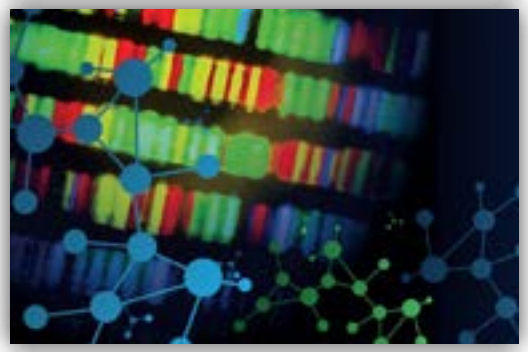
9th International Conference and Exhibition on

Metabolomics and Systems Biology

August 29-30, 2017 Prague, Czech Republic

Scientific Tracks & Abstracts

Day 1



Cancer Metabolomics | Diagnostic Biomarkers | Analytical-bioanalytical Techniques | Personalised Medicine

Session Chair
Richard J Naftalin
King's College School of Medicine London, UK

Session Introduction

Title: **Evaluating heme flux and function in lung cancer**
Li Zhang, The University of Texas at Dallas, USA

Title: **Blood-based metabolomic biomarkers for human neurological disorders**
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Title: **Metabolomics on mouse models of disease for personalized medicine**
Preeti Bais, The Jackson Laboratory for Genomic Medicine, USA

Title: **Comprehensive LC-MS reference library: Construction strategy and application in metabolic profiling and metabolomics**
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Title: **Stable isotope-assisted metabolomics of *Fusarium* head blight on wheat**
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Title: **High resolution metabolomics to identify novel biomarkers in corticosteroid resistant asthmatic children**
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Title: **Building and optimising multi-enzyme *in vitro* cascade reactions**
Nicholas Harmer, University of Exeter, UK

Title: **Pharmacometabolomics-guided pharmacogenomics in precision medicine**
Theodora Katsila, University of Patras, Greece

Li Zhang, Biochem Mol biol J, 3:2
DOI: 10.21767/2471-8084-C1-002

Evaluating heme flux and function in lung cancer

Li Zhang
The University of Texas at Dallas, USA

Emerging experimental data increasingly show that despite the enhanced glycolytic flux, many types of cancer cells exhibit intensified oxygen consumption or mitochondrial respiration. Even under hypoxia, cancer cells can maintain oxidative phosphorylation at a substantial rate. Heme is a central factor in oxygen utilization and oxidative phosphorylation. It serves as a prosthetic group in many proteins and enzymes involved in mitochondrial respiration. Our recent work showed that non-small-cell lung cancer (NSCLC) cells and xenograft tumors exhibit substantially increased levels in an array of proteins promoting heme synthesis, uptake and function. These proteins include the rate-limiting heme biosynthetic enzyme ALAS, transporter proteins, and various types of oxygen-utilizing hemoproteins, such as cytoglobin and cytochromes. In contrast, lowering heme biosynthesis and uptake, like inhibiting mitochondrial respiration, effectively reduced oxygen consumption, cancer cell proliferation, migration and colony formation. To further ascertain the importance of elevated heme flux and function in lung tumorigenesis, we use multiple experimental approaches to detect the levels of heme synthesis, uptake, and degradation in an array of NSCLC cell lines and in *de novo* tumors in genetically engineered mouse models for lung cancer. We also measure oxygen consumption and ATP generation in these cell lines and tumors. These experiments should reveal the degree to which elevated heme flux—heme synthesis, uptake, and degradation—contribute to lung tumorigenesis and how heterogeneity in heme flux contributes to metabolic and bioenergetics heterogeneity in lung tumors.

Biography

Li Zhang completed her PhD from UCLA and Post-doctoral studies from MIT Department of Biology. She is the Cecil H and Ida Green Distinguished Chair in Systems Biology Science at University of Texas at Dallas. She has worked on studying heme signaling and function for 20+ years. She has published many original research articles and a book entitled “Heme Biology: The Secret Life of Heme in Regulating Diverse Biological Processes”. Her research work has also made important contributions in understanding the roles of molecular chaperones in cellular signaling, molecular mechanisms of oxygen signaling, and the actions of neurotoxicants. Recently, her work focuses on investigating heme function in lung cancer. She and colleagues have provided a unifying view of cancer bioenergetics in a review article entitled “A Holistic View of Cancer Bioenergetics: Mitochondrial Function and Respiration Play Fundamental Roles in the Development and Progression of Diverse Tumors” published in the journal *Clinical and Translational Medicine.*

