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MEETING REPORT

Driving Precision Medicine through Proteomics and Metabolomics - 12th Central and Eastern European Proteomic Conference (CEEPC), Bucharest, Romania

Suresh Jivan Gadher[a], Felica Antohe[b] and Hana Kovarova[c]

[a]Life Science Solution, Thermo Fisher Scientific, Carlsbad, CA, USA; [b]Institute of Cellular Biology and Pathology, "Nicolae Simionescu" (ICBP-NS), Bucharest, Romania; [c]Life Science Solution, Institute of Animal Physiology and Genetics, Academy of Sciences of Czech Republic, v.v.i, Libechov, Czech Republic

ABSTRACT

As Romanians prepared to celebrate 100 years of the "Great Unification of 1918" which united all provinces into one Romania, the 12th Central and Eastern European Proteomic Conference (CEEPC) jointly with the 39th Anniversary of the Institute of Cellular Biology and Pathology "N. Simionescu" (ICBP-NS), held their inaugural meeting at the Romanian Academy in Bucharest – a national forum of highest scientific recognition. With an exciting theme entitled, 'Advances in Proteomics and Progress in Precision Medicine', delegates gathered to debate Precision medicine's revolution in diagnosis and treatment, which now accounts for predictive, preventative, and targeted treatment strategies with informed decisions according to individual's unique clinical, molecular and genetic profile. Proteomics has a pivotal role to play in furthering precision health and medicine for the benefit of mankind. To this end, CEEPC continues to drive advances in proteomics, metabolomics, and diseases as well as raising awareness of pressing global humanitarian and health-care issues including mental health diseases, aging, chronic diseases, global epidemics and environmental issues. Today, CEEPC is a well-recognized major annual conference with a focused vision and a highly valued ideology as it continues to propagate scientific, medical and proteomic collaborations whilst expanding as more Eastern European countries prepare to join.

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With heightened expectations and amidst preparation to celebrate 100 years since Romania became a modern-day state, Bucharest welcomed the 12th CEEPC which was hosted by both the Romanian Academy housed in a century-old building with a unique façade, and its incredible auditorium [1] together with the 'George Palade' auditorium of ICBP-NS [2], giving excellent ambiance to the 3-day conference from October 24th – 26th, 2018. Maya Simionescu, Felicia Antohe, and the Organizing Committee of Viorel Suica, Elena Uyy, Raluca Boteanu, and Luminita Ivan, put together a multidisciplinary program encompassing Proteomics and Precision Medicine [3]. The theme of the Conference was 'Advances in Proteomics and Progress in Precision Medicine' and a whole plethora of proteomic disciplines were discussed including discovery proteomics, targeted proteomics and diverse 'multi-omic' topics including 'enabling technologies'.

The conference was a great success and many delegates stayed over to enjoy Bucharest, its beautiful historical past, hidden 'secret alleyways' and tree-lined boulevards, which earned Bucharest the nickname of *'Little Paris'* in the 1900s.

Victor Voicu, Vice-president of the Romanian Academy inaugurated the Conference by warmly welcoming all participants, followed by Professor Diana Loreta Păun, State Adviser to Public Health and Presidential Administration, Romania who alluded to the importance of scientific and medical collaboration. A long-awaited dream to host the CEEPC in Bucharest had come true and Romania stood to benefit from CEEPC's ethos and ideology [4].

Maya Simionescu (ICBP-NS, Bucharest, Romania) followed with a presentation entitled, 'Path to precision medicine: understanding diseases of cell organelles'. This thematic introduction nicely entwined with the priorities of CEEPC that were presented by Suresh Jivan Gadher, Founder Member of CEEPC, charting the credibility, cohesion, vision, and reasons for its success [5–13].

Suresh highlighted CEEPC's uniqueness in promoting socio-humanitarian issues [14] as well as proteomics related challenges including personalized and precision medicine. Current variability to treatment therapies and uncertainties in health risk assessments has provoked an urgent need for Precision Medicine. In order to determine the real disease and its effective treatment, spotlight is now on the individual, the individual's lifestyle together with one's environment of existence. Studying the proteome of an individual and incorporating gleaned data with diverse 'omics' data seems to be a plausible way forward. Such an approach, whilst incorporating predictive, preventative and defined strategies, needs to capture multiple proteomic aspects including transcriptional, post-translation modifications as well as genomics, metabolomics, genetics, and epigenetics in order to improve strategies for disease treatment and prevention. To achieve this, a need

CONTACT Suresh Jivan Gadher Suresh.Gadher@lifetech.com Thermo Fisher Scientific, 5781 Van Allen Way, Carlsbad, CA 92008, USA

for sensitive technologies and sophisticated bioinformatics, biostatistics, and data mining capabilities was highlighted.

