Proteomics Society , India (PSI)

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From the Editors

Dear Members,

The highlights of the current news letter include information about new conferences and workshops being organized by PSI later this year and a user-friendly narrative on protein-protein interaction networks by Dr. Padma Nanaware. Furthermore an informative article by Dr. Bimal Mohanty related to application of proteomics to the field of Fisheries takes us in the mystical world of underwater creatures.

Two important events are lined up for 2015 that will be a 'knowledge feast' for young minds. Please mark the dates for the 7th Annual Meeting of the PSI to be held at VIT University from Dec 3rd to Dec 6th 2015 at Vellore. In addition a Targeted Proteomics Meeting is being organized at IIT Mumbai from December 10th to 14th 2015. Both these meetings will have educational sessions with workshops students to get started in the exciting world of proteomics.

Most imprtantly Dr. Avik Basu's article in this newsletter marks the beginning of the ***"Student's Corner".*** *We invite contributions from students and request our faculty colleagues to encourage them to write and contribute articles for the News Letter of PSI.*

We look forward to hearing from you.

With Best Wishes

Editors

PS: Please send your contributions for the News Letter to abhijit.chakrabarti@saha.ac.in

From the President, PSI

Dear Members,

Proteomics has provided insight into the protein components of a variety of biological systems. The technologies routinely used today to separate the complex mixture depend on the properties of the proteins such as their charge and molecular weight. The identity of the protein is then obtained by mass spectrometry using a top down or bottom up approach. It is apparent that detection of a separated protein will depend on its amounts in the biological mixture, while resolution depends on whether they are membrane proteins, cytosolic proteins, associated with other proteins, the post translational modifications, folding etc. Global analysis without pre fractionation will provide a limited protein profile due the aforesaid complexities. A holistic picture of the protein composition can be obtained with defined pre-fractionation and enrichment dependent on the properties of the proteins followed by piecing together the information obtained from each of the fractionation methods.

The forthcoming 7th Annual meeting of the PSI, at Vellore Institute of Technology, Vellore (3rd to 6th Dec 2015) is focusing on the technologies which are relevant to pre-fractionation for proteomics in addition to other interesting themes such as biomarkers, post translational modifications, structural and functional proteomics and applications of proteomics for Biopharma applications.

IIT Bombay is organizing a workshop and International Symposium on "Targeted Proteomics" during 10th -14th Dec 2015. This will focus on the

quantitation and analysis of proteins and their modifications for clinical analysis and development of bioassays. An education day for students and teachers is organized on 10th Dec 2015.

PSI members must take advantage of attending the conferences to learn about the latest in these areas from the experts in the field from India and abroad.

The strength of the Society depends on its members and their participation in the various activities. We would be very happy to accept suggestions for Proteomics related meetings/workshops/mini conferences in your host institutes. PSI would support you with expertise and provide some nominal financial assistance. Do contact the Secretary, Dr Shantanu Sengupta (shantanus@igib.res.in) or me with your ideas.

We look forward to meeting you at the meetings in Vellore and Mumbai.

With Best Wishes
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Proteomic Society, India (PSI)

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Integrative Approaches for Discovery of Protein-Protein Interactions

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Biological phenotypes are the result of the interactions of thousands of macromolecules that are the part of several inter-related pathways and the interacting functional networks. Physical and functional interactions among the various players and the network of communications between them regulate these various processes and any aberration may result in disease. Direct protein-protein interactions (PPI) are central to such integrated functioning as they provide the crucial link between divergent networks such as the signaling networks, transcriptional networks etc which modulate cellular behavior providing elasticity to adapt to various stress and environmental perturbations. For example, it is clear that many oncogenes, tumor suppressors and other cell cycle related proteins act as crucial hubs in functional networks made of different circuits. These hubs are known to play a pivotal role in maintaining the integrity of the system as compared to non-hub proteins [1, 2]. Due to the importance of PPI, many high throughput approaches have been developed to screen and identify them as one on one interaction's or as a part of complexes. Recent high throughput experiments like protein-protein interaction assays, global mRNA expression analysis, systematic protein localization studies, structural studies by the medium of consortium and integration of mathematics, computer science and bioinformatics has provided a platform for a more comprehensive knowledge to test how a cellular system may work.

Biological databases play a critical role to make annotation and decision making about biological events however gaining highest confidence from one database seems very difficult and may lead us to omit major biological events. Here is the great need for merging related databases and ranking them. Wrong inclusion of databases in merging process may also lead to wrong conclusions. Available databases for Protein–Protein Interaction are MIPS [3], HPRD [4], BioGrid [5], BIND [6], IntAct [7] etc (Table 1). To achieve highest confidence database should be highly curated and must accompany maximum no of proteins/interactions keeping synonyms/duplicates aside. These databases integrate knowledge from different approaches like genomic context, high

throughput experiments, co-expression systems and known experimental knowledge to build up the PPI network.