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Massimo S Fiandaca et al., Biochem Mol biol J, 3:2
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Blood-based metabolomic biomarkers for human neurological disorders

Massimo S Fiandaca[1], Mark Mapstone[1], Amin Mahmoodi[1], Thomas Gross[1], Amrita K Cheema[2], Fabio Macciardi[1], Kian Merchant-Borna[3], Jeff Bazarian[3] and **Howard J Federoff[1]**
[1]University of California, Irvine, USA
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[3]University of Rochester Medical Center, USA

For many human maladies, especially neurodegenerative disorders (e.g., Alzheimer's disease, AD, and Parkinson's disease, PD) the ability to predict disease risk during asymptomatic stages is essential for earlier and more efficacious interventions. Blood-based biomarkers for AD (and PD), once defined and validated, may facilitate the participation of at-risk asymptomatic individuals in therapeutic clinical trials, and thereby increase the potential for successful prevention and/or disease modification. In conditions such as mild traumatic brain injury (mTBI), relevant blood bio-signatures could provide unbiased diagnostics that significantly improve clinical decision-making and improved treatments. Blood-based metabolomic biomarkers may offer such diagnostic and therapeutic potential in both AD and mTBI, as evidenced by our recent work. In this seminar, I plan to discuss our group's approaches to blood-based metabolomic biomarker development and present results from our most recent metabolomic investigations related to AD and mTBI. We are encouraged by the potential provided by both untargeted and targeted metabolomic platforms in defining annotated species that are germane to the respective clinical conditions. We also provide caution to those exploring this area of research since there are many confounding factors that need close scrutiny in an effort to maximize clinical utility.

Biography

Massimo S Fiandaca is a Neuroscientist and Associate Professor in the Department of Neurology and Neurological Surgery at University of California Irvine (UCI). As Co-director of the Federoff Translational Laboratory and Biorepository (TLaB) at UCI, he is currently focused on blood-based biomarkers related to neurological disorders. Through established local, national, and international collaborations, he and his colleagues hope to impact the development of relevant blood-based biomarkers for a variety of conditions affecting the nervous system. He is a board certified Neurological Surgeon, who retired from surgical practice after 25 years, and returned to full-time academic research and teaching. His past research experiences have focused on direct brain delivery of therapeutics for neurodegenerative disorders and neuro-oncology, including cellular and tissue transplantation, viral-vector based therapeutic gene delivery, MRI-directed convection-enhanced delivery, and nano-liposomal therapeutics.

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Preeti Bais, Biochem Mol biol J, 3:2
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Metabolomics on mouse models of disease for personalized medicine

Preeti Bais
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Metabolomics is a newer omics technology that can help in generating a more comprehensive view of a biological system when combined with the genomic, transcriptomic and proteomic technologies. In this seminar, I will discuss the bioinformatics infrastructure that we have developed at Jackson Laboratory to perform mass spectrometry based metabolomics experiments on mouse based studies. I will highlight some case studies where I have used metabolomics in mouse models of neuromuscular degeneration and patient derived xenograft (PDX) for cancer studies and personalized medicine. Charcot-Marie-Tooth (CMT) disease encompasses a genetically heterogeneous class of heritable motor and sensory neuropathies that result in axonal degeneration in the peripheral nervous system. Charcot-Marie-Tooth type 2D (CMT2D) is caused by dominant mutations in Glycyl tRNA Synthetase (GARS). Samples from the spinal cord of GARS mutant mice and littermate control animals were compared using mass spectrometry based metabolomics. The changes associated with GARS mutations suggested possible treatment strategies through supplementation. In another case study, Gas Chromatography Mass Spectrometry (GCMS) based analysis was used to derive a metabolic signature of triple negative breast cancer (TNBC) by comparing the metabolites present in three study arms of patient-derived xenograft (PDX) mouse urine. This analysis not only suggested metabolic uniformity of the JAX mice but also showed cancer specific changes in the vehicle (tumor with no treatment) arm, known drug side effects in the treatment arm (tumor engrafted and treated) and the age related changes in the pure (no tumor no treatment) arm.

