regulation of programmed cell death, apoptosis and chemotaxis are enriched significantly by the activated genes. Treatment of cells with GPR160-targeting shRNA lentiviruses or duplex siRNA oligos increased the transcription of *IL6* and *CASP1* gene significantly. Our data suggest that the expression level of endogenous GPR160 is associated with the pathogenesis of prostate cancer.

**Prof. Krishna Kumar** (Tufts Medical Center, Boston, USA) presented about a new paradigm for the design of peptide therapeutics, which is a powerful methodology to engineer orthogonal noncovalent behavior in biological systems, and in the stabilization of therapeutic peptides and carbohydrates from enzymatic degradation. A chemical-genetic strategy for the

discovery, optimization and pharmacological characterization of membrane-anchored ligands for modulating G Protein-Coupled Receptors (GPCRs) will be discussed. These assemblies have been utilized in the discovery of compounds targeting inflammation (asthma), neuropathic pain and cardiovascular disease. Strategies by which fluorinated components are introduced into peptides and proteins within membranes; the modulation of cellular adhesion by modification of glycolipids and glycoproteins with fluorine containing sugars and stabilization of therapeutic peptides (for anti-diabetic candidates) by means of synthetic modification will form part of the discussion. Together, these studies present a powerful methodology to engineer orthogonal noncovalent behavior in biological systems, and in the stabilization of therapeutic peptides and carbohydrates from enzymatic degradation.

## Session 2: Chemical Biology of Pathways

*Chair: Prof. Saumitra Das*

Complex chemical pathways of thyroid hormone action was elaborately described by **Prof. G. Mugesh** of Indian Institute of Science, Bangalore. Thyroid hormones regulate almost every process in the body, including body temperature, growth, and heart rate. They influence carbohydrate metabolism, protein synthesis and breakdown, and cardiovascular, renal, and brain function. The deiodination of thyroxine (T<sub>4</sub>) by iodothyronine deiodinases (IDs) play a crucial role in thyroid hormone action. The phenolic ring (5') deiodination of T<sub>4</sub> by the type 1 and 2 enzymes (ID-1 and ID-2) produces the biologically active hormone, 3,5,3'-triiodothyronine (T<sub>3</sub>), whereas the tyrosyl ring (5) deiodination of T<sub>4</sub> by the type 3 enzyme (ID-3) produces the biologically less active hormone rT<sub>3</sub>. Therefore, the complex biochemical dehalogenation pathways play an important role not only in human hormone action, but also in the development of drugs for thyroid-related disorders. In this lecture, I will discuss the chemical mechanism by which the deiodinases and their synthetic mimetics selectively activate and inactivate the thyroid hormones.

Mapping enzymatic interactions of bacterial cell wall biosynthesis with photo-affinity probes was the topic of presentation by **Dr. Sourav Sarkar** from Lehigh University, USA. Antibiotic resistance is rapidly becoming a global healthcare crisis. Bacteria have evolved clever strategies to escape the toxic effects of antibiotics at the same time that the number of FDA antibiotic approvals has dwindled. The discovery of new drug targets and re-evaluation of established targets will be critical in reversing this trend. Potent antibiotics (e.g. vancomycin) target the bacterial cell wall by arresting key intermediates in the cell wall biosynthetic pathway. We hypothesized that installation of chemically modified intermediates in the bacterial cell wall biosynthetic pathway could map out key enzymatic interactions that are crucial for the generation of the bacterial cell wall and thus provide interesting targets for the development of novel antibiotics. Therefore we synthesized photo-affinity based cell wall precursor analogues as metabolic probes and incorporated them in live bacterial cells by hijacking the cell wall biosynthetic pathway. Photo-irradiation in live bacterial cells followed by activity based protein profiling (ABPP) afforded a detailed map of several key enzymes that are supposed to be involved in the biosynthesis of the bacterial cell wall. Out of a total of ~900 proteins identified, ~600 proteins were found to be more abundant in the presence of light. We anticipate that our strategy will be an integral component in revealing the full picture of enzymatic interactions along the bacterial cell wall biosynthetic pathway and can be used as a model for the development of next generation antibiotics.

