BITS & BYTES Newsletter

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Contents

Message from the Chair

An eventful year passed in no time. I wanted to be part of science and technological development of the nation in the larger perspective, beyond my own area of science, beyond my own laboratory. Never even dreamed to get the opportunity to lead one of the best institute of our nation which has tremendously contributed not only in the area of drug development and disease biology, but also the entire field of biomedical research.

Over the past one year, we have achieved several milestones and created several new avenues. Our institute has filed new IND application for development of anti-thrombotic and preparing to file IND applications for a fracture healing compound and phytopharmaceutical lead for glucocorticoid induced osteoporosis. We also envisage to lead a PAN-CSIR cancer program towards affordable healthcare. Besides the existing focused research programs, a new research in aging biology has been initiated to align ourselves with areas of national significance. To strengthen inter-institutional activities, collaborations with CSIR labs, IITs, IISERs and other prestigious R&D organizations have been established. Our talented scientists, brilliant and hardworking students and staff are relentlessly contributing for the scientific and technological development of the nation, ignoring any shortcomings and difficulties. We also look forward to work with young ignited minds, in this line, recruitment process is ongoing to strengthen our existing workforce.

This newsletter reports a glimpse of our ongoing sincere effort. It is uniquely designed by our talented editorial board. I hope you all will enjoy it and inspire us to perform even better in coming days for the science, technology and mankind.

Kind regards,

Prof. Tapas K Kundu
PhD, DSc., FNASc., FASc., FNA, Sir J.C. Bose National Fellow
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Dear Readers,

During last one year, initiatives were undertaken to add new dimensions to our research activities. These include popular health talks, distinguished scientist lecture series and faculty colloquium. Apart from this, students initiated the Nobel symposium series by presenting original research findings of current year's Nobel laureates in Chemistry, Physiology & Medicine.

In this line, another initiative was also to start a new-kind of newsletter to give a glance into our "tryst with science" and to share our views besides just becoming lab rats. In this edition, we have tried to touch upon less discussed issues like; do we need a mentor throughout our scientific career, can we strike a balance between opportunities and difficult choices and what alternative careers exist in science? The readers will also get glimpse into new scientific explorations and emerging niche for drug discovery.

No doubt, science is our primary activity, but as a learned group of unabashed science lovers, we can celebrate and encourage the informality, irreverence, and inclusiveness in our work.

Scientific journeys are long; and we all undergo octaves of exciting and not so exciting phases in our career. Sometimes, sharing our views on one platform like the newsletter may pave way for others. Having said this, we are still open to more and better ideas for the upcoming issues of the newsletter.

I am hoping that this newsletter lays a template and brings in more scientific creativity from all of us, especially the students.

The role of the infinitely small in nature, is infinitely great. (Louis Pasteur)

Thanks to the editorial team and the contributors who helped us compile the newsletter in a short span of time.

(**Ritu Trivedi**)
Editor-in-Chief

Editorial Team

In Focus

Walk the Talk with Prof. Usha Vijayraghavan

Prof. Usha Vijayraghavan from Indian Institute of Science, Bengaluru visited CSIR-CDRI for the 16th Dr. B. Mukerji Memorial Lecture on July 16, 2019. She delivered a talk on "Codes for making of a rice flowering stem: Roles for evolutionary conserved transcription factors". She readily accepted "Walk the Talk" interview with Ritu Trivedi and Niti Kumar to share her views about different facets of science.

Why did you choose this particular field?

I feel much of the inspiration had come from middle school and high school to be precise. I studied in Delhi, CBSE board, Bal Bharti Air Force School, as my father was a Senior Air Force Officer in telecommunication engineering. At school, all my teachers, especially that of physics, chemistry and biology were very dedicated and equally inspiring. They were the ones who recognized that I had an inherent curiosity and ability to take challenges, so they gave me all the possible opportunities to fuel my growth. One opportunity that I still remember, and now cherish, was that I was asked to teach for two hours to my own class of students on two topics outside of standard text books. This is something unheard of, I am talking about 1976-1977. So I feel the fundamentals are built at high school, and abilities of students need to be recognized in every way possible and after that home environment should be enabling.

You have years of experience in research, what makes you love your work?

Regardless of what you choose in your career, it must be something you connect with and you are passionate about whether it is art, science, architecture, gardening or anything else. You must find it to be an exciting thing to do and every day you must think to build on whatever happened yesterday, this thought process is important. Problem solving and problem seeking cycle is something that keeps me motivated.

> "Regardless of what you choose in your career, it must be something you connect with and you are passionate about whether it is art, science, architecture, gardening or anything else"

When you look back into your career, what possibilities in education/ academic careers do you think that your younger self would have tried, had it been possible?

I feel potential to combine different quantitative sciences to understand fundamental questions in biology is something very feasible now, and one that I would have taken up, if I had the chance in my early studies. For example, if courses in geology, geophysics, geochemistry or planetary

sciences, for instance could be combined with evolution of life or if it was possible at that time to combine a set of engineering courses with a set of natural sciences, then I would have been interested in studying these combination also. So basically, it requires one to do your own homework of all possible range of options and keep pushing at it. In that sense, I would like to mention that the American undergraduate system is one that allows broader sampling at undergraduate level before studying a subject in greater depth and then researching a further narrower/ specific topic.

Tips you follow to keep yourself focused and motivated?

I think, I need tips from everybody rather, and indeed I try to learn from experiences around me. I think, one in general should keep on reminding oneself that everything that you build is on the foundation of things you do. So you must always go to work and try your best to go to the next step, regardless of the circumstances being on positive or negative trend.

> "I think, even peers could be your mentors"

At this stage of your career, do you need a mentor?