Biography

Preeti Bais is a Scientist at Jackson Lab's new research institute- JAX Genomics Medicine (JGM). It is an independent, nonprofit organization focusing on mammalian genetics research to advance human health. She holds a PhD degree in Bioinformatics and Computational Biology. She has worked on projects involving metabolomics analysis of Human Embryonic Stem (hES) and Induced Pluripotent Stem (IPS) cells based assays for drug toxicity screening, autism biomarker detection using blood samples, mouse models of neuromuscular degeneration and cancer drug efficacy testing using orthotropic mouse models triple negative breast cancer.

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Ilana Rogachev et al., Biochem Mol biol J, 3:2
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Comprehensive LC-MS reference library: Construction strategy and application in metabolic profiling and metabolomics

Ilana Rogachev[1], Nir Shahaf[1], Sagit Meir[1], Sergey Malitsky[1], Uwe Heinig[1], Maor Battat[1], Hilary Wyner[1], Ron Wehrens[2] and **Asaph Aharoni[1]**
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Unambiguous metabolite identification is an essential but yet unresolved problem in mass spectrometry-based (MS) metabolomics assays. It is particularly critical in studies of rich metabolic matrices such as those present in plant extracts. Generating a comprehensive mass spectra library from highly pure reference compounds isolated from an extensive repertoire of plant species is currently the most reliable strategy for advance in MS based identification of natural products. To address the issue of generating large MS libraries in a high-throughput manner, two computational pipelines were developed: one allows an automated construction of a reference library from LC-MS injections of authentic chemical standards and the other, termed 'MatchWeiz', allows for an efficient and accurate matching of high resolution experimental LC-MS data to the reference library data. We applied the presented methods by injecting a comprehensive collection of several thousands of plant secondary (specialized) metabolites using a UPLC-qTOF MS in the MSE mode in order to generate a large and structurally diverse MS spectra library, termed 'WEIZMASS'. In this presentation, I will demonstrate the experimental methods used for the rapid generation of the WEIZMASS library: the main considerations during sample preparation and the choice of instrumentation parameters for the rapid construction of such a large MS reference library. I will highlight the building blocks of the software pipelines used and, present the chemical rationale behind the computational algorithms. Finally, I will demonstrate the application of the WEIZMASS library for identification of secondary metabolites in different plant extracts.

Biography

Ilana Rogachev is a trained Analytical Chemist, an expert in Metabolomics, specializing in the analysis of natural products using LC-MS and GC-MS instruments. Her knowledge in the analysis of complex plant extracts and in structural identification of natural products formed the basis of the chosen experimental methods and the analytical rationale behind the computational algorithms used to create the WEIZMASS library.

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Rainer Schuhmacher et al., Biochem Mol biol J, 3:2
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Stable isotope-assisted metabolomics of *Fusarium* head blight on wheat

Rainer Schuhmacher, Christoph Bueschl, Asja Ceranic, Maria Doppler, Bernhard Kluger, Rudolf Krska, Alexandra Simader, Bernhard Wolf, Barbara Steiner, Hermann Buerstmayr, Marc Lemmens and **Gerhard Adam**
University of Natural Resources and Life Sciences, Austria

Metabolomics studies show great potential to provide an improved understanding of the molecular mechanisms underlying plant diseases such as *Fusarium* head blight (FHB) on wheat. Here, we present the successful combination of LC-HRMS based global ^{13}C labeling- & ^{13}C tracer techniques to probe both the attack of the mycotoxigenic fungus *Fusarium graminearum* as well as the metabolic response of near isogenic wheat lines, differing in a major resistance QTL against FHB. To do so, parent and corresponding wheat NILs were cultured in the greenhouse and treated with *F. graminearum* spores at anthesis. In addition, custom-tailored, globally ^{13}C-labelled wheat plants of the resistant and susceptible parent lines were grown as a reference in a tailor-made labeling chamber. To further elucidate the phenylalanine (Phe)- and tryptophan (Trp)-derived submetabolome, wheat ears were also treated with U-^{13}C phenylalanine or U-^{13}C tryptophan (Trp) under control- and infection conditions. LC-HRMS and subsequent data analysis clearly revealed some 1.000 metabolites in the tested biological samples. Among those ca. 100 and 70 were found to be derived from the metabolic precursors Phe and Trp, respectively. Substance with levels, which were significantly affected by *Fusarium* have been further investigated for their putative role in QTL mediated resistance against FHB. The abundance of various substance classes differed significantly between the tested wheat lines with respect to both the timing of formation and relative amount. Our results for hydroxycinnamic acid amides, phenolic acids, flavonoids and lignans suggest that different molecular mechanisms contribute to defense and resistance against FHB. In this talk, I will present the isotope-assisted metabolomics protocols which we have developed and how we have investigated defense responses and resistance mechanisms of wheat against *Fusarium* head blight.