**Day 2: March 2, 2016**

**Session 4: Natural Products and Drug Discovery**

***Chair: Prof. K. S. Rangappa***

**Dr. R. Chaguturu** (Founder and CEO, iDDPartners, Princeton)'s lecture topic 'Renaissance in pharmacognosy: the need is great and the time is now' was an important one. Discovering safe and effective medicines, one of the greatest gifts to humanity, relies intensely upon the availability of detailed, unassailably accurate biomedical scientific knowledge. Unfortunately, such critical technical endeavors are being jeopardized by an epidemic of false-science unfolding around us. There has been an alarming increase in the number of scholarly articles retracted, and almost two thirds of the retractions have been traced to scientific misconduct and fraud, not error. Although science, like Wall Street, is self-correcting to a certain extent, the outcome of the recent housing bubble reminds us vividly how much pain and destruction can be incurred by passively awaiting organic self-correction. The talk centers on research malfeasance in the biomedical arena, characterizes some of the key forms of deliberate misconduct, including falsification of results, peer-review rigging, data over-interpretation and improper or willfully selective sampling practices. The discussion also explores problematic grey areas such as choice of inappropriate analytical protocols, the failure to retract erroneous findings and the use of textual plagiarism for manuscript assembly. The investigator, the publisher, the institution, the funding agencies, and the national policy-makers have the imperative, the ability and the resources to identify research improprieties and prevent such misconduct from inflicting negative consequences on their research priorities.

**Dr. V. Nagaraja** (JNCASR) mentioned that the torsional strain in the genome arising from various protein:DNA interactions is relieved by the action of dedicated bunch of enzymes known as topoisomerases. Understanding how these molecular machines function in mycobacteria has been a major topic of our study in order to develop specific inhibitors that would affect the growth of the organism. The reactions carried out by these essential house-keeping enzymes involve DNA cleavage, strand passage and rejoining step to maintain topological state of the genome. Studies will be presented showing how these reactions can be affected by developing new inhibitors. In the process, we have identified first set of inhibitors for bacterial topoisomerase I.

**Dr. Thulasiram H. V** (CSIR-National Chemical Laboratory): Neem tree (*Azadirachta indica*) serves as a cornucopia for triterpenoids called limonoids (meliacins) which are agronomically and pharmacologically active isoprenoids belonging to the class of tetranortriterpenoids. Our work revolves around chemistry and biology of isoprenoids. In this presentation, I will speak about the systematic molecular dissection of isoprenoid pathway in Neem, *Azadirachta indica*. We are involved in targeted metabolic profiling of limonoids including, isolation, characterization, and tissue specific metabolic profiling of limonoids in Neem tree. In collaboration, these purified limonoids are being screened for various biological activities. We have carried out chemo-enzymatic modification of limonoids for localization studies and also to produce novel metabolites. Systematic dissection of biosynthetic pathway for the limonoids in Neem by cloning and functional characterization of genes which encodes enzymes involved in limonoid biosynthesis is in progress. Furthermore,

we have developed suspension cultures of *A. indica* from kernels to elucidate the biosynthetic route of limonoids. As the origin of isoprene units in terpenes occurs through either of the two pathways: classical mevalonate pathway (MVA) or the methyl erythritol phosphate pathway (MEP) or through combination of both pathways, feeding experiment with stable isotope labeled glucose was carried out with neem cell culture. The  $^{13}\text{C}$  labeling pattern in various limonoids obtained in mass spectrometry gives the metabolite signature of isoprene units, the building blocks of terpenoids thereby providing valuable information that these compounds are biosynthesized exclusively through the classical mevalonate pathway. This evidence was corroborated by the proof of inhibition of limonoid biosynthesis by MVA pathway specific inhibitor mevinolin.

