DAY 1

Plenary Sessions

EuroSciCon conference on

Protein, Proteomics and Computational Biology

December 06-07, 2018 | Amsterdam, Netherlands

DAY 1

December 06, 2018

Sessions

Proteomics in drug discovery | Genetics and molecular biology | Proteomics and its medicinal research |Cancer proteomics | Protein engineering and enzymology |Biomarkers | Biochemistry and Biophysics | Computational biology

Session Chair	Session Co-Chair
Soren Naaby Hansen	Julien Boudet
Aalborg university hospital, Denmark	ETH Zurich, Switzerland

Session Introduction

Title: **The Way to Deep Cover of Human Proteome in Gene-centric Mode**

Alexander I. Archakov, Institute of Biomedical Chemistry, RAS, Moscow, Russia

Title: **Structure based drug discovery on membrane protein targets**

Nicolas Bocquet, leadXpro AG, Park Innovaare, Switzerland

Title: **Deciphering the Structural Basis of Translocator-Chaperone Interaction of Type III Secretion System-A Key to Drug Design against Pathogenic Yersinia enterocolitica**

Abhishek Basu, Sripat Singh College,University of kalyani,West Bengal, India

Title: **Efficient Genome-Wide Association Studies and Post-GWAS Integrative Analyses for Human Cancer and Neurodegenerative Diseases**

Zahra Mortezaei, Tehran, Iran

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Alexander I et al., Biochem Mol biol J Volume:4
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THE WAY TO DEEP COVER OF HUMAN PROTEOME IN GENE-CENTRIC MODE

Alexander I. Archakov, Ekaterina V. Ilgisonis, Arthur T. Kopylov, Andrey V. Lisitsa, Elena A. Ponomarenko, Victor G. Zgoda

Institute of Biomedical Chemistry, RAS, Moscow, Russia

Currently, great interest is paid to the identification of "missing" proteins that have not been detected in any biological material at the protein level (PE1). Using the UPS1 and UPS2 Sigma Aldridge sets as the “gold standard”, we characterized mass spectrometric approaches from the point of view of sensitivity (Sn), specificity (Sp) and accuracy (Ac). This sets consists of 48 high purity human proteins without SAP or PTM. UPS1 set consists of the same 48 proteins at 5 pmols each, in UPS2 proteins were unified into five groups in accordance with their molar concentration, ranging from 10-11 M to 10-6 M. Single peptides from the ninety-two and ninety-six percent of all set proteins could be detected in a pure solution of UPS2 and UPS1, respectively, by Selected reaction monitoring with stable isotope-labeled standards (SRM SIS). We also found that in the presence of a biological matrix such as *E.coli* extract or human blood plasma (HBP), SRM SIS makes it possible to detect from 63% to 79% of proteins of the UPS2 set (sensitivity), with the highest specificity (~100%) and an accuracy of 80%. To increase the sensitivity of shotgun and SRM SIS monitoring samples were fractionating by RP using chromatography under alkaline condition (2D-LC_alk). It is shown that this technique allows the SRM SIS to detect 98% of the the single peptides from the proteins present in the pure solution of UPS2 (47 out of 48 proteins). When the extracts of *E-coli or P. Pastoris* are added as biological matrixes to the UPS2, 46 and 45 out of 48 proteins (~95%) can be detected respectively. The combination of the 2D-LC_alk SRM SIS and shotgun technologies allows to increase the sensitivity up to 100% in case of the proteins of UPS2. The usage of that technology can be a solution for identifying the so-called "missing" proteins and, eventually, creating the deep proteome of a particular chromosome of tissue or organs. Data in PASSEL PASS01192 and PRIDE PXD007643.

Biography

Professor, Scientific Advisor of Institute of Biomedical Chemistry, Was born January 10, 1940, in Kashin, Kalinin (Tver) region – scientist, biochemist. A.I. Archakov had organized a scientific school to study molecular organization and functioning of oxygenase cytochrome P450-containing systems, molecular mechanisms of the structure and function of membranes and biological oxidation. Under the guidance of A. I. Archakov, the institute's members have developed a fundamentally new pharmaceutical composition “Phosphogliv” with antiviral activity for the treatment of liver diseases of various etiology. A.I. Archakov's present-day/current areas of expertise relate to research in the field of post-genomic technologies, nanobiotechnologies, proteomics, development of approaches to create personalized medicine of the future. A.I. Archakov is the pioneer in the development of proteomics in Russia. Currently, he is the international “Human proteome” project coordinator in Russia/ the coordinator representing Russia in the international “HP” project.