Biography

Rainer Schuhmacher is an Associate Professor at University of Natural Resources and Life Sciences (BOKU), Vienna where he is heading the working group Metabolomics and Bioactive Compounds. His research focuses on LC-HRMS and GC-MS based metabolomics of microbes and plants with a special focus on the interaction between these living organisms. He received his degrees in Chemistry at University of Konstanz, Germany and Vienna University of Technology, and in 2009 he completed his Habilitation in Analytical Chemistry at BOKU University, Vienna. He is co-author of more than 120 SCI publications.

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Fumiko Matsuzaki, Biochem Mol biol J, 3:2
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Metabolic systems analysis with multi-omics data

Fumiko Matsuzaki
Kyushu University, Japan

Advances in omics technologies have enabled us to measure a large number and variety of molecular components of cells. This should enormously assist in our understanding of complex biological phenomena and the improvement of more quantitative omics methods will accelerate this understanding. However, effective ways to take advantage of such data have not yet been developed. A need exists for an analytic methodology to extract biological characteristics, as well as for more sophisticated quantification methods to advance our understanding of how organisms achieve highly regulated systems. In our current research, we have developed a new technology termed *in vitro* proteome–assisted multiple reactions monitoring for protein absolute quantification (iMPAQT) to measure the absolute quantities of all human proteins. With the use of iMPAQT, we have measured the absolute quantities of almost all metabolic enzymes in human cells and uncovered the weights of each node in human metabolic networks. In addition, we have developed a new computational method based on biochemical systems theory to integrate the absolute quantities of metabolic enzymes, as well as those of metabolites measured by metabolomics, experimentally available fluxes and metabolic network structure. It is now possible to estimate each flux, calculate sensitivities of fluxes and metabolite concentrations with respect to the concentration of each enzyme, and simulate metabolite concentrations under some perturbations. In order to extend the combined approach of large scale quantification and computational analysis, in our institute we have set up the Research Center for Transomics Medicine, where proteome, transcriptome, metabolome and other omes can be measured. Furthermore, we are now attempting to integrate multi-omics data and analyze insulin action on metabolism in the liver as a pilot study. We expect that a further development of this approach will lead to comprehensive understanding of how the metabolic network system or various biological systems are regulated and will establish a new leading edge of modern biology.

Biography

Fumiko Matsuzaki is a Molecular and Systems Biologist with a PhD in Medical Science from Kyushu University, Japan. Her work has involved proteomics, metabolomics and molecular and biochemical approaches to the investigation of cancer metabolism, xenobiotic metabolism and membrane trafficking. Recent developments in omics technologies led her to start computational work with bioinformatics and mathematical approaches to take advantage of omics data. She aims to deliver practical methods to decipher complicated biological systems.

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Youngja H Park et al., Biochem Mol biol J, 3:2
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High resolution metabolomics to identify novel biomarkers in corticosteroid resistant asthmatic children

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[2]Emory University, USA

Corticosteroid (CS) treatment is the preferred anti-inflammatory treatment for adults and children with asthma. However, a subset of patients fails to respond to combined systemic and inhaled CS treatment despite very high doses and prolonged treatment. Due to the uncertainty of the molecular mechanism for CS-resistant asthma, this study is aimed at discovering diagnostic biomarkers for early identification of children resistant to CS. High resolution metabolomics (HRM) was performed on plasma and urine samples from CS-respondent and CS-non-respondent children to determine putative biomarkers related to CS resistance. The metabolic phenotypes of CS-responders and CS-non-responders were analyzed using bioinformatics including Manhattan plot with False Discovery Rate (FDR), Hierarchical Cluster Analysis (HCA), Kyoto Encyclopedia Genes and Genomes (KEGG) and Mummichog pathway analysis. The Manhattan plot with false discovery rate determined 1894 metabolites in plasma and 30 metabolites in urine significantly altered between CS-responders and CS-non-responders. The important metabolites annotated were S-adenosylmethionine (439.1395 *m/z*, $[M+ACN+H]^+$) and S-adenosylmethionine (378.1448 *m/z*, $[M+Na]^+$) in plasma as well as ϒ-glutamylcysteine (236.06 *m/z*, $[M+S(34)+H]^+$) and Cys-Gly, (253.06 *m/z*, $[M-NH_3+H]^+$), reduced FMN (517.0794 *m/z*, $[M+NaCl]^+$). Thus, the metabolites in glutathione metabolism were altered significantly regarding CS resistance. The identified biomarkers in urine of asthmatic children would be extremely beneficial not only for early detection, but also in the development of therapies aimed at preventing the irreversible airway damage and lung function decline associated with CS resistance in severe asthma among children.