### **Session 5: CNS and Drug discovery**

*Chairs: Prof. Hemanta Majumdar, Dr. Snehasikta Swarnakar*

**Prof. Anna Philpott** from University of Cambridge presented a fascinating topic about cell cycle regulation of differentiation in development and disease, and asked a question whether it is a potential therapeutic intervention point. It is essential that division and differentiation are carefully co-ordinated during development. Moreover, a disruption of this co-ordination is a central characteristic of many forms of cancer. They are investigating the molecular mechanisms by which the cell cycle machinery can directly control the activity of key transcription activators, the proneural proteins, which are responsible for regulating differentiation in the nervous system, pancreas and multiple other tissues. They have found that chromatin binding and transcriptional activity of proneural proteins is regulated by multi-site phosphorylation driven by cell cycle kinases. We see that inhibiting proneural protein phosphorylation preferentially activates targets associated with driving differentiation, and this is key to altering the balance away from maintenance of a proliferative state. This leads us to a model whereby transcription factor post-translational modification intersects directly with the epigenetic landscape of downstream targets to determine whether cells maintain their progenitor status or undergo differentiation during development and in adult homeostasis. In the paediatric cancer neuroblastoma we see that the proliferation versus differentiation balance is disturbed in favour of stem/progenitor maintenance, due to ongoing cdk-dependent phosphorylation of the proneural transcription factor *Ascl1*. We are exploring the possibility of using cyclin-dependent kinase inhibitors to simultaneously slow the cell cycle and alter the post-translational modification of *Ascl1*, resulting in direct potentiation of differentiation as a new approach for therapy in this unusual childhood malignancy.

**Dr. V. Nagarajan** (Director, Vn Neuro Care Center): Various research for effective drug development to cure Central Nervous System diseases were not progressing to the adequate level in the past scenario. This was due to the ethical issues and difficulty in direct observations of the effect of the drug, especially psychotropic drugs, as a human element and management of mental functions is involved. These parameters can never be inferred with animal experiment. Appropriate translation becomes highly difficult in such situations. Genetic issues in CNS disorder cannot be resolved or arrested by measurable pharmacological intervention. Beyond this drug delivery to CNS tissue is highly complicated because of the presence of blood-brain barrier system. Pharmacogenetic modulation is currently attempted to control the degenerative CNS disorders. Similar interventions in the enzymatic modulation by pharmacological intervention is being pioneered now. March towards the nano molecular system and pharmacogenetical intervention will help bypass the blood-brain barrier.

**Dr. Tapas Kundu** (JNCASR, Bangalore) discussed about glucose derived carbon nanosphere to deliver epigenetic therapeutics for Neurodegenerative diseases. They have developed a glucose derived self-fluorescent, cell permeable carbon nanosphere (CSP) which upon IP injection is able to cross the blood brain barrier and deliver the adsorbed or covalently conjugated molecule in the brain. We have also synthesized different shape based iron nanoparticle coated with carbonaceous polymer which is be able to deliver the desired molecule specifically in the nucleus. However, by employing CSP-conjugated small molecule activator of lysine acetyltransferases p300/CBP, TTK21, we could activate histone acetylation in the mice brain. The hyper-acetylation of histones in the mice brain induces the neurogenesis and long term spatial memory. Recently, using the same CSP-TTK21 conjugate we have been able to completely recover the lost memory function in Alzheimer's disease mice model. The molecular mechanisms of this process are being elucidated.

### **Session 6: Panel Discussion on Rare diseases**

*Chair: Prof. B. Suresh, Vice Chancellor, JSS University*

The panel discussion on rare diseases involved panelists including Dr. K. K. Datta (NIPER, Kolkata), Dr. Subrata Dey, Dr. Netai Bhattacharya, Dr. Santanu Tripathy, Dr. R. N. Chaudhury and Dr. Shrikanta Chattopadhyay. The panellists hope that the proceedings and the recommendations will go a long way to raise awareness of rare diseases among professionals and health administrators. They are hopeful that if this novel initiative is taken to its logical conclusion it will raise hope to the millions of rare disorder patients for appropriate support from the health care providers.

### **Session 7: Drug Discovery**

*Chairs: Dr. Arun Bandopadhyay, Prof. Prasanta Kumar Das*

Lecture on synthesis and anticancer activities of palladium(II) complexes of chelating carbene ligands was delivered by **Dr. Hon Man Lee** of National Changhua University of Education, Taiwan. Palladium(II) complexes show considerable promise as anticancer drugs due to their structural and chemical similarities with platinum(II) compounds. However, Pd—ligand bonds are considerably more labile than their Pt—ligand counterparts. It has been shown that both preventing possible *cis-trans* isomerization and slowing the rate of dissociation or hydrolysis of palladium(II) complexes are crucial in aiding their reactive species to reach their pharmacological targets. Thus, the stabilization of palladium(II) complexes by strong M–N/M–C bonds or the formation of cyclometallated structures are desirable for palladium-based anticancer complexes.