Database Source	Number of Proteins Identified
Human Proteome Map (http://www.humanproteomemap.org/)	30,057
Plasma Proteome Database (PPD) (http://www.plasmaproteomedatabase.org/)	10,546
DIP (http://dip.doe-mbi.ucla.edu/dip/Stat.cgi)	27,599
MINT(http://mint.bio.uniroma2.it/mint/Welcome.do)	35,553
HPRD (http://www.hprd.org/)	30,047
BIND (http://bind.ca)	31,423

Table1: Databases Sources for Protein-Protein Interactions

Approaches- Predicting Protein-Protein Interactions (PPI)

PPI may either occur through a single interface or multiple interfaces at different spatio-time to result in different phenotypes as in cases of complex formation machinery like translational machinery inside the cellular system.

Domain-Domain interactions (DDI) are known to play the critical role in protein-protein interactions [8] and protein rich in domains are known to be the critical hub protein. Hence, understanding DDI helps us to build the global view of the protein-protein interactions. Databases like DOMINE provides the information of all experimentally known and predicted interactions extracted from PDB and different computational approaches like Pfam [9]. **DOMINO** database provides the information of domain-peptide interactions and helps in predicting the probable domains or sites involved in interactions [10].

Short Linear Motif (SLiM)- Proteome peptide scanning and whole interactome scanning experiments (WISE) which rely on short sequences within the proteins (SLiM) are widely and most promising approach to identify PPI [11]. SLiM can be part of structured or unstructured regions of 3-10 residues within the protein which assigns function to proteins and hence it makes difficult to identify such regions for accurately predicting protein-protein interactions. These motifs have been used to identify novel substrates of kinases harboring SH2-SH3 domains and proteins like 14-3-3 which recognize such short sequences in phosphorylated proteins [12]. These 3-10 amino acids are generally conserved, present on the interface contributing to maximum binding energy of interaction with $\Delta\Delta G \geq 2$kcal/mol. These residues when mutated result in either rapid dissociation of the complex or prevent stable association and are defined as hot spot sites

[13, 14]. SLiMs of this type can be found by searching for motifs which are shared between proteins with a common attribute such as biological function, subcellular location or a common interaction partner. Algorithms available to identify these regions are SLiMDisc [15], Interactions of Eukaryotic Linear Motif (iELM) [16], Scansite 2.0 [17], DILIMOT [18].

Ongoing studies at Protein Interactome Lab for Structural and Functional Biology, ACTREC believes that judicious combination of functionally important short linear sequences with filters based on structure and other biological properties can help in the identification of truly positive interactions in proteome wide screening. PNSAS -'Prediction of Natural Substrates from Artificial Substrate of Proteases', an algorithm developed predicts natural substrates of endoproteases using such principles [19]. In addition, they also demonstrated that a 13 residue peptide based on the sequence of apomyoglobin can inhibit interaction of the full length protein with the proteasome [20]. Working towards my Ph.D. thesis with the same group, we used a structural bioinformatics method to predict novel interacting partners of a 26S Proteasomal chaperone and an oncopotein-Gankyrin, which is involved in multiple interactions. 'EEVD' sequence present in the solvent accessible region was found to be the hot spot site among gankyrin interacting proteins. In particular, we substantiate that short linear motif at protein-protein interfaces can be potentially used to identify novel functionally relevant protein complexes formed by key hub proteins. Further, we provide evidence for the potential use of protein interfaces as drug targets to inhibit protein-protein interaction mediated by gankyrin [21]. Capitalizing on the fact that PDZ domains interact with C-terminal motifs, novel interacting partners of a PDZ domain containing 19S proteasome subunit PSMD9 were identified using SLiMs which were C-terminal peptide sequences, representative of C-termini of a group of proteins [22]. PSMD9 interaction with hnRNPA1 through C-termini was found to enhance IκBα degradation and NF-κB activation [23].

Hot spot residues- Out of 3-10 residues not all but only 2-3 residues sometimes contribute to the maximum binding energy. Interactions are often governed by hot spot residues present at the interface rather than the entire site. Identification of these hot spot residues further is a challenging process and few computational wizards like iPRED [24], CPORT predicts these residues depending upon the propensity of the occurrence of particular residues in the interface region [25]. The interface of hub are enriched in residues like Arginine (Arg), Tyrosine (Tyr), Histidine (His) and Methionine (Met) which facilitates different types of interactions. The enrichment of these residues at the hot spots enhances the ability of the protein to form multiple interactions.

The above mentioned efforts which are also depicted in Figure 1 has helped us to map many if not all interactions which are regulated by physiological demands and are time dependent. Motif/Residue level details give us better understanding of the interactions so as to screen small molecular inhibitors or peptide mimetics further making PPI druggable and therapeutically vulnerable targets. Further biological databases are multi dimensional, process oriented and

complex. Repurposing of these databases needs a lot of work in the background starting from their merging, text mining, literature validation, functional validation, logical curation, assembling, and selection.