Biography

Youngja H Park completed her MS and PhD in Pharmacology and Toxicology under Dr. James P Kehrer at University of Texas at Austin in 1990. She previously had worked as an Assistant Professor in the Department of Medicine and as the Assistant Director of the Clinical Biomarkers Laboratory at Emory University School of Medicine since 2013. At Emory University, she developed LC-MS based metabolomics pipelines to identify novel biomarkers and the pathways associated with diseases. She published number of metabolomics papers in *Science and Journal of Allergy and Clinical Immunology*. Currently, she moved back to College of Pharmacy, Korea University where she has built metabolomics core facility after years of experience in research, evaluation and teaching both in hospital and education institutions. Her career goal is to identify the novel biomarkers and develop the sensors in early diagnoses of disease.

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Christoph Bueschl et al., Biochem Mol biol J, 3:2
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Automated annotation of the wheat metabolome during *Fusarium* infection using stable isotopic labeling and custom-tailored data processing workflows

Christoph Bueschl, Bernhard Kluger, Maria Doppler, Asja Ceranic, Rudolf Krska and **Rainer Schuhmacher**
University of Natural Resources and Life Sciences, Austria

Fungi of the genus *Fusarium* infect crop plants thereby causing plant diseases and contamination of food with its toxic secondary metabolites so-called mycotoxins. To characterize the plant's metabolic defense mechanisms to *Fusarium* infection, we have developed several analytical protocols accompanied by custom-designed automated data processing tools. The first workflow, entitled all extract, is designed for the detection of all LC-HRMS accessible metabolites of wheat. It uses either uniformly ^{13}C-labeled or ^{15}N-labeled wheat reference material, which has been grown in-house and has an isotopic enrichment of ~99%, for metabolite detection and annotation (~1.000 carbon- and ~300 nitrogen-containing metabolites). Moreover, the ^{13}C-labeling step enables metabolome-wide internal standardization thereby improving relative quantification and subsequent statistical comparison of the experimental groups. A second workflow, named TracExtract, allows probing the metabolism of exogenous or endogenous ^{13}C-labeled tracer compounds in wheat plants and reports only biotransformation products that the plant has produced from the respective tracer. Using this approach, uniformly ^{13}C-labeled phenylalanine and tryptophan tracers have been used to annotate respective tracer-derived wheat biotransformation products (120 and 60 respectively). This annotation is especially helpful since many of the already known defense-related metabolites in wheat are descendants of these two tracer compounds. Furthermore, the tracer approach was successfully used to investigate the plant's detoxification mechanisms of *Fusarium graminearum* most potent mycotoxin deoxynivalenol. A total of nine mostly novel detoxification products were detected. Finally, all information about the wheat metabolites is aggregated thus describing each detected metabolite with its total number of carbon and nitrogen atoms and if it is derived from phenylalanine or tryptophan. This untargeted annotation is an invaluable resource for further investigation of wheat-*Fusarium* interaction on a metabolic level and enables a more focused investigation of potential novel defense-related metabolites.

Biography

Christoph Bueschl is a Postdoctoral Researcher at Metabolomics group at IFA-Tulln with expertise in automated data processing of LC-HRMS data. He is specialized in data evaluation and software development of stable isotope assisted and LC-HRMS based untargeted metabolomics experiments as well as stable isotope assisted tracer experiments that probe the secondary metabolism of either endogenous or exogenous secondary metabolites in biological systems. His developed software tools are actively being used, steadily improved and extended with new functionality and applied in various projects and co-operations. Besides data processing of LC-HRMS data, one of his research interests is statistical evaluation of large datasets especially in the area of metabolomics research.