I think, even peers could be your mentors. They may not be directly working in your field of interest, but surely they recognize what you are doing is important and they promote and help to make it happen. So yes, mentorship is surely very valuable at every step.

Any unique characteristic that you have and you feel proud of?

I am a doer and have a positive attitude and that is why I don't get down, if the environment is not enabling. I always find a way.

Any happy moment you remember in your career which was happy or sad like while settling your lab?

At various stages of my career, there were different levels of excitement. I must say the thing that really shaped my career and scientific thinking was me getting into the graduate school at Caltech, USA. It is a top class institute with amazing atmosphere and one learns from the best teachers and highly accomplished scientists who are wonderful and astonishingly humble people absolutely no ego. I mean you might be sitting next to a Nobel laureate, having lunch with them discussing simple things like class exams as a teaching assistant and this would all be "job for the day". I think that exposure for me was just phenomenal. So overall, I can say, scientifically and intellectually one must make the best of the environment that you are in, learn and make the best of it.

What is the best advice to the next generation girls that you want to give?

Don't be put down by anything, if you have the talent for it, just do it. It's a two-way street, parents may not be positive or knowledgeable about a career in science, so they push their opinions on a career for their child. So basically, I think parents also should be counselled in order to make the girl-child independent and empowered for her

entire life by educating her and boosting her self-esteem and career. The mind-set that a daughter is taken care off by marrying her to a rich/ well-endowed family has to go. Even young women, regardless of her socio-economic status must have her self-esteem and her own individual personality. It's important to build a girl child as a person, who is strong enough to do whatever she wants to do. If she chooses art, sports, music, science etc., encourage her. A child or a person's individual worth should be valued and that is something a parent should look into or take care of.

> "There are many science based opportunities that are not lab associated like science communication, organizing and conducting innovative experimental camps, coming out with educational tools, bringing teachers into modern ways of teaching and science communication"

What can be done to make science more attractive, because after all, its employment that is the need of the hour. Today there are so many problems like age bar, competition etc. How can career in science be made more lucrative so that it interests the younger generation at an early age?

I feel other than parents there should be counsellors in school and various peer groups who should have first-hand information about science careers because they play an important role when choices are to be made by school students. Apart from talking about careers in science, grades/marks at the school level should not be given too much emphasis because there are late bloomers who take their own time to be excited about what they study and take time to discover things in life. One surely needs to increase the number of women as career scientists, team leaders, directors etc. Also nowadays, careers in science themselves are wide open. I would like to mention that Welcome Trust (UK) runs excellent exhibitions and these are great ways to bring contemporary arts and communication to "Science". So nowadays, one can dream to be a scientist who is in theatre because knowing science doesn't necessarily mean that you have to be the quintessential scientist doing only laboratory experiments, I mean, that is also science in public sphere is also great science. There are many science based opportunities that are not lab associated like science communication, organizing and conducting innovative experimental camps, coming out with educational tools, bringing teachers into modern ways of teaching and science communication, bringing science from international forum to local groups and taking local problems to an international scale. One can learn a lot from how different countries tackle problems and situations that could occur in India by being a science diplomat, science politician or a science socialist. Every social science person should do a little bit of science and every science person should do a little bit of social science. Many NGOs also need scientific approach, so careers in science are not at all limiting.

Switching role between a researcher and a mother

Dr. Rupali Sani Kumar (DST-WoS)

Science is a thought-provoking job which requires dedication and self-motivation in what you believe in. It's not a regular (9am to 5pm) job. Being a researcher, is a very demanding profession, irrespective of gender. However, things get tougher when woman becomes a 'mother', which entails additional responsibilities on her shoulders. In general, despite being super motivated and committed to work, most women take career breaks while stepping into motherhood. The real challenge comes when she has to make a decision whether to continue as a home-maker or get back to bench for research. Different socio-economic and emotional issues influence a mother's decision, whether she can handle stress and failures associated with research or in a broader sense maintain the work-life balance. When she decides to come back to research after a break, she is left with fewer opportunities to rejoin as a full time researcher. Fortunately, there are few programs like DST-WoS-A and DBT BioCARe that help them to restart their career as an independent researcher. As these project grants are time-bound, it is very challenging to get sufficient output, especially if you are working on a risky idea. Further, most of the times restriction also lies in choosing the host institute/city where their family is settled, which confines their scientific exploration avenues. With career break, challenges also lie in age limit for seeking a permanent research position. Research associate positions can only be availed till the age of 45, after which, the path is not clear.

> "My grown-up son thinks that I am a mouse doctor, his curios and innocent questions which invigorates my moral to strike back again with more vigour and not be deterred by failed experiments or administrative issues"

For me, when I go back home after a long and exhausting day at bench, a warm hug from my four-year-old son Siddharth, refreshes me. My grown-up son thinks that I am a mouse doctor, his curios and innocent questions invigorate my moral to strike back again with more vigour and not be deterred by failed experiments or administrative hassles.

So the bottom line is switching role as a mother and a researcher is exciting but it is overwhelming at the same time. Definitely, it's not impossible when you believe in yourself, love your work and have a supportive family.

Unconventional career path: A primer on patent practice

Dr. Sripathi R. Kulkarni

We all nurture dreams to establish great careers and strive hard for their fulfilment. When it comes to science, it is all about completion of post-graduate and doctoral studies from a reputed university or institute, followed by post-doctoral experience mostly in foreign universities. This again is substantiated by publishing good papers to obtain prestigious fellowships, awards, and secure a permanent position.

In today's scenario, the employment has become extremely competitive and fierce, wherein, recruiters evaluate applicants based on their research experience and contributions. However, with changing scientific landscape and employment requirements, the recruiters are also looking for candidates with additional qualifications. One of the less explored career path is patent practice. The plausible reasons of why patent practice is not very popular career path is due to certain myths associated with it for instance (a) lesser number of existing jobs, (b) it is the forte of the lawyers, (c) the jargon is hard to understand, (d) monotonous work profiles and (e) minimum appreciation for the contributions and limited scope of career growth.