Felicia Antohe (ICBP-NS, Bucharest, Romania) set the scene with a presentation entitled, 'Omics frontiers for personalized medicine' and presented the chronic diabetic kidney disease impacting the whole world. Quest for novel precision medicine-based diagnostic biomarkers has involved biochemical, histological and high-performance mass spectrometry-based proteomics to identify potential molecular markers in kidney harvested from experimental diabetic mice. Studies highlighted High mobility group box 1 protein (HMGB1), an active regulator of inflammation with significant impact on microvascular permeability and dysfunctionality of microvascular endothelial cells in the kidney.

Ales Svatos (Max Planck Institute for Chemical Ecology, Jena, Germany) shared the yellow mystery of Papaver nudicaule with an integrated omics approach to understand this obscure biosynthetic pathway for nudicaulins. Buds in different developmental stages were harvested from plants and RNA, proteins and metabolites were extracted using specific protocols. Trypsinolysed peptides were analyzed and molecular base of pelargonidin glucosides and indole in yellow poppy flowers was characterized to elucidate nudicaulins for their possible medicinal use.

Shlomo Sasson (Institute for Drug Research, Faculty of Medicine, The Hebrew University, Jerusalem, Israel) explored the glucolipotoxicity in pancreatic beta cells by combining advanced confocal analysis of the subcellular lipid map with proteomics. Despite advances in lipidomic analysis and lipid profiling of cells, little is known about the distribution and roles of structural lipids and lipid mediators in beta cells under normal and nutritional overload. The study aimed at monitoring lipid turnover in live beta cells (INS-1E cell line) under glucolipotoxic conditions by looking at lipid maps of beta cells. The generated complex lipid maps added to the proteomic analyses of beta cells, highlighting the crosstalk between lipids, protein expression and their functionality in normal and dysfunctional beta cells.

Day 2 of the Conference commenced with a Plenary lecture on 'Biomarker discovery and validation – from shotgun proteomics to targeted methods' by Rainer Bischoff (Department of Analytical Biochemistry, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands). Rainer presented the development and validation of three LC-MS/MS methods that allowed accurate and precise quantitation of soluble receptor of advanced glycation end products at the ng/ml level and related these results to various phenotypes of chronic obstructive pulmonary disease. A highly discriminatory protein biomarker for cervical cancer was discovered by shotgun proteomics in extremely small samples obtained by LCM. Such highly sensitive LC-MS/MS methods with sub-ng/ml level detectivity allow new ways of studying biochemical pathways using concatenated signature peptides.

An exciting 'Pitchfork Strategy' – a multi-pronged approach for membrane proteome profiling of human pheochromocytoma and paraganglioma (PHEO & PGL) samples was unveiled by Jiri Petrak (BIOCEV, First Faculty of Medicine, Charles University in Prague, Czech Republic). This strategy targeted different features of integral membrane proteins (IMPs) and allowed broader range of identification of IMPs than the classical proteomic strategies. Amongst the identified proteins routinely observed, numerous so-called *'missing proteins'* were discovered. Similarly, Brindusa Alina Petre (Faculty of Chemistry, Alexandru Ioan Cuza, University of Iaşi, Romania) presented the molecular identification of nitro-tyrosine modification in human eosinophil proteins using proteolytic affinity extraction mass spectrometry and found it to be a sensitive tool for the molecular identification of tyrosine nitration in proteins.