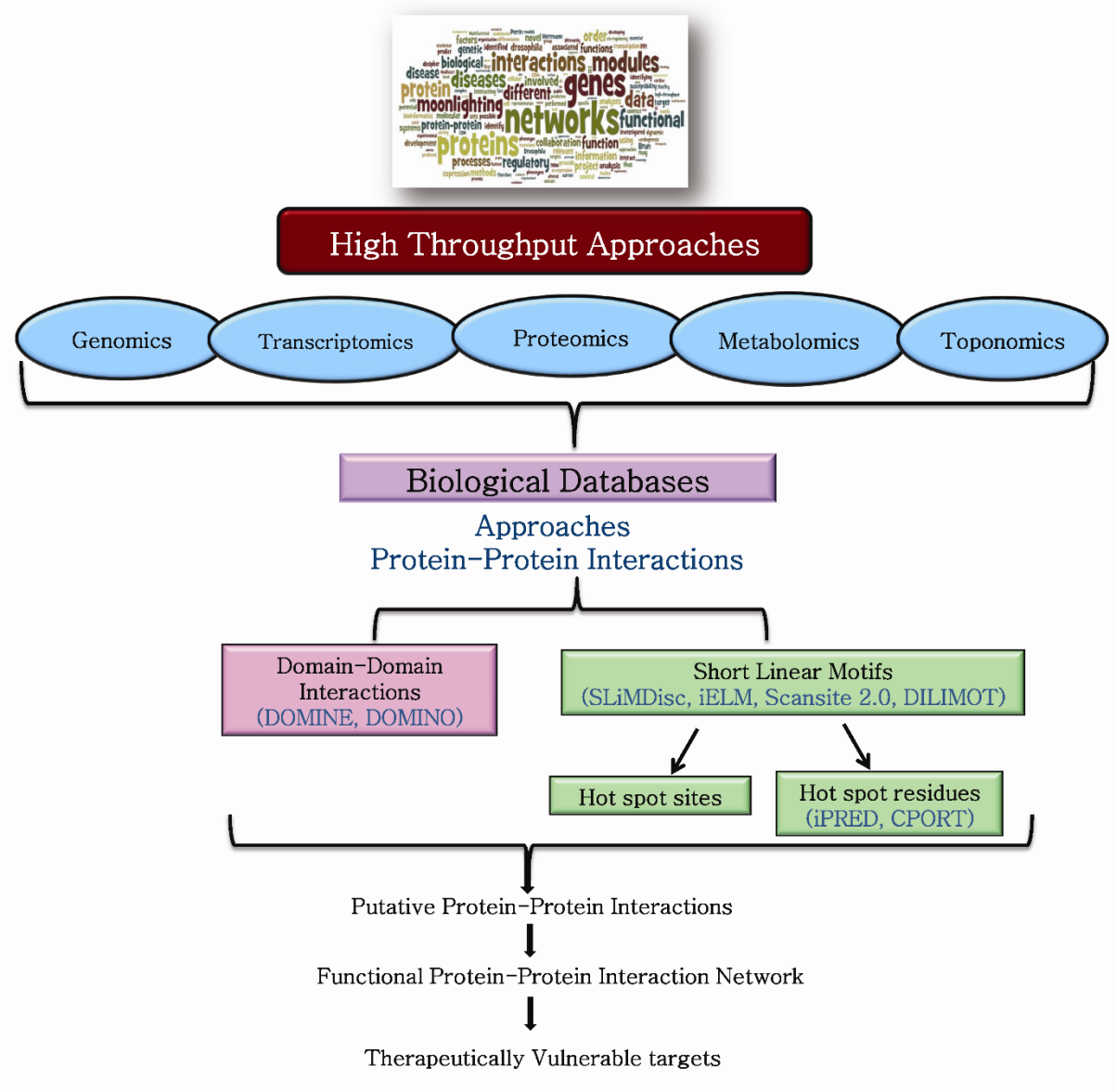

Figure 1. Schematic Representation for predicting PPI. To understand the biology of the cellular system many high throughput screening approaches are available. The information obtained in terms of molecules is available in biological databases which are further applied in different PPI prediction strategies to identify PPI. Identifying Domain-domain interactions followed by identifying Short Linear Motifs to further pinning the hot spot sites/residues at the interface are used to identify PPI (Few of the databases used are indicated within the brackets).These PPI are further experimentally validated so as to build the functional PPI Network which will further help us to identify druggable protein-protein interactions.

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Proteomics in Fisheries and Aquaculture

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Fisheries and aquaculture are important food production sectors which contribute to food and nutritional security. Fish plays major role in human nutrition providing at least 20% of protein intake for a third of the world's population. It is an important component of human diet and is a rich source of quality animal proteins, essential and functional amino acids, ω-3 rich oils (especially EPA and DHA) and micronutrients. The small indigenous fish are micronutrient dense and can play pivotal role in eradication of micronutrient deficiency diseases prevalent in the developing and underdeveloped countries. They supply more than half of the protein and minerals for over 400 million people in the under developed and developing countries. Fish oils (mainly the ω-3 PUFAs, EPA and DHA) have a number of nutraceuticals and pharmaceutical applications. Aquaculture production has increased drastically in the recent years; from a production of less than 1 million ton per year in the early 1950s to 51.7 million tons in 2006 (FAO 2013).

Proteomics is a highly powerful technology in protein analysis which supplements gene sequence data with protein information about where, in which ratio and under what condition proteins are expressed. In the last decade, proteomic technologies have been increasingly used in fish biology research (Rodrigues et al. 2012). Proteomics has been applied primarily to investigate the physiology, nutrition, health, quality and food safety, development biology and the impact of contaminants in fish model organisms, such as zebrafish (Danio rerio), as well as in some commercial species produced in aquaculture, mainly salmonids and cyprinids. However, the lack of previous genetic information on most fish species has been a major drawback for a more general application of the different proteomic technologies currently available (Forne et al. 2010).