> For any organization or company, Intellectual property (IP) is as vital as the heart in our body. Stronger the IP, longer and safer will be their standing in the markets with goodwill and brand image

For any organization or company, Intellectual Property (IP) is as vital as the heart in our body. Stronger the IP, longer and safer will be their standing in the markets with goodwill and brand image. This could be possible with the constant vigilance of the IP experts. When we hear or read about the damages and reliefs in a patent infringement related legal battle between the two companies running into billions of dollars, we understand the significance of the contributions made by a group of IP experts. We also have witnessed several multinational companies having lost their existence just because of set-backs in their IP portfolio management. Such news leads us to look into the possibilities of aversions from these catastrophies, which mostly point towards effective IP portfolio management strategies.

Patent practice comes as a potential alternative career. One needs to possess an artist's heart to excel in the domain of IP practice because drafting a patent is considered as an art and not science. Even in the lawyers dominated IP field, there is space for the scientists with legal knowledge. The patent attorneys, not being the subject-experts

Opportunities

have to rely heavily on the specialized group of people who have the deep knowledge about science and considerable awareness of the Patents Act and Rules. It is a well-known fact that the game of IP deals with huge revenues and the attorneys who mediate the deals can perform only by effective scientific support by the small group of para-legal experts who work hard in the background. Therefore, one could turn out to be an outlier and catch the attention of the distinguished recruiters with an additional degree, diploma or certification in IPRs having flair towards the legal matters. Moreover, if one enjoys playing with the words, sentences, and reading between the lines in identifying, establishing the inventions having the elements of novelty, inventive step and utility, then the purpose of being IP professional is served. This would fetch rewards, name and fame. Further, it requires the art and skill in splicing up the information into pieces and preparing a robust patent application with the solid scope of coverage of claims which might act as fortress and does not allow the persons having ordinary skill in the art to break it open. Furthermore, management of IP portfolio of an organization is a challenge in itself with demands on timelines, correspondence with the foreign IP offices, patent attorneys, examiners, administrators, policy-makers etc. Therefore, it would be a rewarding alternative career path to choose to be a patent and technology transfer specialist.

To help such enthusiasts in gaining awareness and acquiring certifications, the World Intellectual Property Organization, a UN body based in Geneva and several national patent offices offer assistance towards IP related awareness. Further, universities such as IGNOU, NALSAR, IITs, Central Universities in India offer specialized courses towards capacity building for the youth looking towards alternate career paths. A qualified science graduate can also look towards becoming a registered patent agent and start-off being a freelancing patent consultant or might consider finishing off the law degree and become a patent attorney for lucrative career option. Companies, KPOs, LPOs are looking forward for scientists with patent expertise.

Wishing good luck to all the enthusiasts who want to enter into this domain!

"Before you leave, we have to do a brain scan to see if you're taking any intellectual property with you."

Source: Google images

From the scientific bench

Short sleep and risk of cancer

Ms. Richa Soni and Dr. Jayanta Sarkar

Unhealthy lifestyle remains to be the major risk factor for cancer development. Sufficient sleep is incredibly important for good health of an individual throughout life. However, several aspects of modern lifestyle, including work schedule, travelling across time zone, stress (physical, emotional and psychological), pain, anxiety etc, deprive people from sound sleep at night. Since it is an essential component and foundation of healthy life, long term sleep deprivation may lead to chronic health complications such as diabetes, obesity, high blood pressure, heart disease, cancer etc. The association between sleep disorder and cancer is supported by emerging evidences.

During sleep, our body gets engaged in repairing and restoration of damaged cells and tissues and thereby helps improving physical and mental health by boosting the immune system. Several reports have shown an association between inadequate sleep over a few days and hormonal imbalance that might have an indirect effect in cancer development. A number of studies demonstrated increased incidence of breast cancer among women who work in night shift. This raised a novel theory of "Light at Night (LAN)" as an important cancer inducing factor. Modulation of melatonin hormone secretion is believed to be primarily responsible for LAN effect. Melatonin, which follows a nocturnal circadian rhythm and secreted mainly during night, activates anti-cancer immunosurveillance by increasing natural killer cell activity and induction of cytokine production (IL-2 and IL-6) to enhance helper T-cell response. Reduced melatonin secretion, due to lack of sleep over a few days, enhances estrogen and other circulatory reproductive hormones (androgen, progesterone etc) which in turn increase cancer risk. Other notable oncostatic effects of melatonin include inhibition of angiogenesis by (a) suppression of VEGF receptor 2 expression upon binding to

The association between sleep disorder and cancer is supported by emerging evidences.

- **"Light at Night" effect driven alteration of melatonin secretion**
- **Disrupted expression of clock genes that are associated with tumorigenesis**
- **Chronic inflammatory mediators dependent increased cancer risk during long-term sleep deprivation**
- **Insomnia induced physical and psychological stress which in turn promotes neoplastic progression in multiple ways.**

melatonin receptors (MT1 and MT2), (b) acting as endogenous free radical scavenger, (c) induction of apoptosis etc. Disruption of clock genes can also be a putative link between sleep and cancer. In a recent "Phenome-wide" study, researchers have shown a clear connection between polygenic link scores and multiple cancers. Clock genes can be defined as components of the circadian clock, whose protein products play essential role in regulation of circadian rhythms. A large number of studies have demonstrated dysregulation of clock gene expression, in addition to other canonical risk factors, as common genetic basis in several cancers including breast cancer, prostate cancer, chronic myeloid leukemia (CML) etc. Examples of some important clock genes, which influence tumorigenesis, include CLOCK, PER1, PER2, PER3, CRY2, NPAS2, RORC etc.