Suresh Jivan Gadher (Thermo Fisher Scientific, Carlsbad, CA, USA) followed with a presentation on, 'Synergistic success of proteo-genomics in interrogating exotic biological fluids using a novel high sensitivity Immunoassay'. Human tears despite their limited volume are an excellent source of disease biomarkers and offer a prognostic and/or diagnostic opportunity in precision medicine. ProQuantum™ Immunoassay incorporating analyte specificity of high-affinity antibody–antigen binding with the signal detection and amplification of real-time PCR was shown to offer analyses of DNA, RNA, and protein biomarkers with greater sensitivity and dynamic range than traditional methods. Interestingly, Theo Marten Luider (Laboratory of Neuro-Oncology/Clinical and Cancer Proteomics, Dept. Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands) approached identification of antibodies specific for cancer by integration of mass spectrometry and DNA sequencing giving a better sensitivity, showing that such 'multi-omic' approach too has a great potential for diagnosis and therapeutic applications.

Complexities of tumor biomarkers were highlighted by Helena Kupcova Skalnikova (Institute of Animal Physiology and Genetics, Czech Academy of Sciences, Libechov, Czech Republic) by monitoring cytokines in melanoma patient serum for cancer progression. Helena demonstrated that malignant melanoma progression was reflected in serum samples by identifying Growth factors HGF, G-CSF and VEGFA, chemokines RANTES and IL-8 and cytokines IL-6, IFNα, IFNγ, and IL-1RA, known influencers of tumor growth, metastasis and anticancer activity.

The Collision Energy (CE) is the most important single parameter influencing the success of MS/MS-based peptide identification. László Drahos (MS Proteomics Research Group, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary) debated the selection of CE in Tandem Mass Spectrometry-Based Proteomics and by utilizing tryptic digests of complex standards (HeLa, E. Coli), highlighting that CE optimization can increase the average score by ~15%, improving sequence coverage, peptide, and protein identification.

Manuela Călin, and Viorel Şuică – both from (ICBP-NS, Bucharest, Romania) concluded the day's proceedings with presentations on Nanoparticles (NP). Manuela championed the development of suitable nanocarriers for effective delivery of therapeutic agents to dysfunctional endothelial cells whereas Viorel discussed the proteomic alterations induced by poly (2-ethyl butyl cyanoacrylate) nanoparticles on the proteomes of different cell lines and murine hepatic tissue. Results suggested an altered protein biosynthetic machinery

of cells exposed to NP, while 'in vivo' imaging experiments demonstrated a temporal bio-distribution and clearance of NP. Protein pre- and post-adsorption studies revealed the importance of NP in *in vivo* and *in vitro* studies.

The eagerly awaited conference dinner with all its Romanian hospitality and traditional cuisine, music, and dancing were enjoyed by all. The 12th anniversary of CEEPC, the 39th anniversary of ICBP-NS, and the 100 years of Romanian Unification were toasted with exquisite local wines from the Carpathians Mountains.

The final day of the conference commenced with Fernando Corrales (Centro Nacional de Biotecnología, CSIC, Madrid, Spain) who presented a lecture on, 'One carbon metabolism (1CM) and protein methylation – Implications in liver disease'. iTRAQ isobaric labeling used to investigate methylthioadenosine phosphorylase deficiency (MTAP) in SkHep1 cells by R-methyl peptide enrichment followed by LCMS/MS, highlighted lack of MTAP – a detrimental prognosis in cancer. Such monitoring of 1CM in the liver may help assessment of liver parenchymal cells homeostasis.

Novel proteomic technologies are a cornerstone of precision medicine and Goran Mitulović (Medical University of Vienna, Vienna, Austria) and Cristina Furdui (Center for Redox Biology and Medicine, Winston – Salem, USA) discussed examples which could benefit disease diagnosis and drug research. Goran showed how Micro-Pillar-Arrayed Column from a silica wafer using lithographic micromachining techniques could give highly reproducible separation of tryptic peptides at low pressures whereas Cristina discussed multiple-combined chemical and high-end technologies in redox biology and medicine which could benefit precision medicine.

'Venomics' and its complexities were presented by Juan Jose Calvete (Venomics Laboratory, CSIC, Valencia, Spain). Juan discussed several proteomic technologies to achieve toxin-resolved venom proteomes for the benefit of mankind.