*N*-heterocyclic carbenes (NHCs) have recently attracted a considerable amount of interest because of their accessibility, high thermal stability, and the remarkable catalytic activities of their transition-metal complexes in diverse organic reactions. We envisioned that new palladium(II) complexes bearing tridentate ligands consisting of NHC, amidate, and pyridine donor moieties may have potential as active anticancer complexes because they feature strong M–C and M–N bonds through the coordination of carbene and amidate moieties, and also because the resulting cyclometallated rings impart high stability to the complexes. The potential of these complexes as anticancer drugs will be presented.

**Prof. S. Muthuvel** from Pondicherry University discussed regarding the identification of novel tyrosine kinase inhibitors for drug resistant T315I mutant BCR-ABL as a virtual screening and molecular dynamics stimulation study. BCR-ABL tyrosine kinase plays a major role in the pathogenesis of chronic myeloid leukemia (CML) and is a proven target for drug development. Currently available drugs in the market are effective against CML; however, side-effects and drug-resistant mutations in BCR-ABL limit their full potential. Using high throughput virtual screening approach, we have screened several small molecule from the database and docked against wild-type and drug resistant T315I mutant BCR-ABL. Drugs that are currently available, such as imatinib and ponatinib, were also docked against BCR-ABL protein to set a cutoff value for our screening. Selected lead compounds were further evaluated for chemical reactivity employing density functional theory approach, all selected ligands shows HLG value  $> 0.09900$  and the binding free energy between protein-ligand complex interactions obtained was rescored using MM-GBSA. The selected compounds showed least  $\Delta G$  score  $-71.53$  KJ/mol to maximum  $-126.71$  KJ/mol in both wild type and drug resistant T315I mutant BCR-ABL. Following which, the stability of the docking complexes were evaluated by molecular dynamics simulation (MD) using GROMACS4.5.5. Results uncovered seven lead molecules, designated with Drug-Bank and PubChem ids as DB07107, DB06977, ST013616, DB04200, ST007180 ST019342, and DB01172, which shows docking scores higher than imatinib and ponatinib.

**Dr. Shrikanta Chattopadhyay**, an Instructor in Medicine from Harvard Medical School, USA described the research findings on the advances in Phenotypic small-molecule screening to discover drug targets. A key challenge in drug discovery is identifying the right target. Historically, therapeutic targets were discovered using biologically active small molecules that had obvious phenotypic effects in organisms or cells. For example psychotropic opioid alkaloids led to the discovery of opioid receptors and anti-leukemic folic acid analogs identified folate metabolizing enzymes as viable therapeutic targets. Recently, target discovery for drug development has largely followed genetic approaches such as genomic sequencing of human disease samples or manipulation of genes in cells. While powerful, these approaches are limited by enormous genomic complexities of human diseases and differing phenotypic effects of genetic and pharmacological interventions. As a result, there has been a recent resurgence of phenotypic small-molecule screening approaches to discover therapeutic targets and lead candidates for drug development. A recent analysis of FDA-approved drugs found that the majority of first-in-class drugs were discovered by a phenotypic screening approach. This review will focus on advances in phenotypic screening and systematic usage of recent technological advances that can enable target discovery of small molecules with phenotypic effects.

## **Session 8: RNA**

*Chair: Prof. Syamal Roy*

**Dr. Souvik Maiti** from CSIR-Institute of Genomics and Integrative Biology gave a talk entitled 'Interfering with Interference: targeting the RNAi pathway using small molecules'. MicroRNAs (miRNAs) play crucial roles in regulating gene expression in many cellular contexts. Deregulation of miRNAs has been implicated in a number of disease conditions and thus, methods that can modulate mature miRNA levels in cells can have immense therapeutic potential. We describe a simple in vitro screening method using a DNA

based molecular beacon which overcomes the limitations associated with earlier screens. We used this method to identify inhibitors of miR-21 function from a library of 14 aminoglycosides as a pilot study. With this proof of concept study we illustrate the utility of a scalable molecular beacon based screening strategy for miRNA inhibitors. We also screened this library to test their inhibitory capacity to silence another oncomir, miR-21. We found that streptomycin was able to do so by structural perturbation of the process of dicing giving it a potential new indication as a candidate anticancer agent. Subsequently, we show that cyclic peptides and naphthyridine are the promising scaffolds to develop small molecules that can selectively inhibit miRNA function.