Model and non-model species

Zebrafish (Danio rerio) has been a potential model organism towards understanding the complexity of evolution, development and function for several reasons including its ease of availability, short generation time, well developed human like brain and the compact genome. It has been used for understanding various neurological disorders like Alzheimer's, Parkinson's and Huntington disease (Singh et al. 2010). Besides zebrafish, a number of non-model fish species like the IMCs Catla catla and Labeo rohita, minor carp Puntius sophore (all these belong to the Cyprinid family as the zebrafish), murrel Channa striatus – a hardy species, and the freshwater

catfish Rita rita have been utilized to understand organismal response towards the altered environment and are discussed below.

Proteomic analysis of sarcoplasmic peptides for food authentication

Fish food-products include an extensive variety of species widely used for human nutrition, having a significant impact in food industry. As fishery products are among the most traded food commodities internationally, species identification of fish-food products is important for implementation of the labelling regulations as set by many countries to assure complete and correct information, guaranteeing market transparency.

We employed proteomics technology for differential characterization of sarcoplasmic peptides of two closely related fish species, Sperata seenghala and Sperata aor. Species-specific peptides were searched in white muscle extracts of the two species for identification of unique peptides that might aid in differentiation of the species, under 2-D GE platform. A total of nineteen proteins were identified by combined MALDI-TOF MS and LC-MS/MS, of which nine and two proteins were found to be unique to Sperata seenghala and Sperata aor, respectively. One of the proteins, triose phosphate isomerase (TPI) was found to have three isoforms, out of which two were specific to Sperata aor and one was specific to Sperata seenghala. All the three isoforms of TPI were present in the mixed samples of raw protein extracts of Sperata seenghala and Sperata aor, an observation that can be exploited to differentiate between the species and detection of deceptive practices of fraudulent substitution of commercially valuable fish species with inferior ones and differential characterization between closely-related fish species (Barik et al. 2013).

Understanding thermal stress response in Channa striatus by liver proteome analysis

Temperature stress is one of the major abiotic factors that hampers the growth and productivity and is a leading cause of mortality and neurologic morbidity. An increased understanding of the distinct temporal patterns of response of gene regulatory processes to changes in temperature is needed to develop a mechanistic understanding of the effects of temperature change on the vertebrates. Identifying gene or protein markers that define the different sub lethal stress levels could be useful in assessing the health of individual organisms in their environment.

A study was undertaken to investigate the proteomic changes in liver of murrel Channa striatus exposed to high temperature stress. Fishes were exposed to 36 °C for 4 days and liver proteome changes were analysed using gel- based proteomics i.e. 2D gel electrophoresis, MALDI-TOF-MS and the results were validated by transcript analysis. The study showed, besides others, up regulation of two sets of proteins, the antioxidant enzymes SOD, ferritin, GST and chaperones HSP60, PDI. Further, gene expression analysis was also carried out in the fishes exposed to thermal stress for longer duration (30 days, in the laboratory and beyond, taking Channa collected from a hot spring runoff at a water temperature 36-38 °C); hsp60, sod and gst were found to continue to remain up regulated at 11, 8 and 3 folds, respectively in the hot spring runoff fish. Thus the study showed that SOD, GST and HSP60 play important role in thermal adaptation and survival under chronic heat stress (Purohit et al. 2014; Mahanty et al. 2015, under publication).

Identification of potential biomarkers of hepatotoxicity by plasma proteomics of Labeo rohita.

Identification of potential biomarkers of hepatotoxicity by plasma proteomics of *Labeo rohita*

Arsenic (As) is a toxic environmental contaminant and a potential human carcinogen. Human exposure to arsenic is caused mainly through arsenic-contaminated underground drinking water, it is now understood that food-chain is another contributor to arsenicosis problem. Widespread use of arsenic-contaminated groundwater for irrigation of rice and other crops leads to accumulation of arsenic in rice plants, grains and other crops and vegetables. The domestic animals and birds are exposed to arsenic through intake of contaminated feed. Fish and other aquatic animals are naturally the worst affected ones as they feed, breed and grow in the contaminated aquatic habitat, thereby getting lifelong exposure. For understanding the molecular toxicology of arsenicosis, which might provide clues for developing mitigation measures, fish is an important model.

Early detection of arsenic toxicity can provide great benefits to patients; however, toxicity detection needs to be done at the earliest and minimally symptomatic stage for which detection tools must be very sensitive and reliable. In this context, we investigated the plasma proteome changes in arsenic-exposed Labeo rohita, with the objective of identifying biomarkers of arsenicosis. Changes in plasma proteome were investigated using gel-based proteomics technology. The unique proteins identified include Apolipoprotein-A1 (Apo-A1), α-2 macroglobulin-like protein (A2ML) transferrin and warm-temperature acclimation related 65kDa protein (Wap65). All these highly up-regulated protein spots identified in plasma are liver-specific and are indicative of Combination of these could be useful as biomarkers of hepatotoxicity and chronic liver disease (under publication).