Heightened inflammation due to lack of sleep is another crucial risk factor for cancer. Research has indicated that even one night insufficient sleep can activate enough pro-inflammatory process. Induction of NF-κB, due to poor sleep, is presumed to mediate a spike in inflammation in our body. Additionally, an enhanced circulating level of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), has been observed in experimental sleep deprivation cases. Chronic inflammation, because of long-term sleep deprivation, facilitates neoplastic process by causing cellular damage and genetic alterations.

The complex relationship between stress and insomnia works in both ways. While stressful life events are responsible for sleeping disorder, lack of sleep can also cause stress on our body and mind. Multiple theories have been proposed to explain a correlation between stress and cancer. Chronic stress causes hormonal imbalance in our body which in turn impairs various important body functions such as digestion, immune suppression and thereby contribute to development of cancer. Alternatively, long term stress, due to sleep deprivation, induces chronic inflammation that may facilitate oncogenic process.

Most importantly, stress pushes individuals to follow unhealthy practices, like over eating, smoking and drinking. All of which are established risk factors for cancer development.

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Worms can't be humans; then why study them to understand human diseases?

Dr. Aamir Nazir

Obtaining the mechanistic understanding of disease processes at fundamental level is important for any effort towards designing an effective cure. The inherent methodological limitations that exist in the process of carrying out such studies in humans, warrant use of effective models for deciphering the cues behind the cause and progression of diseases that challenge humankind. Non-rodent models such as *Caenorhabditis elegans* (soil nematode), *Drosophila melanogaster* (fruit fly) and *Danio rerio* (zebra fish) are considered to be precious models because of their genetic relevance, ease of genetic manipulation and in-cumbersome laboratory rearing. Of late, these models have been utilized towards generating a wealth of data from pharmacological, genetics, proteomics, behavioral, developmental and toxicological studies, thus raising a question about the relevance of such data vis-à-vis human functioning. The diversity in phenotype, functioning and even longevity is such that questions arise about how genetic or pharmacologic target from one small organism could act in a similar fashion within higher models, more specifically, humans. Researchers working within the field of model organism biology, draw inspiration from multiple success stories that have proved the utility of genetic conservation and uniformity of certain functions across taxa. For starters, the idea of genome sequencing used to appear as a humongous task, but *C. elegans* was the first multi-cellular organism to have its genome sequenced which encouraged and paved way for multiple other sequencing projects that were concluded successfully. Talking about human diseases, there was a time, when nothing was known about genetic mechanism of Alzheimer's disease (AD) in humans; research employing *C. elegans* identified a gene called sel-12 that was exhibiting association with amyloid beta plaque formation- a hallmark of AD. Subsequent research proved that the human orthologue of sel-12, called Presenilin-1 (PS-1) was acting similarly in humans. It was not merely the homology of gene sequence, complementation studies, wherein *C. elegans* sel-12 was mutated and replaced with human PS-1, restored the functions of lost sel-12, thus revealing conservation of function, which means a lot in terms of employing smaller model systems for understanding human processes. Similarly, the genes involved in the process of apoptosis were first of all identified in *C. elegans* and later validated in higher mammalian systems as well. Not only was each member of apoptosis

> Small models like *C. elegans* offer immense advantages as these nematodes offer a whole organismal environment, with intact metabolism and yet presenting with simple anatomy which can be handled with ease

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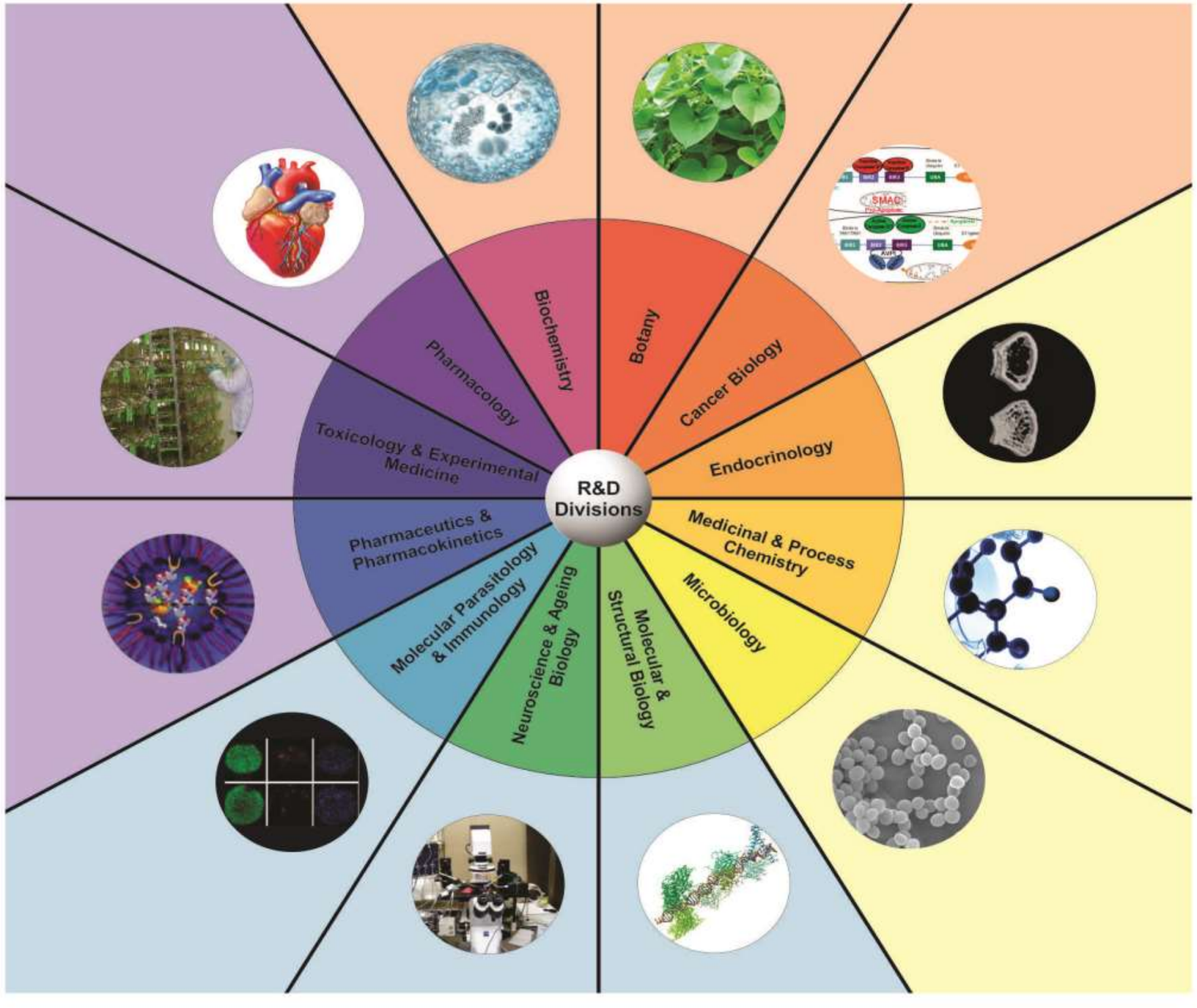
Reorganization, strengthening, expansion and creation of new R&D structure to augment 'fundamental science driven innovative drug research'