Chemical biology of plant defenses and the role of regulatory small RNAs were presented by **Dr. Shree Prakash Pandey** (IISER, Kolkata). Plants are literally rooted into the complex environments where they encounter a plethora of abiotic and biotic stresses, several of which, such as attack from pathogens and herbivores, dominate their biological niche. They display remarkable biochemical diversity that they easily form the basis of their phenotypic plasticity. When under attack for example from herbivores, plants reconfigure their signaling and metabolic networks to defend themselves. This reconfiguration comprises a complex chain of events involving cell membrane depolarization, calcium flux and MAPK activation, increases in reactive oxygen and nitrogen species, and finally an intricate phytohormone response involving jasmonic acid [JA], ethylene and salicylic acid [SA] signaling networks. These complex signaling networks regulate large-scale and complex metabolomic reconfigurations that arm plants with chemical arsenals for defense. These chemical arsenals include array of metabolites, including nicotine, phenolics, phenolamides, polyamines, diterpenoids, and volatiles. How are these complex, adaptive chemical responses regulated, remains a daunting question. In this talk we will try to answer this question by exploring how the regulatory small-RNAs [smRNAs; such as miRNAs and siRNAs] may be master regulators of plant defenses. We propose a novel, previously undescribed herbivore-induced smRNA machinery that has been specifically tailored for modulating the sophisticated plant-biotic interactions. We will attempt to gain insights into understanding the evolutionary basis of diversification of smRNAs.

### Day 3: March 3, 2016

#### Session 9: Peptides

*Chairs: Gautam Basu, Dr. Sibsankar Roy*

Therapeutic synthetic peptides, their history and challenges in quality standards was talked by **Dr. R. Chakrabarti** (Vice President & Head, Global Biologics Laboratory Operations). Peptide therapeutics has become a key strategy for development of innovative medicine because of its efficacy and safety. In past few decades, the number of peptide drugs entered into the clinic and in the market have increased exponentially. The chemical composition of these peptide drugs include simple linear sequence with natural and non-natural amino acids, multiple disulfide bonds, peptide conjugated with variety of scaffolds. These chemical compositions engender complexity in the characterization of peptide identify. The presentation will cover the current status of peptide based therapeutics and industry trends for synthetic peptides and a brief overview of manufacturing technologies will be provided, to explain the types of impurities that may exist in peptides. U.S. Pharmacopeia (USP) is working with manufacturers and regulators to evaluate quality attributes for synthetic peptide therapeutics based on currently available regulatory guidance and expectations. The presentation will describe USP's current synthetic peptide program and our continued effort to set quality standards for this product class incorporating the recommendations on the quality attributes. Compendial challenges such as impurities are illustrated using case studies.