Age-related changes and cataract development - Lens proteome analysis of Rita rita.

Eye lens is a unique tissue which is necessary for image focusing in both vertebrates and invertebrates. Eye lenses are composed of fiber cells of which α-, β- and γ-crystallins accounts for about 90% of the total soluble proteins. Fish lens has striking similarities with those of mammalian lenses and therefore fish has become a valuable experimental model for comparative study of mammalian eye for investigations on eye development, cataract and degeneration due to ageing.

Age-related changes in the lens crystallins lead to protein aggregation, resulting in loss of lens transparency (cataract). Identifying the major protein(s) which undergo such modifications can help in preventing or delaying the onset of the process. The changes in a tropical fish lens have been investigated in an attempt to identify such proteins (Bhattacharjee et al. 2011). Lens proteins of Rita rita, from three different age groups, were separated by 2-DE. Changes in the abundance of individual crystallins were analysed by image analysis of 2-DE gels and the proteins were identified by MALDI-TOF-MS and immunoproteomic approach. A reference lens proteome for Rita rita was developed in which 30 spots (30/75) were identified (Mohanty et al. 2011). Proteomic analysis of lens crystallins of Rita rita demonstrated changing levels of ⊚A-, B1-, and ⊚M7-crystallins expression which are 2-3 folds upregulated with age. In transcriptome analysis, αA- and γM-crystallin was significantly increased during developmemt and ageing whereas βb-crystallin was down-regulated in aged group of fishes. The information generated in this study could add to the ongoing efforts for identifying age-related changes in lens proteome and crystallin modifications which lead to cataract formation.

Muscle proteogenomics of Indian major carp Catla catla and freshwater catfish Rita rita

Muscle fibers represent one of the most abundant cell types in both invertebrates and vertebrates. The contractile fibers of skeletal muscle tissues not only provide coordinated excitation-contraction-relaxation cycles for voluntary movements but also play central role in homeostasis. Characterization of the muscle proteome is a key to many aspects of aquaculture, encompassing physiology, growth, food safety, seafood authentication and quality, traceability and shelf-life. Carps are the mainstay of aquaculture in India contributing over 85% of the total aquaculture production. A reference muscle proteome map for Catla catla has been generated and 70 protein spots from 2-D gels, representing 22 proteins, have been identified. The partial gene sequence information on the identified proteins have been deposited to GenBank (Mohanty et al. 2013).

The freshwater catfish Rita rita of the family Bagridae inhabiting the tropical rivers and estuaries is an important food fish with high nutritive value and is also considered as species of choice in riverine pollution monitoring. Proteomic analysis of Rita rita muscle has been carried out and functional genomics data have been generated. A reference muscle proteome has been developed, and 23 protein spots, representing 18 proteins, have been identified by MALDI-TOF/TOF-MS and LC-MS/MS (Mohanty et al. 2015). Besides, transcript information on a battery of heat shock proteins (Hsps) has been generated. The functional genomics information generated could act as the baseline data for further molecular research on this species.

FISHPROT-A biological fish proteomic database

Proteomic technologies are being increasingly used in fish biology research to investigate the fish physiology, developmental biology, disease mechanism, habitat degradation, species identification etc. Although large amount of proteomic data on both model and non-model fish species has been generated, there is no exclusive database on fish proteomics. We have developed a database, named FISHPROT (http://www.cifri.ernet.in/fishprot.html), which is created exclusively for fish proteomics data storage and retrieval. This web-based database runs open source LAMP (Linux, Apache, MySQL and PHP) technology at the front end, MySQL at the back end and PHP is used as the server script. FISHPROT contains 2D proteome maps of a wide range of fish tissues and mass spectrometric information. The information is retrievable by filling in the interactive form or by directly clicking on the gel spot. This database presently contains information on proteins from muscle, lens, liver and plasma proteomes of various fish species. It is linked to other important proteomics and bioinformatics database like NCBI, SWISSPROT and proteomic societies like SPS, BSPR, PSI. The database is being updated regularly and is envisaged to serve as a global repository on fish proteomic information (Mohanty et al. 2014).

To date, the use of proteomics in fish biology and aquaculture has been limited. It is envisaged that in the coming years currently available proteomics tools, as well as of other related emerging technologies, will be applied more extensively in fish biology research. Nutrigenomics is an important area for manipulation and evaluation of fish physiology and biochemistry through feeding designer diets to enhance the ω-3 PUFA levels. As such fish is a rich source of quality proteins and enhancing its PUFA level and producing ω-3 carps would be a great boon to the

country in achieving nutritional security. In fact, the combined omics technology (genomics-transcriptomics-proteomics-metabolomics) have a greater scope of application in fisheries and aquaculture sector for achieving the objectives of 'Second Blue Revolution'; ensuring high quality fish meat and quantum jump in fish production and at the same time guaranteeing food safety.