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STRUCTURE BASED DRUG DISCOVERY ON MEMBRANE PROTEIN TARGETS

Nicolas Bocquet, Sandra Markovic-Mueller, Robert Cheng, Mathieu Botte, Wassim AbdulRahman, Sophie Huber, Eric Pflichta, Denis Bucher and Michael Hennig

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Today, soluble proteins are managed routinely within the project timelines and scope with the rapid portfolio changes in pharmaceutical industry. Establishment of biophysical and structure-based methods for transmembrane proteins still represents a significant challenge to have an impact on drug discovery. leadXpro combines membrane protein expression, purification and structure determination coupled to premium access to the synchrotron Swiss Light Source (SLS), the Free Electron Laser (SwissFEL) and single particle cryo-electron microscopy (cryo-EM) at the University of Basel. LeadXpro also confronts structural data to different biophysical measurements like thermal shift assays, radiobinding assay and wave guide interferometry in order to generate better lead molecules with appropriate features. The talk will show advancements in projects and technologies with examples for serial crystallography performed at synchrotron and free electron laser enabling structure determination of challenging drug targets. Moreover, recent efforts and implementation of wave-guide interferometry method for analysis of small (fragment-like molecules)/large ligand binding kinetics on membrane proteins will be discussed in the context of i) lead discovery and optimization ii) biologics targeting membrane proteins. Finally, recent progress in cryo-EM will also be discussed.

Area of Interest:

- X-ray Crystallography
- Cryo-Electron Microscopy
- Biophysical methods & characterization (TSA & SPR)
- Membrane Proteins & Hot Structures

Biography

Nicolas studied at the University of Compiegne (France) and completed his Engineer in Biotechnology degree. For his master and PhD in Neuroscience from the University Pierre et Marie Curie, he moved to the Pasteur Institute in Paris, where he worked in the group of Dr. Pierre-Jean Corringer and Prof. Jean-Pierre Changeux (Channel receptors group) on the elucidation of the crystal structure of a pentameric ligand gated ion channel in an open conformation. From 2009 to 2013, Nicolas moved to FMI (Friedrich Miescher Institute for Biomedical research) as a post-doctoral fellow in the group of Dr. Nicolas Thomae, where he worked on the mechanisms of Holliday junction dissolution by solving the structure of the human Topoisomerase III in complex with a modulatory protein called RMI1. From 2013 to 2017, he worked at Roche, first as a Roche post doctoral fellow and after as a scientist in the Chemical biology department developing biophysical methods for membrane proteins as well as producing, purifying, stabilizing and characterizing GPCRs, transporters and membrane enzymes. Starting February 2017, Nicolas will work on biophysical and structural biology programs within LeadXpro AG as a senior scientist.

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DECIPHERING THE STRUCTURAL BASIS OF TRANSLOCATOR-CHAPERONE INTERACTION OF TYPE III SECRETION SYSTEM-A KEY TO DRUG DESIGN AGAINST PATHOGENIC *YERSINIA ENTEROCOLITICA*

Abhishek Basu[1], Debjani Mandal[1], Manali Biswas[1], Indranil Saha[2] and Shamsuzzaman Ahmed[2]

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[2]Department of Chemistry, Sripat Singh College, University of Kalyani, India