**Dr. Glenn Butterfoss** from New York University of Abu Dhabi brought up the topic of peptoids, which are N-substituted glycine oligomers. Peptoids (N-substituted glycine oligomers) possess a number of attractive peptidomimetic features. For example, peptoids are amenable to solid-phase sub-monomer synthesis via iterating primary amines and bromoacetic acid. The amine functional group becomes the side chain of the growing chain—allowing for sequence-specific oligomers with easy access to high chemical diversity. Additionally, the tertiary amide of the peptoid backbone is not subject to proteolysis, giving peptoids higher biostability than peptides of similar size. However the placement of the side chain on the backbone nitrogen means peptoids have quite different structural characteristics in comparison to peptides and proteins, including: a lack of inherent backbone chirality, inability to form backbone-backbone hydrogen bonds, and amide backbone *cis/trans* orientations which are frequently isoenergetic. This talk will cover computational and experimental work to elucidate inherent peptoid structural propensities and potential mechanisms of controlling local structure. Early structural work demonstrated peptoids have a capacity to form polyproline type I and II helices (depending on whether a *cis* or *trans* amide is propagated in the backbone, respectively). The *cis/trans* preference can be modulated with certain choices of side chains, for example N-aryl side chains drive *trans* conformations, while branched and bulky N-alkyl side chains favor *cis*. We have also found that backbone reverse turns that are stabilized by van der Waals contacts rather than hydrogen bonds (so called touch-turns) are possible in peptoids. Peptoids, in general, have been amenable to computational modeling. The fact that peptoid conformation is frequently driven by local and steric interactions (rather than hydrogen bonds—which can be longer range interactions along the chain sequence), simplifies some aspects of peptoid structural prediction and design relative to peptides. We have shown that combined molecular dynamics and quantum mechanics modeling approaches can be used to predict the 'fold' large peptoid macrocycles. Moreover, we have incorporated peptoid residue representations into the Rosetta rational protein design suite. Peptoids have recently been noted for their capacity to form nanostructures. For example some alternating (charged residue, hydrophobic residue) peptoid

sequences will, after gentle agitation in water, self-assemble into stable bilayers up to hundreds of microns in lateral breadth but only two molecules (~30 nm) in height (an extremely high aspect ratio). We have found, using molecular modeling and comparisons with data from x-ray scattering, microscopy, and other techniques, that the peptoid backbones within these nanosheets assume a secondary structure motif previously unobserved in either peptoids or peptides. Namely, the backbones are not linear, but the linearity is generated by alternating and opposed torsional states of individual peptoid residues.

**Dr. Arindam Banerjee** (IACS Kolkata) chose to discuss regarding self-assembling peptides which can be used ranging from molecular design to functional soft materials. Molecular self-assembly plays a pivotal role in chemical, biological and material sciences. Peptides are good candidates for the self-assembly by using various non-covalent interactions including hydrogen bonding, pi-pi stacking, electrostatic, solvophobic and others. Under appropriate condition, a peptide can be self-associated to form a micro/nano-network structure occupied by a large amount of solvent molecules (water/organic solvent) and this forms a soft material called gel. The major challenge is to control the assembly of designer oligopeptides to make useful gels and also to explore various interesting applications of these gel based soft materials.

### Session 10: Drug Delivery

*Chairs: Prof. Pinakpani Chakrabarti, Dr. Rajkumar Banerjee*

CSIT-IICT scientist Prof. **Arabinda Chaudhuri** talked about fighting cancer with targeted chemotherapy in combination with *in vivo* dendritic cell targeted genetic immunization. Liposomes, the fatty bubbles containing an aqueous interior, are finding widespread uses in directing potent anti-cancer drugs/genes/siRNAs selectively to tumor and tumor endothelial cells. To this end, recently we have developed efficient integrin receptor selective liposomal systems for delivering potent anti-cancer drugs/genes to tumor vasculature and have demonstrated their significant tumor growth inhibition properties in syngeneic mouse tumor model. However, eradicating established tumor by targeted chemotherapy alone remains an unmet challenge in medical science. In the rapidly emerging field of dendritic cell (DC) based genetic immunization, previously we showed that immunization with autologous DCs ex-vivo pre-transfected with electrostatic complexes (lipoplexes) of a plasmid DNA encoding melanoma tumor associated antigen (DNA vaccine) and liposomes of cationic amphiphiles with mannose-mimicking quinoyl- & shikimoyl head-groups induces long-lasting immune responses against melanoma tumor. However, there are a number of time-consuming and cost-ineffective steps to be followed in such ex-vivo DC-transfection based cancer immunotherapy. One needs to painstakingly isolate the autologous DCs from the recipients. The isolated DCs then need to be ex vivo pre-transfected with DNA vaccines of interest and finally the ex-vivo transfected DCs need to be re-implanted back into recipient's body. Stated differently, the currently practiced ex vivo DC-transfection based genetic immunization procedures are labor-intensive and are likely to be prohibitively costly for large scale applications. We have recently succeeded in designing efficient liposomal DNA vaccine carriers for direct in vivo targeting of tumor antigen encoded DNA vaccines to dendritic cells. Importantly, this newly developed liposomal DNA vaccine carriers are capable of inducing long-lasting immune response including strong memory response against melanoma tumors in a syngeneic mouse tumor model. Most recently, we have succeeded in developing a platform technology for eradicating/regressing established tumors through a combination of in vivo DC-targeted genetic immunization and targeted chemotherapy. My presentation will be centered around discussing these translationally important recent findings from our laboratory.