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Students Corner

A Decade of Proteomics Activity at Saha Institute of Nuclear Physics

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Proteomics has emerged as more than a successor to genomics and is now gaining importance day by day in biomedical research. India has a long legacy in protein research, but proteomics activities, in which mass spectrometry (MS) based approaches are applied to solve biological problems or study protein dynamics in health and diseases, are however very recent until several institutes and groups incorporated the proteomics approach at the turn of the century. A clinical proteomics activity was initiated in Saha Institute of Nuclear Physics during the Xth five year plan period starting in the year 2002 within the project entitled *Structural Genomics in Human Health & Disease*. During this period, one of the youngest proteomics laboratories of the country and first in the eastern region was set up. The Structural Genomics Section, formed in the year 2005 which later became a Division in the year 2009, has been pursuing proteomics research, since then in the area of hematological disorders e.g. thalassemia, sickle cell disease(SCD) and childhood leukemia, mitochondrial proteomics in hematopoiesis and neurodegenerative diseases e.g. Huntington's disease, Alzheimer's disease and Spinal Cord Injury. In the XIth five year plan period, within the project entitled *Structural Proteomics & Genomics of Human Genetic Diseases*, fruits of the proteomics activities started ripening - seven students have already completed their PhD and two more are working in this challenging area, altogether producing more than 17 papers in peer reviewed international journals. The proteomics laboratory is completely managed by graduate students, running and maintaining one tandem MALDI TOF/TOF spectrometer, one LC-MALDI spotter and another recently installed ESI-MS QTOF spectrometer, besides the gel-based workstations. This laboratory also caters to the need of external users coming from all corners of the country. The last ten years journey in proteomics path was bumpy, testing yet satisfactory to those who fell in love with it. In this issue I would try to pen down this decade of voyage, our humble beginning and future prospect.

Dr. Dipankar Bhattacharya was the first graduate student who initiated the proteomics exercise at SINP under the guidance of Prof. Abhijit Chakrabarti. After initial standardization of 2DGE and newly installed MALDI TOF/TOF mass spectrometry they concentrated on erythrocyte proteomics, as the lab has previous expertise on erythrocyte membrane proteins. A continuing problem during that time in red cell proteomics was the masking effect of hemoglobin (Hb) on other red cell proteins, creating a dynamic range of few orders of magnitude which resulted in difficulty of gel based proteomics of erythrocyte cytosol. All the previous reports of erythrocyte proteomics have encountered the same issue by increasing the analytical prowess of detection instrumentations. Chakrabarti lab overcame the issue of Hb abundance with a simple and

effective gel filtration with a cation exchange column using SP-Sephadex which selectively binds Hb at pH 6.7. After analyzing the flow-through they observed a dramatic improvement in visual protein spots in 2D gels of Hb depleted *vis-a-vis* un-depleted Hb lysate. By a stringent protein-detection criterion where they took only proteins those were detected by at least 2 peptides in MSMS, they could identify 10 novel proteins hitherto unreported in erythrocyte database [1]. This pioneering work was globally acknowledged and cited by many leading research article by groups working on the related areas. With the help of few excellent clinical collaborators, Prof. Chakrabarti and his lab members have used this technique to carry out differential proteomics of Eβ- thalassemic erythrocytes. Thalassemias are a group of inherited hemolytic anemias with differential expression of either α or β-globin genes. Hemoglobin E (β-26 Glu-Lys) is the most prevalent hemoglobin mutant in South East Asia including India. HbEβ-thalassemia has been characterized by interaction of HbE with β thalassemia. Although HbE does not result in clinical severity, its combination with β-thalassemia increases the pathophysiological severity of the disease to varying phenotypes ranging from severe transfusion-dependent thalassemia major to thalassemia intermedia. Their work showed that redox regulators such as peroxiredoxin-2(Prdx2), Cu-Zn superoxide dismutase (SOD) and thioredoxin and chaperones such as alpha-hemoglobin stabilizing protein and HSP70 were up regulated in Hb Eβ-thalassemia. They have also observed larger amounts of membrane associated globin chains and indications of disruption of spectrin-based membrane skeleton of Hb Eβ-thalassemic erythrocytes [2].From the results of their proteomic endeavor, they have reported a strong correlation or association of the extent of such proteomic changes with HbE levels. This could be of future importance in understanding the role of HbE in disease progression and pathophysiology.

In the time period another highly enthusiastic and motivated graduate student joined Prof. Chakrabarti's group. With an objective of defining potential diagnostic and/or therapeutic markers and the mechanism of cellular transformation, a comparative proteomic study of B-lymphocytes from B-cell acute lymphoblastic leukemia (B-ALL) patients was initiated by Dr. Sutapa Saha. The study led to the identification of 79 differentially regulated proteins in the malignant cells including proteins participating in proteostasis, cytoskeletal organization, redox homeostasis, and signal transduction pathways relevant to leukemogenesis. Principal component analysis displayed immunophenotype-/genotype-dependent variations in the malignant cell proteome [3]. With the help of a novel ammonium sulphate based depletion strategy she ventured into extremely challenging field of plasma proteomics. Their study reveals altered plasma levels of proteolysis-modulating, carrier and acute phase proteins in B-ALL [4].To get a complete system wide understanding, she also analysed the proteomes of erythrocytes from B-ALL patients along with an unrelated hemolytic anaemia named Hereditary spherocytosis (HS). While Hb-depleted HS erythrocyte cytosol showed up-regulation of redox regulators and down-regulation of a co-chaperone and a nucleotide kinase; the B-ALL patients showed somewhat opposite trends with down-regulation of oxidoreductases and proteoform shift of HSP70. Comparison of the erythrocyte membrane proteomes led to the observation of elevated levels of membrane associated globin chains and reduced membrane association of key glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase in both B-ALL and HS patients. Increased levels of

low molecular weight fragments of several major cytoskeletal proteins were also observed in both B-ALL and HS erythrocyte membrane proteomes [5].