Sophisticated Analytical Instrument Facility

National Repository of Organic Compound

National Laboratory Animal Facility

Knowledge Resource Centre



GLP Test Facility for Acute Toxicity & Safety Pharmacology

Structural Biology Facility

Clinical Trial Facility

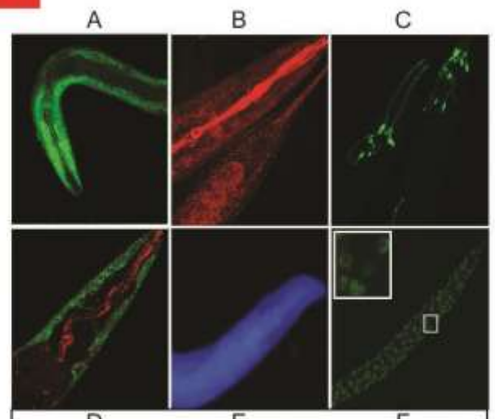
Computational Biology and Bioinformatics

machinery found to function similarly in humans, but the entire process was replicated in humans. The knowledge of the process of apoptosis later brought breakthrough changes to the way critical human diseases as cancers were treated.

While studying potential pharmacological agents for the effect they would have on humans, researchers have option of employing simpler tools like *in vitro* cell based systems, or they can carry out studies employing mammalian systems as rodents. A major limitation with *in vitro* systems is the lack of "whole organismal environment" thus missing "metabolism" as the potential drug would encounter if recommended for human use. The disadvantage of carrying our certain studies in mammalian systems is the complexity of the models and related functions. Small models like *C. elegans* offer immense advantages as these nematodes offer a whole organismal environment, with intact metabolism and yet presenting with simple anatomy which can be handled with ease. The metabolic outcome is very relevant as the cytochrome P450 genes of *C. elegans* possess significant homology with that of their human counterparts, thus contributing to similar metabolic outcome.

In addition to the genetic and functional similarity, the *C. elegans* model also provides with technical ease of carrying out multiple biological studies; e.g. in worms, RNAi induced gene silencing can be carried out via simple feeding of worms with genetically engineered bacteria. An RNAi library of approximately 17,000 bacterial clones is available, which aids in carrying out whole-genome or systematic RNAi screens with terrific time efficiency and sensitivity.

There however, are certain limitations to use of *C. elegans* in studying human functions; e.g. the lack



Transgenic *C. elegans* expressing various reporter genes/fluorophores: (A) *C. elegans* expressing "human" alpha synuclein tagged with YFP, (B) *C. elegans* stained with lipid specific dye Nile Red, (C) Transgenic *C. elegans* strain expressing GFP in subset of neurons, (D) *C. elegans* expressing YFP stained with Mirotracker Red, (E) *C. elegans* stained with Thioflavin, (F) Transgenic *C. elegans* expressing FOXO Transcription factor Daf-16 tagged with GFP, Specific Cytoplasmic presence of the protein is highlighted in the box.

of fully developed organs and organ systems keeps worms devoid of certain critical functions which cannot be studied or compared with humans. For some disease conditions, the low homology of related disease genes poses a challenge and hence cannot be studied with high confidence. However, the advantages far outnumber the limitations as *C. elegans* offers an excellent screening tool thus eliminating need of testing thousands of chemicals or genes in complex mammalian systems. It efficiently helps in reducing the junk and carrying out focused validation studies in with the class of chemicals/genes that has higher likelihood of tending a positive outcome. This reduces the burden of time as well as expenditure while also providing mechanistic cues to key functional outcomes.