A Scientist from JNCASR, Bangalore (**Dr. M. Eswaramoorthy**) elaborately mentioned about his research project on carbon and silica based materials for the delivery of small molecules. Carbon spheres obtained from a commonly available, non-toxic carbohydrate, glucose, was used as the drug carrier inside the cell nucleus. In this talk, glucose derived carbon structures for nuclear delivery applications will be discussed. Furthermore, the use of mesoporous silica and clay based drug delivery systems will also be highlighted.

Development of novel delivery vehicles for targeted delivery of docetaxel was described by **Dr. Surajit Ghosh** of CSIR-IICB, Kolkata. Delivery of therapeutic molecules in a targeted fashion to the tumor site is extremely important for the treatment of cancer, because it helps in increasing the drug concentration to the tumor site and reduces the side effects. Microtubule, polymerized form of  $\alpha,\beta$ -tubulin heterodimer is one of the key dynamic cytoskeleton filament, which plays crucial role in cellular function, intracellular space and eukaryotic cell division. Perturbation of this process either by stabilizing or destabilizing microtubules causes severe cytotoxic effect. Docetaxel (DX), approved by the FDA as a therapeutic molecule, shows anticancer activity against various cancers including breast and prostate. DX affects normal microtubule dynamic instability by targeting  $\beta$ -tubulin to promote microtubule polymerization, and bipolar spindle structure to induce mitotic block in proliferative cancer cells. Although DX is used as chemotherapeutic agent for various cancers, the efficacy of this drug is poor and shows non-selective toxicity to normal cell. To overcome these issues, many groups are trying to improve the efficacy and selectivity of DX to tumor site through development of new delivery systems. However, all these attempts did not show significant success in terms of target specific DX delivery to minimize the dose and in nonspecific toxicity. For this purpose, further extensive research is necessary for the development of a high potential novel DX-conjugate, which can deliver DX in a targeted manner to specific cancer cell. This presentation will focus on recent development of two delivery system of DX through targeting two important cancer cell surface receptors, such as MUC1 and neuropilin-1 (NRP-1)

## Session 11: Drug Targets

*Chair: Dr. S. N. Kabir*

Arginase of *Helicobacter* gastric pathogens utilizes a unique set of non-catalytic residues to regulate catalysis. This topic was clarified by **Dr. Apurba K. Sau** from National Institute of Immunology, New Delhi. Urea producing bimetallic arginases are essential for the synthesis of polyamine, DNA and RNA. Despite conservation of the signature motifs in all arginases, a non-conserved <sup>153</sup>ESEEKAWQKLC<sup>165</sup>SL motif is found in the *Helicobacter pylori* enzyme, whose role was yet unknown. Using various biochemical and biophysical methods, we show the significance of this motif in catalytic function, metal retention, structural intactness and stability of the protein. The enzyme did not exhibit detectable activity upon deletion of the motif as well as on individual mutation of Glu155 and Trp159 while Cys163Ala displayed significant decrease in the activity. Trp159Ala and Glu155Ala show severe loss of thermostability (14-17<sup>0</sup>) by decrease in the  $\alpha$ -helical structure. The role of Trp159 in stabilization of the structure with surrounding aromatic residues is confirmed when Trp159Phe restored the structure and stability substantially compared to Trp159Ala.