Prof. Debasish Mukhopadhyay's lab works on molecular aspects of neurodegenerative disorders with primary focus on Alzheimer's disease (AD). Amyloid precursor protein intracellular domain (AICD) is becoming one of the potential candidates in deciphering the complexity of AD. The well-established intracellular effects of AICD in determining cell fate and neurodegeneration are thought to occur due to its interaction with other proteins. In his PhD work Dr. Arunabha Chakrabarti tried to identify the proteins interacting with AICD and their possible functional implications in AD. Towards this goal he have identified interacting partners of AICD from mouse and human neuroblastoma cell lines (N2A and SHSY5Y respectively) [6] as well as from cerebrospinal fluids (CSF) from AD patients. His comparative proteomics also revealed that most of the identified interactors of AICD from CSF showed altered expression in AD condition [7]. Enrichment analysis of the identified interacting partners of AICD revealed the involvement of those interactors in diverse molecular functional classes and some of them could also be correlated to AD pathogenesis. Being an intrinsically unstructured protein, AICD can interact with so many intracellular proteins. It is expected that AICD may alter the expression of several other proteins due to those interactions. Keeping this fact in mind, they over expressed AICD into N2A and SHSY5Y cell lines and characterized the alterations in the proteome of those cell-lines due to AICD over expression. They have identified around 45 altered proteins and few proteins were altered in both the cell lines. Interestingly those proteins were found to be AICD-interacting partners and also could be related to AD [8].

Prof. Nitaipada Bhattacharyya's lab works on another interesting neurodegenerative disorder, Huntington's disease (HD), caused by expansion of polymorphic CAG repeat in the exon1 of *htt* gene. HYPK is an Htt interacting chaperone protein which was shown earlier to revert the toxicity and aggregation induced by mutant huntingtin in mouse and human cell lines. However, the underlying mechanism(s) of HYPK-mediated modulation of Huntington's disease remain largely unknown. To unveil the pathways modulated by HYPK, Dr. Kamalika Roy Choudhury tried to identify HYPK-interacting partners using pull-down/MALDI-mass spectrometry. She initially identified 27 such HYPK interacting proteins and further validated some of these interactions. The study reveals that HYPK and its interactors were involved in a array of biological pathways like cell growth, cell cycle regulation, autophagy, apoptosis, protein folding and transcription regulation [9]. Transcriptional deregulation is one of the major hallmarks of HD. She also tried to identify proteomic deregulations in HD, using widely used cell model of HD. Her study, reports deregulation of 32 proteins in the cell model of HD. Interestingly, HYPK was found to be down regulated in HD cells and over expression of HYPK in HD cells lead to trend reversal for 12 proteins. This study reinforces the proposed protective role of HYPK in HD pathogenesis.

Realizing the potential of the developing proteomics platform, Prof. Subrata Banerjee's lab also started working on mitochondrial proteomics in hematopoiesis. To gain more insights into the Notch signalling and its role in regulation of metabolism, Nandini Pal Basak studied the mitochondrial proteome in Notch1-activated K562 cells using a comparative proteomics approach. The proteomic study led to the identification of 10 unique proteins that were altered due to

Notch1 activation. Eight of these proteins belonged to mitochondria-localized metabolic pathways like oxidative phosphorylation, glutamine metabolism, Krebs cycle, and fatty acid oxidation. Validation of some of these findings showed that constitutive activation of Notch1 deregulated glutamine metabolism and Complex 1 of the respiratory chain. Furthermore, the deregulation of glutamine metabolism involved the canonical Notch signalling and its downstream effectors. Thus their results show the effect of Notch signalling on mitochondrial proteome, which in turn affects the functioning of key metabolic pathways, thereby connecting an important signalling pathway to the regulation of cellular metabolism [10].

A year later I joined Prof. Abhijit Chakrabarti's group and showed interest in the proteomic activities. My whole graduate study centred around proteomics studies of erythrocytes. We believed understanding erythrocyte proteome and its dynamics is important as plenty of hematological disorders are associated with erythrocytes and its proteins. Following the technique earlier developed by Dr. Dipankar Bhattacharya, we had undertaken a comparative proteomic study of SCD erythrocytes using a DIGE based approach to analyze the hemoglobin depleted cytosolic fractions [1]. We have found differential regulations of various redox regulators and chaperone proteins along with proteasomal subunits in SCD cytosol. Elevated reactive oxygen species and oxidative stress was also observed**.** It testifies that proteostasis and redox regulation got altered in case of SCD [11]. We have also analyzed interacting partners of hemoglobin and found that expression of most of these Hb interacting proteins got altered in hemoglobinopathies like SCD and thalassemia[12, 13]. We believe our results could provide insight into a protein network evolved around hemoglobin molecule inside erythrocyte that may add a new perspective in understanding these disease manifestations.