Rare genetic disorders: A goldmine for drug discovery

Prof. Alok Bhattacharya
Ashoka University, Haryana
World Without GNE Myopathy, New Delhi

Neuromuscular disorders cause defect in peripheral nervous system and or muscles. Generally, these defects lead to impairment of voluntary movement and can cause disability ranging from inability to walk properly to complete paralysis. These are normally progressive, that is, disability becomes more pronounced with age if treatments are not available. Unfortunately for most Neuromuscular diseases, currently there are no treatments. It is becoming clear over last 2-3 decades that most of these disorders have genetic origin, partly due to development of DNA sequencing technologies and platforms. In the year 1987 only one gene (dystrophin) was known to be involved in a neuromuscular disease. Currently hundreds of genes have been identified and it is expected that more disease associated genes will be found thanks to enormous amount of whole genome sequence data that are becoming available. Not all patients of neuromuscular disorders inherit the mutations from their parents. Increasing number of *de novo* mutations are being identified. Different types of mutations, such as single nucleotide polymorphisms, small insertion and deletion, large insertion, duplication and deletion and repeat expansion have been found to be associated with different diseases. Moreover, disease associated genes have been found in both mitochondrial and nuclear genome as well as are known to participate in a number of different pathways. Some of the common pathways include different aspects of cytoskeletal function, signalling, organelle function and vesicular transport system. In most cases it is not clear how the mutations in the respective genes affect neural and or muscle functions. There is very little information available about mechanisms of genotype-phenotype relationship in these diseases and this lacuna in our understanding prevents the development of therapy for these diseases. For example, only muscles get affected in patients with mutations in a lysosomal processing gene. Unfortunately, there are not many researchers working on these diseases that offer exciting scientific challenge as well as a possibility of finding a therapy for incurable diseases. We believe that all stakeholders including patient bodies should come together to embark on the mission to find cures for these thousands of incurable diseases.

Guest Speakers

Re-engineering healthcare regulation in India using Pharmacovigilance

Soumya Sikder

Entrepreneur | Agile Evangelist | Technology Enthusiast

Pharmacovigilance (PV) as defined by the World Health Organization is "The science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem". Advances in the scientific field have revolutionized the field of drug discovery and pharmaceuticals, leading to the discovery of medicines designed to cure, prevent or treat diseases. However, there are also risks associated with the use of drugs, particularly adverse drug reactions (ADRs) which can cause serious harm to patients. Thus, for safety medication ADRs monitoring is required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. Pharmacovigilance (PV) encompasses a plethora of activities such as detection, assessment, understanding and prevention of ADRs. The emerging trend in PV is to link premarketing data with human safety information observed in the post-marketing phase. This necessitates an utmost requirement for effective regulations of the drug approval process and conscious pre and post approval vigilance of its undesired effects, especially in India. PV actively helps in the well-being of the patients by optimally or ideally managing the drug usage. A fit and healthy society is a collective responsibility of industry, drug regulators, clinicians and other healthcare professionals to enhance their contribution to public health.

CDRI Award for Excellence in Drug Research

Probing mood (structure) swings of therapeutic non-canonical nucleic acid motifs

Dr. Seergazhi G. Srivatsan

Indian Institute of Science Education and Research, Pune

Numerous biophysical tools have provided efficient systems to study nucleic acids. However, our current understanding on how nucleic acid structure complements its function, particularly in cellular environment, is limited. This general limitation is largely due to the lack of probes that can be used in both cell-free and cellular assays, and in more than one biophysical technique. Hence, correlating the information obtained under equilibrium conditions, in solid state and in cells becomes very difficult using uniquely-labeled oligonucleotide sequences. In this context, moving away from the tradition approach of "one label one technique" we adopted an innovative approach to investigate the nucleic acid structure and function in cell-free and cellular environments by using conformation-sensitive multifunctional nucleoside analog probes. Based on this strategy, we have developed nucleoside analogs equipped with two or more labels (eg., fluorophore, NMR isotope label and X-ray crystallography phasing atom), which serve as common probes for analyzing nucleic acid motifs simultaneously by using a combination of fluorescence, NMR and X-ray crystallography techniques. This platform has provided greater insights into the structure and drug binding abilities of therapeutically very important nucleic acid targets such as bacterial ribosomal decoding site RNA, hepatitis C IRES RNA motif and oncogenic G-quadruplex-forming DNA and RNA sequences.

Targeting redox heterogeneity to counteract drug tolerance in replicating *Mycobacterium tuberculosis*

Dr. Amit Singh

Indian Institute of Science, Bengaluru

The capacity of *Mycobacterium tuberculosis* (*Mtb*) to tolerate multiple antibiotics represents a major problem in tuberculosis (TB) management. Heterogeneity in *Mtb* populations is one of the factors that drives antibiotic tolerance during infection. However, the mechanisms underpinning this variation in bacterial populations remain poorly understood. Here, we show that phagosomal acidification alters redox physiology of *Mtb* to generate a subpopulation of replicating bacteria displaying drug tolerance during infection. RNA sequencing of this redox-altered population revealed the involvement of iron-sulfur (Fe-S) cluster biogenesis, hydrogen sulfide (H_2S) gas, and drug efflux pumps in antibiotic tolerance. The fraction of the pH and redox-dependent tolerant population significantly increases when *Mtb* infects macrophages with actively replicating human immunodeficiency virus type-1 (HIV-1), suggesting that it could contribute to high rates of TB therapy failure during HIV-TB co-infection. Pharmacological inhibition of phagosomal acidification by the antimalarial drug chloroquine (CQ) eradicated drug-tolerant *Mtb*, ameliorated lung pathology, and reduced post-chemotherapeutic relapse *in vivo*. The pharmacological profile of CQ (C_{max} and AUC_{last}) exhibited no significant drug-drug interaction when co-administered with first line anti-TB drugs in mice. Our data establish a link between phagosomal pH, redox metabolism and drug tolerance in replicating *Mtb* and proposed repositioning of CQ to shorten TB therapy and achieve a relapse-free cure.