Yersinia enterocolitica is an opportunistic pathogen which causes enteric diseases like gastroenteritis and mesenteric adenitis in immune-compromised individuals. The gastrointestinal phase of *Y. enterocolitica* infection is mediated by *Yersinia* secretion apparatus - *Yersinia* secretion protein (Ysa-Ysp) Type III Secretion System (T3SS). Enhanced virulence of *Y. enterocolitica* Biovar 1B is attributed to the activation of Ysa-Ysp T3SS, which is further regulated by the formation of functional injectisome. YspB and YspC are hydrophobic translocator proteins which are responsible for the formation of functional translocon at the tip of the needle complex. These translocators are sequestered in the bacterial cytoplasm by their cognate chaperone SycB. SycB plays the dual role of a class II chaperone and a regulator of Ysa-Ysp T3SS. Homology model of SycB depicts a structure with a concave core formed by tetratricopeptide repeats (TPRs) and a flexible N-terminal helix. Deletion mutants of SycB showed that the N-terminal helix of SycB is responsible for its dimerization, which is further corroborated by molecular docking analysis. The dimeric state of SycB dissociates during the interaction with YspC due to steric hindrance. It forms a 1:1 heterodimeric YspC-SycB complex as confirmed by size-exclusion chromatography, chemical cross-linking and molecular docking studies. FRET analysis indicated that the tyrosine residues present in first two TPRs of SycB is responsible for its interaction with YspC. Deletion mutants of SycB possessing the first two TPR regions interacted with YspC, as depicted by the YspC-SycB interaction model. YspC is a unique minor translocator protein having monomeric form with high stability and rigid tertiary structure unlike any other translocator proteins. It shows structural alteration in the complex form with SycB as shown by spectroscopic data and proteolytic digestion. YspC has a Y-shaped three dimensional structure and SycB completely localizes within the fork formed by the two arms of Y-shaped YspC. Like other major translocator proteins YspB possesses a highly helical structure and transmembrane helices required for its translocation through the narrow conduit of the needle and its insertion within the host cell plasma membrane. Being a translocator protein it has to interact with chaperones and other translocators, which is evident from the existence of intramolecular coiled-coil regions in YspB structure. The YspB model depicted a star-shaped structure with alpha helices interspersed by random coil regions. The inner concave core of SycB forms the interface of interaction with YspB. This interaction is polar or ionic in nature and mediated by the first two TPRs of SycB. Therefore, simultaneous binding of YspB and YspC to SycB is not possible due to the common interaction domains. ConSurf analysis predicted that the evolutionarily conserved residues are mostly present in the regions of YspB involved in interaction with SycB. Exposure of translocator proteins to the extra-cellular milieu makes them potential drug targets. Therefore, elucidation of the three dimensional structure of translocators would enable us to determine precise antigenic epitopes for drug targeting. Structural analysis and understanding the mechanism of interaction between translocators and chaperones would be beneficial in designing peptide drugs to deregulate the Ysa-Ysp T3SS and attenuate the virulence of *Yersinia enterocolitica*.

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Biography

Abhishek Basu completed his PhD at the age of 29 years from the Structural Biology and Bioinformatics division of CSIR-Indian Institute of Chemical Biology. He was the recipient of prestigious CSIR-NET Fellowship during the course of his research. He also qualified GATE with 99.8 percentile. At present, Dr. Basu is working as the Head of Molecular Biology and Biotechnology department in SS College, under University of Kalyani. He is continuing his research in the DBT-BOOST sponsored laboratory of the same department. Dr. Basu has published 16 research articles in reputed international journals and he is the author of two book chapters. Besides having a master degree in Biophysics and Molecular Biology and a PhD in Biochemistry, Dr. Basu also possesses an MBA degree in Financial Management.

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EFFICIENT GENOME-WIDE ASSOCIATION STUDIES AND POST-GWAS INTEGRATIVE ANALYSES FOR HUMAN CANCER AND NEURODEGENERATIVE DISEASES

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It is evident that in etiologies of human complex diseases, genetic factors play some important roles. Genome-wide association study (GWAS) is a standard technique to identify heritable genetic basis of complex diseases. In relation with GWAS, there exist some challenges in selecting input samples completely randomly, to biologically describe GWAS results, to translate them into clinical benefits and to compare germline variants achieved from GWAS with somatic mutations in creating, development and treatment of human complex diseases. Likelihood-based statistical methods are robust in estimating linkage disequilibrium when factors like non-randomness and population structures exist. Then the results of GWAS can be used for post-GWAS analyses to predict multiple biological components like genes, non-coding RNAs and transcription factor binding sites in association with complex diseases. An integrative analysis seeks to pool information from multiple GWAS results, somatic mutations and genetic drug targets of human complex disorders and the results of such analysis can provide new insight into the genetic and treatments of complex diseases. This presentation is prepared from the viewpoint that the robust statistical method can be applied to arrive at valuable results from GWAS and that primarily genetic information derived from GWAS is subject to further post-GWAS analysis to provide more biologically informative results in relation with genetics of human complex diseases that can be applied to real time clinical applications. Then the results of such analyses can be used to discuss and compare human cancers and neurodegenerative diseases from a genetic perspective. We concluded that in spite of the differences between human cancers and neurodegenerative diseases, the roles of germline and somatic mutations in creating, developments and treatments of those two kinds of human complex diseases are similar.