The molecular dynamics simulation studies at 450 ns support the above results and show that the motif, which was previously solvent exposed, displays a loop-cum-small helix structure (Lys161-Cys163) and is located near the active-site. We identified two key non-conserved residues, whose interactions with Trp159 through aromatic-aromatic stacking interactions are indispensable for tertiary structural intactness and thereby for function. Therefore, the enzyme seems to be evolved with a non-conserved motif, whose positioning at the active-site by the above unique interactions generates a conformation, which is catalytically competent to carry out the hydrolysis reaction of L-arginine. Thus, these three aromatic residues may act as a non-catalytic triad to regulate catalysis. The identification of this non-conserved stretch with the catalytic triad in arginase of other *Helicobacter* gastric pathogens implies that they have similar role to that of *H. pylori* counterpart. Thus, our findings reveal for the first time that arginase of all *Helicobacter* gastric pathogens utilizes a unique non-catalytic triad to regulate catalysis, which could be exploited for therapeutics.

**Dr. Chetana Sachidanandan** (CSIR-Institute of Genomics and Integrative Biology, New Delhi) discussed drugging iron regulatory disorders using zebrafish disease models. Hcpidin, the peptide hormone that regulates systemic iron levels is at the heart of maintaining iron homeostasis in the vertebrate body. Iron although an essential element of life is also toxic when overloaded. Extremes of iron regulatory imbalance lead to Anemia (iron deficiency) and Hemochromatosis (iron overload). Hcpidin deregulation is a common theme in most iron regulatory disorders.

Using zebrafish (*Danio rerio*), we set out to model human iron regulatory disorders. Our models recapitulate the hallmarks of the human disease such as anemia linked to hepcidin overproduction and iron overload due to inadequate induction of hepcidin. They have used focused *in vivo* chemical screens in zebrafish to identify chemical modulators of hepcidin. They have picked out potent inducers and repressors of hepcidin transcription. These molecules show varying ability to rescue the disease phenotypes and potential for use in corrective-regulation of hepcidin in iron regulatory diseases. From lessons learnt in our screens we go on to identify new drug targets and drug candidates from the existing cornucopia of marketed drugs.

**Dr. Rathnam Chaguturu** (Founder and CEO of, iDDPartners, Princeton Junction, NJ) gave a special lecture on scientific ethics. Pharmaceutical industry has forgotten its roots. Pharma's innovation crisis is perhaps tied to its neglect of natural product-based drug discovery. Both academia and pharma are now engaged in screening large compound libraries to identify lead drug candidates. Since the chemical diversity of these libraries is not always relevant to biological function, this approach has not been as successful as was hoped. With increased emphasis on high-throughput screening and combinatorial chemistry, and the clarity that target-based research provides with regard to the site of action as well as intellectual property, there has been a de-emphasis on natural product-based drug discovery programs over the last 20 years. The wealth of chemical diversity that has evolved with biological diversity is underrepresented in the commercial chemical library offerings, but needs to be expanded to strategically cover available chemical space and include drug-like compounds with improved pharmacologic, pharmacodynamic, and pharmacokinetic properties as compared to their current nitrogen-rich counterparts. The talk will center around the need for a renaissance in pharmacognosy. *The Need is Great and the Time is Now.*

### **Panel Discussion on Rare diseases**

A special panel discussion session on Rare Diseases was held and the speakers were Prof. Dutta, Dr. Subrata Dey, Prof. Netai Bhattacharya, Prof Shantanu Tripathi and Prof. Shrikanta Chattopadhyay. Rare diseases should be considered an important public health problem taking into consideration overall magnitude its complex clinical diagnostic and therapeutic perspective. The panellist discussed various issues clinical to covering diagnostic, molecular laboratory support needed, pharmaceutical and public health perspectives.

### **Presentation by Young researchers**

Young researchers from various disciplines including *Disease and Targets*, *Chemical Biology of Pathways*, *Natural Products and Drug Discovery* presented their current research in the form of poster. Around 70 posters from various disciplines were presented. The posters were evaluated by Prof. Anna Philpot, Dr. Glenn Butterfoss, Dr. P Shanmugam, Dr. K. T. Manisenthilkumar, Dr. Arindam Talukdar, Dr. R. Natarajan. **American Chemical Society (ACS) Chemical Biology** sponsored and awarded presenters of four best posters with a certificate and cash prize. The awardees were:

1. Sourav Chatterjee, CSIR-IICB
2. Tanima Benerjee, CSIT-IICB
3. Ashok Behara, NIPER-Kolkata
4. Piyush Chaturbedy, JNCASR Bangalore