At the same time Suchismita Halder also joined Prof. Chakrabarti's lab and started working on proteomics study of the body fluids such as plasma and urine in case of β-thalassemia and HbEβ-thalassemia. Proteomic study of these two body fluids reveals that proteins participating in cholesterol metabolism, iron transport, coagulation, hemoglobin scavenging and redox regulation were altered [4, 14].She extended her proteomics study of body fluids in case of patients with urothelial neoplasm [15]. She also initiated a lipidomics study of plasma, erythrocytes and erythrocytes membrane.The changes observed clearly indicate that the erythrocytes are in a proapoptotic condition in the diseased state and the data is in agreement with the fact that , premature eryptosis leading to acute anaemia, is one of the key pathological features of Eβ thalassemia.

A year later Shilpita Karmakar joined Prof. Chakrabarti's lab and started to venture into platelet proteomics. Platelets are normally involved in hemostasis, adhesion and aggregation but are also associated with various pathological conditions including thrombosis, inflammation and immune responses. Understanding platelet proteome and its dynamics is important as a number of hematological disorders including hypercoagulability are associated with platelet proteins. Her work is based on studies of comparative platelet proteomics in certain hematological disorders such as asymptomatic constitutional macro thrombocytopenia (ACMT), HbEβ and β thalassemia and a few hematological malignancies to enlighten the factors responsible for the pathophysiology of the diseases. Shilpita's comparative proteomics work on ACMT, have revealed altered levels of

actin binding proteins such as myosin light chain, coactosin like protein, actin related protein 2/3 complex and transgelin2, that hint towards the cytoskeletal changes, necessary to maintain the structural and functional integrity of macrothrombocytes. The study also reports over expression of Prdx2, that signifies the prevailing oxidative stress in these cells [16]. As Prof. Chakrabarti's lab have a long standing interest in thalassemia , Shilpita also tried to identify the factors being altered in HbEβ and β thalassemia that may provide an explanation to the associated problem of hypercoagulability. She found altered levels Prdx2 and SOD indicating the prevailing oxidative stress in thalassemic samples whereas elevated HSP70 and Protein disulfide isomerase emphasizes the role of chaperones in maintaining the cells against oxidative stress. The study also reveals the dramatic cytoskeletal changes involved. Presently she is carrying out projects on platelet proteomics related to Myeloproliferative disorders mainly Chronic myeloid leukaemia, Polycythemia vera and essential thrombocythaemia, that might enlighten the factors responsible for the indispensable alterations in platelet parameters that are clinically considered reliable indicators of the above mentioned disorders.

The latest addition to the proteomics gang is Mohor Sengupta, who started her work under the guidence of Dr. Debashis Mukhopadhyay, on perturbed molecular pathways in the secondary phase of spinal cord injury (SCI). It is estimated that SCI is one of the primary causes of disabilities worldwide and also a leading cause of mortality and morbidity. Dr. Mukhopadhyay's group in collaboration with the NRS Medical College & Hospital, Kolkata, worked on a cohort of rural East Indian population. It is also known that the prognosis of SCI is dependent on the severity of injury classified by the American Spinal Injury Association Impairment Scale (AIS). Whereas AIS A denotes complete injury, AIS B-D denote incomplete injury with decreasing severity and AIS E is classified as normal. They used comparative proteomics of CSF collected from two different AIS grades of SCI patients (A and C/D) and zeroed in on the proteins that show differential abundance at 1-8 days post injury. As the molecular scenario around the injury site is expected to undergo vast changes as the secondary phase progresses, they analysed the abundance of these proteins at a later time period post injury (15-60 days). Finally, they created a protein-protein interaction network and modularised it. Biological functions of this protein network reveals pathways related to mRNA metabolism, protein phosphorylation, lipid and ATP catabolism, iron transport, tRNA and rRNA transcription and DNA repair are associated with SCI [17].

Current Biophysics and Structural Genomics Division have been continuing proteomics activities in the XIIth five year plan project under the project *Integrative Biology on Omics Platform (IBOP)*.Latest addition to our proteomics family is Dr. Soumen Kanti Manna, a young dynamic faculty member who joined the division in 2014.We sincerely hope he will continue to develop and lead the proteomics programme in future. We started in the beginning of the last decade with just a handful of enthusiasts trying their bit and today we have achieved a laboratory with modern infrastructure and many groups are actively participating in the proteomics work. From the stage of generating small datasets, we now have moved to large scale proteomics and started combining functional proteomics with that. There have been further efforts to integrate other "omics" approaches like transcriptomics, lipidomics, glycomics and metabolomics, coupled with conventional proteomics where the future of Proteomics research has to move forward.

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In the next issue:

Students Corner

A report on the Metabolomics Meeting organized at IISc, Bangalore in January 2015

Upcoming Events

7th Annual Meeting of the Proteomics Society, India
December 3-6, 2015,
Vellore Institute of Technology

Abstract submission: 1st May – 31st July 2015

www.psivellore2015.org

This conference is themed on BioChromatography, Molecular Recognition and Proteomics and it aims to integrate cross disciplinary subjects for better understanding of complexity of proteome, metabolome, glycome, lipidome of humans, plants, microorganisms, etc for various applications.