CDRI Award for Excellence in Drug Research

Autoimmunities and metabolic disorders in a pathogenic continuum: Revealing shared therapeutic targets

Dr. Dipyaman Ganguly,
CSIR-Indian Institute of Chemical Biology, Kolkata

Plasmacytoid dendritic cells (pDC) are major producers of type I interferons (IFN-I) in response to recognition of pathogen-derived nucleic acid molecules by endosomal toll-like receptors (TLRs). Involvement of pDC-derived IFN-I in a number of autoimmune diseases is also established. Recognition of self nucleic acids leads to induction of IFN-I from pDCs and drives innate initiation of inflammation in Systemic Lupus Erythematosus (SLE), Psoriasis and a number of other autoimmune contexts. Interestingly, we also identified role of pDC-derived IFN-I in obesity associated metaflammation and insulin resistance. We found that there is recruitment of pDCs in obese adipose tissue and TLR9 activation in recruited PDC induces IFN-I that in turn drives *in situ* macrophage polarization and adipose tissue insulin resistance. Of note, systemic autoimmune contexts are often associated with insulin resistance. We actually could link systemic IFN-I response with susceptibility to insulin resistance in an autoimmune context. In rodent models as well as in patients with other components of metabolic disorders TLR9 activation and IFN-I have been shown to affect disease outcomes. Thus induction of pDC-derived IFN-I seems to be a shared initiator event in discreet clinical contexts, leading to a model where these clinical contexts are grouped together as a syndrome of systemic IFN-I response. Important cues on this putative syndromic description linking systemic autoimmunities and metabolic disorders also came from our experiments on effect of IFN-I on gut microbiota in preclinical models. On the other hand we were able to link a prominent serine hydrolase ABHD6 and the endocannabinoid pathway, originally implicated in metabolic diseases, to have a critical role in a subset of patients with the systemic autoimmunity SLE. Thus diverse data generated in our lab supports a syndromic description of these different clinical contexts, from systemic autoimmune diseases to metabolic derangements, which also enabled identification of important shared biomarkers as well as novel therapeutic targets.

Multipronged therapeutic strategies for Alzheimer's disease

Dr. T. Govindaraju
Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru

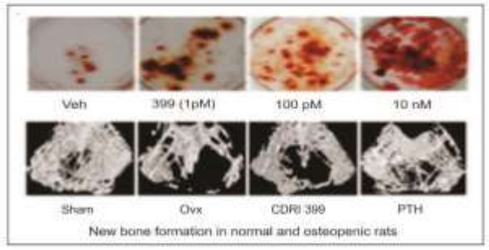
Alzheimer's disease (AD) is a common form of dementia and multifactorial neurological disorder. There are no approved diagnosis or disease modifying therapies for AD. Current treatments are only symptomatic and temporary, and do not directly target the mechanisms underlying the disease pathogenesis. The production, accumulation and aggregation of proteins in the human brain are considered as one of the hallmarks of disease. Oxidative stress, neuroinflammation, mitochondrial dysfunction and microglia contribute significantly to the disease pathogenesis. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the major sources of oxidative stress in cells, which damage proteins, lipids, and DNA. In this context, we have adopted multipronged strategies to develop therapeutic agents to modulate multifaceted toxicity.

Newsmaker

CSIR Technology Award for Innovation 2019

Technology of Novel Osteo-inductive Agent CDRI S008-0399

CDRI has identified a synthetic small-molecule (S008-0399) that promotes osteoblast differentiation and mineralization at dose as low as one picomolar concentration. It also increases bone mineral density (BMD), mineral apposition rate (MAR) and bone formation rate (BFR) in osteopenic rat model. This bone inducing agent improves bone quality and restores trabecular micro-architecture in ovariectomized osteopenic rats. **The molecule has been licensed to M/s. OrthoRegenics Pvt. Ltd., Hyderabad**. The technology has been transferred to M/s. OrthoRegenics for fabrication of orthopaedic implants in combination with biodegradable bone inducing materials to enhance healing at the fracture site. This is a cost effective biodegradable bone implants as compared to metallic bone implants. There will be no need for re-surgery to remove the implants or some other infection, wear and tear induced debris, as in case of non-degradable implants.



New bone formation in normal and osteopenic rats

The Hon'ble President of India, Shri Ram Nath Kovind presenting the 'CSIR Technology Award for Innovation - 2019' to Prof. Tapas K. Kundu, Director, CSIR-CDRI, Dr. Atul Goel, Senior Principal Scientist, and Dr. Divya Singh, Principal Scientist during CSIR Foundation Day Celebrations at New Delhi on 26 September 2019. The Hon'ble Minister for Science & Technology and Earth Sciences and Health & Family Welfare, Dr. Harsh Vardhan graced the occasion.

NASI – Reliance Industries Platinum Jubilee Award 2019

Dr. Atul Goel

Dr. Atul Goel has been awarded prestigious NASI-Reliance Industries Platinum Jubilee Award-2019 for his significant contributions for application oriented innovations in the area of developing drugs and diagnostics. Dr. Goel has licensed and transferred technology of compound S008-399 to Hyderabad-based company for developing biodegradable medicated orthobiologicals (bone implants) for faster healing of fractures. Dr. Goel and his team are trying to develop diagnostics for cancer and neurodegenerative disorders. He has discovered and reported 'FIRST' dual colorimetric-ratiometric fluorescent probe NAP-3 for selective and direct visualization of endogenous Labile Iron (III) pools in *C. elegans* model. The probe may be useful as theranostics (a new field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests) for Thalassemia patients. Very recently, they have observed that there is an excessive accumulation of Lipid Droplets (LDs) in Third Stage Human Cervical Cancer Tissues taken from patients. They discovered yellow Fluorescent Probes FLUN-550 and FLUN-552 for imaging and quantification of these LDs, which will help in early diagnosis.