Biography

Zahra Mortezaei has completed her Undergraduate in Mathematics from Amirkabir University of technology (Tehran Polytecnique), Iran and studied for Mphill degree in Mathematical physics at University of Nottingham (UK). She then completed her PhD in Bioinformatics at University of Birmingham (UK) and the University of Tehran (Iran). She is working as bioinformatician at human genetic research centre in Iran. Her recent papers in the field of Bioinformatics are:

- Mortezaei, Z., Lanjanian, H., Masoudi-nejad, A., (2017) Genomics Candidate novel long noncoding RNAs , MicroRNAs and putative drugs for Parkinson's disease using a robust and efficient genome-wide association study. Genomics, 109(3–4):158–164.
- Mortezaei, Z., Cazier, J-B., Mehrabi, A.A., Cheng, C. and Masoudi-Nejad, A. (2018) Novel Putative Drugs and Key Initianting Genes for Neurodegenerative Diseases Determined Using Network-Based Genetic Integrative Analysis. J Cell Biochem, 1-13.

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Proteomics and Computational Biology 2018

DAY 1

Video presentation

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Henry M. Sobell, Biochem Mol biol J Volume:4
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THE CENTERS OF PREMELTONS SIGNAL THE BEGINNING AND ENDS OF GENES

Henry M. Sobell
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Premeltons are examples of emergent structures (i.e., structural solitons) that arise spontaneously in DNA due to the presence of nonlinear excitations in its structure. They are of two kinds: B-B (or A-A) premeltons form at specific DNA-regions to nucleate site-specific DNA melting. These are stationary and, being globally nontopological, undergo breather motions that allow drugs and dyes to intercalate into DNA. B-A (or A-B) premeltons, on the other hand, are mobile, and being globally topological, act as phase-boundaries transforming B- into A- DNA during the structural phase-transition. They are not expected to undergo breather-motions. A key feature of both types of premeltons is the presence of an intermediate structural-form in their central regions (proposed as being a transition-state intermediate in DNA-melting and in the B- to A- transition), which differs from either A- or B- DNA. Called beta-DNA, this is both metastable and hyperflexible – and contains an alternating sugar-puckering pattern along the polymer-backbone combined with the partial-unstacking (in its lower energy-forms) of every other base-pair. Beta-DNA is connected to either B- or to A- DNA on either side by boundaries possessing a gradation of nonlinear structural-change, these being called the kink and the antikink regions. The presence of premeltons in DNA leads to a unifying theory to understand much of DNA physical-chemistry and molecular-biology. In particular, premeltons are predicted to define the 5' and 3' ends of genes in naked-DNA and DNA in active-chromatin, this having important implications for understanding physical aspects of the initiation, elongation and termination of RNA-synthesis during transcription. For these and other reasons, the model will be of broader interest to the general audience working in these areas. The model explains a wide variety of data, and carries within it a number of experimental predictions – all readily testable – as will be described in my talk.

Biography

Henry M. Sobell completed his studies at Brooklyn Technical High School (1948-1952), Columbia College (1952-1956), and the University of Virginia School of Medicine (1956-1960). Instead of practicing clinical medicine, he then went to the Massachusetts Institute of Technology (MIT) to join Professor Alexander Rich in the Department of Biology (1960-1965), where, as a Helen Hay Whitney Postdoctoral Fellow, he learned the technique of single crystal X-ray analysis. He then joined the Chemistry Department at the University of Rochester, having been subsequently jointly appointed to both the Chemistry and Molecular Biophysics departments (the latter at the University of Rochester School of Medicine and Dentistry), becoming a full tenured Professor in both departments (1965-1993). He is now retired and living in the Adirondacks in New York, USA.

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