Differentiation of cancerous and normal epithelium remains a major problem in head and neck cancer. Discrimination of oral cancer from normal oral mucosa by MALDI mass spectrometry imaging of proteins and lipids was presented by Piotr Widlak (Maria Skłodowska-Curie Institute – Oncology Center, Gliwice, Poland) who compared proteome and lipidome components. Squamous cell cancer and normal epithelium were analyzed by MALDI mass spectrometry imaging. Both were found to be promising sources of biomarkers of oral malignancies. A similar study was narrated by Mirela Sârbu (National Institute for Research and Development in Electrochemistry and Condensed Matter, Timişoara, Romania) who recommended the use of ion mobility tandem mass spectrometry (IMS MS) in glycoproteomics and glycolipidomics of human biopsies for detection and characterization of potential biomarkers.

Plant proteomics has a special role to play in precision medicine as shown by Xaveer Van Ostade (University of Antwerp, Wilrijk, Belgium) with the Withaferin A (WA), a steroidal lactone from the plant Withania Somnifera. An MM1R cell line was Stable isotope labeled using amino acids in cell culture and treated with and without WA to examine WA antitumor responses on the cancer proteome with beneficial outcome in a multiple myeloma model.

Katarina Davalieva1 ('Georgi D Efremov', Macedonian Academy of Sciences and Arts, Skopje, R Macedonia) presented a 'proteomics analysis of prostate tissue for valuable biomarkers for early diagnosis, cancer progression and new drug targets'. Proteomics profiling of Prostate cancer (PCa) tissue samples ranging from Gleason 6–9 obtained with radical prostatectomy was performed on High Definition Mass Spectrometry Quadruple Time of Flight using label-free data-independent acquisition. Several biomarker proteins involved in cell signaling and transduction, cell growth and energy pathways were identified which may exert a role in PCa progression.

Raluca Boteanu (ICBP-NS, Bucharest, Romania) focused on proteomics of bone healing using titanium implant with bioactive-targeted surface in a rat tibial defect model to understand how the interactions of differentially expressed proteins exert their role on the repair process of bone fracture.

CEEPC had managed to fulfill one of its greatest dreams of facilitating expert scientific interaction and collaborations between scientific specialties and precision medicine communities interested in resolving mysteries about protein functionalities in health and disease. Additionally, CEEPC provided a new momentum and a fresh outlook to young generation of researchers fascinated by proteomics related precision medicine. The Romanian hospitality and warmth spilled over into the weekend with a visit to the *'Dimitrie Gusti National Village Museum'* [15], allowing all to dwell into the historical past, culture, and traditions of Romania.

In keeping with tradition, the 13th CEEPC, 2019 will be held in *Ustroń, Poland* [16], from 23rd to 25th September, 2019 where once again exciting advances in proteomes, proteomics, and biological system related topics will be debated to address newer challenges.

Expert opinion:

Founders of the Central and Eastern Proteomic Conference (CEEPC) could visualize the pivotal role of 'Proteomics' more than a decade ago. Careful balancing of proteomic excellence with evolving societal needs, has led to its present-day success in these series of conferences. In the era of emerging personalized medicine where treatment selection for each patient is becoming individualized, CEEPC stands to play a major role in promoting multifaceted proteomics in Central and Eastern Europe. Since protein expression is dynamic and changes in relation to disease onset, severity or response to therapy difficult to understand, proteomics is helping characterize diseases at protein level. This is something that Genomics alone has not been able to facilitate despite intense focus.Proteomic technologies have progressed over the last decade allowing in principle the comprehensive analysis of expressed proteins in time and space. Until now, quantitative proteomics has been pin-pointing minor differences in the protein levels between normal and pathological samples. There is now an urgent need for sophisticated *'enabling technologies'* to identify structural differences in proteins introduced by mutations or structural variations induced by post-translational modifications or protein truncation that are associated with a disease. Additionally, comprehensive characterization of the small molecule metabolites in biological systems and *'biological applications'*

of the 'Metabolome' together with the 'Proteome' in precision medicine of the patient, stands to revolutionize global health.

The complexity of the data generated has also been a stumbling block in understanding diseases because proteome analysis does not provide a simple yes/no answer but rather requires deep interpretation. To this end, utilization of data and information from proteomics, genomics, metabolomics and various 'multi-omics' studies, together with *Artificial Intelligence (AI)* in the hands of skilled researchers and clinicians, will have significant societal impact moving forward. Dr. Suresh Jivan Gadher.

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Declaration of interest

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