Dr. P. Sheel Memorial (Young Women Scientist) Lecture Award 2019

Dr. Ritu Trivedi

Dr. Ritu Trivedi has been selected for this award for her outstanding research in the area of metabolic bone disorders specifically on osteoporosis and osteoarthritis. She has worked on several molecules derived from either natural resources or chemically synthesized for improvement of bone health. She has worked on the standardized fraction of *Dalbergia sissoo* that acts as an osteogenic agent that has led to translational benefits as a rapid fracture healing agent as well as is valuable in primary osteoporosis. Further, her work on the nano-formulation of *Spinacea oleracea* has led to a product for osteoarthritis. **These technologies have been licensed to Pharmanza Herbals Pvt. Ltd. for post-menopausal osteoporosis and osteoarthritis and both are in the market by the name Reunion® and Joint Fresh®, respectively.** In addition to translational work, Dr. Trivedi's lab has established involvement of microRNA's in bone formation and has shown how miRNA exerts skeletal anabolic effects epigenetically during weaning (bone formation period) by suppressing Hdac1. Other interesting questions addressed by her lab are obesity induced bone loss, growth-plate (longitudinal growth) mechanisms and pharmacological targeting in bone using specific delivery systems.

CSIR-Young Scientist Award (Biological Sciences)

Dr. Bidyut Purkait

Dr. Bidyut Purkait has made significant contributions in the field of drug resistance in visceral leishmaniasis (VL) or kala-azar (neglected fatal tropical disease) caused by *Leishmania donovani*. He decoded the mechanism of amphotericin B resistance in this clinical isolates of *Leishmania donovani* and demonstrated the synergistic involvement of membrane composition (membrane ergosterol is replaced by a modified sterol), ABC transporter (MDR1 involving AmB efflux) and thiol metabolic pathway (involving in AmB induced ROS detoxification) in conferring AmB resistance. In connection with this resistance mechanism, he has explored that at molecular level histone deacetrylase enzyme, Silent Information Regulator 2 (Sir2) regulates amphotericin B resistance mechanism by controlling drug efflux mechanism (MDR1), AmB induced ROS concentration and apoptosis-like phenomena and also proposed Sir2 as a new resistance marker for visceral leishmaniasis. He also explored DDT resistance mechanism in the sand fly, *P. argentipes* (vector of VL in India) and showed that mutations in voltage-gated sodium channel (*Vgsc)* is a primary mechanism underlying DDT resistance in *P. argentipes*. In search for the new drug targets, Dr. Purkait is currently working on both the VL and Lymphatic Filariasis (LF) and started characterizing RNA editing pathway, a unique post-transcriptional modification process of *L. donovani* and trehalose biosynthetic pathway, an important sugar metabolizing pathway controlling female reproduction in LF causing *Brugia malayi*.

TATA Innovation Fellowship 2018-19

Dr. Prabhat Ranjan Mishra

Dr. Prabhat Ranjan Mishra has been conferred with prestigious TATA innovation fellowship which is a competitive scheme instituted by the Department of Biotechnology, Ministry of Science and Technology, Govt. of India. This award recognizes scientists with outstanding track record in biological sciences/ biotechnology and deep commitment to find innovative solutions to major problem in healthcare. His research interest includes nanomaterial based targeted delivery to tissue of interest especially for infectious diseases and endocrine disorders. His lab is involved in development of layer-by-layer technology, Nanocrystal technology, Solid lipid nanoparticles and Ligand/receptor based targeting. His main focus is on (a) development of strategy for cost-saving, patient-friendly and evidence-based products for industry; and (b) bringing good to patient suffering from bone health, cancer and parasitic diseases. This award has been conferred for outstanding contribution in the area of translational research based on controlled and targeted drug delivery technologies for enhanced therapeutic efficacy.

Newsmaker

Lecture awards of Indian Council of Medical Research (ICMR) for their significant contributions in Biomedical sciences

Kshanika Oration Award

Dr. Anuradha Dube

Dr. Anuradha Dube, INSA Senior/Emeritus Scientist & Sir JC Bose National Fellow, Division of Molecular Parasitology and Immunology is selected for this award. Dr Anuradha has made significant contributions in the area of immunobiology of visceral leishmaniasis, a fatal neglected tropical disease if not treated properly. Using the immuno-proteomic approach, she has identified Leishmania parasite proteins/molecules with Th1-stimulatory property as potential vaccine targets. Presently, she is working in the direction of designing polyvalent synthetic and recombinant chimeric vaccines that include promiscuous T-cell epitopes derived from the potential Th1 stimulatory proteins of *Leishmania* as effective interventions (prophylactic as well as therapeutic) to control the disease in endemic areas. With comprehensive as well as differential proteomic analysis of *Leishmania* clinical isolates, she identified some key biomarker proteins which may have crucial biological functions in *Leishmania* pathogenesis and may serve as new targets for therapeutic interventions against the disease.

Shakuntala Amir Chand Prize

Dr. Satish Mishra

The Shakuntala Amir Chand Prize is given by Indian Council of Medical Research, Government of India and Dr. Satish Mishra, Senior Scientist, Division of Molecular Parasitology and Immunology has been selected for this prize for the year 2018 for his significant scientific contributions in the field of biomedical sciences.

Dr. Mishra has contributed towards understanding of molecular mechanisms that underlie *Plasmodium* liver stage biology. This includes target-based drug discovery and development of a malaria vaccine using state-of-the-art technologies for inducing multi-stage immunity. The vaccine has been developed in a mouse model by knocking out a gene required by the parasite to complete development in the liver. This gives more time to the host immune system which can then prepare itself to fight against future infections.

He has also been instrumental in the identification of host factors that influence the parasite's development in host liver which would have therapeutic value aimed at eliminating malaria liver stage forms.