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Notes:

Nicholas Harmer, Biochem Mol biol J, 3:2
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Building and optimizing multi-enzyme *in vitro* cascade reactions

Nicholas Harmer
University of Exeter, UK

Biocatalysis is becoming increasingly attractive for the development of more efficient and cleaner chemical synthetic processes. The combination of multiple enzyme steps for cascade reactions allows for attractive one-pot processes with reduced operating costs. While the use of whole-cells have a number of advantages for these reactions, the competing needs of the cell and limited transport across the cell membrane can result in a low final product concentration. In contrast, the use of isolated enzymes allows reactions to be easily controlled, with the use of stable enzymes such as those from thermophiles offering economically competitive processes. For the construction of novel enzymatic cascade reactions, there is a need for well-defined modular enzyme building blocks that can be quickly assembled for new reactions. Carboxylic acid reductase (CARs) is a relatively undeveloped class of enzyme which meets a demand in synthetic chemistry for a green and regiospecific route to aldehydes from their respective carboxylic acids. A thorough biochemical characterization of four new CARs provides insight into the operating parameters of these enzymes, while the integration of a CAR into a seven enzyme *in vitro* cascade reaction demonstrates their potential for green chemistry. Mathematical modeling of the cascade allows for a detailed understanding of the reaction and gives opportunity for its optimization with respect to flux and cost. Our work highlights the virtue of thorough enzyme characterization, and of modeling reactions, to deliver new understanding and build robust pathways.

Biography

Nicholas Harmer completed his PhD in the laboratory of Professor Sir Tom Blundell in Cambridge, UK, researching the structure and interaction of fibroblast growth factors, their receptors, and heparin. Following this, he took a Post-doctoral position in Cambridge, investigating the structure and function of a range of signaling proteins and bacterial enzymes. He then moved to AstraZeneca R&D Mölndal, Sweden, where he worked as a Structural Biologist in Drug Discovery. In 2007, he established his own laboratory at University of Exeter, UK. His research work focusses on Synthetic Biology and Drug Discovery applications for neglected diseases. His main interest is in understanding enzymes more deeply, and in exploiting this understanding to develop useful chemicals and biochemical. In 2017, he moved to Living Systems Institute, Exeter.

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Theodora Katsila et al., Biochem Mol biol J, 3:2
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Pharmacometabolomics-guided pharmacogenomics in precision medicine

Theodora Katsila and **George P Patrinos**
University of Patras, Greece

Inter-individual variability has been a major hurdle to optimize disease management. Precision medicine holds promise for improving health and healthcare via tailor-made therapeutic strategies. Herein, we outline the paradigm of pharmacometabolomics-guided pharmacogenomics. We envisage merging pharmacometabolomic and pharmacogenomic data (to address the interplay of genomic and environmental influences) with information technologies to facilitate data analysis as well as sense and decision-making on the basis of synergy between artificial and human intelligence. Humans can detect patterns, which computer algorithms may fail to do so, whereas data-intensive and cognitively complex settings and processes limit human ability. We propose that better-informed, rapid and cost-effective multi-omics studies coupled to information technologies allow for data reproducibility and robustness in genotype-to-phenotype correlations.

Biography

Theodora Katsila currently serves as a Senior Research Fellow and academic scholar. Her research work focuses on “Spans pan-omics strategies coupled to information technologies toward better-informed decision-making and genotype-to-phenotype correlations”. Sharing both academic and industrial research experience, she has a multidisciplinary expertise.

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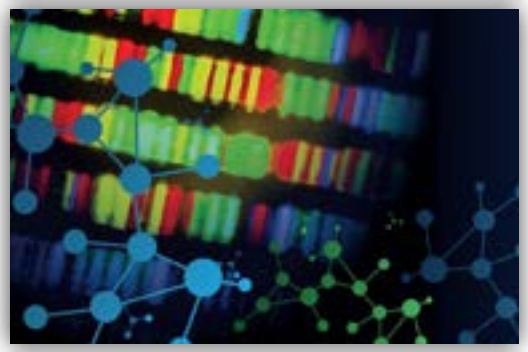
Day 2



Plant & Environmental Metabolomics | Metabolites| Metabolomics in Diseases

Session Chair
Youngja H Park
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Session Co-Chair
Anne-Marie Delort
Université Clermont Auvergne, CNRS, France

Session Introduction

Title: **Modulation and resilience of the metabolome of *Pseudomonas graminis*, a cloud bacterium, facing H_2O_2 atmospheric stress**

Anne-Marie Delort, Université Clermont Auvergne, CNRS, France

Title: **Antihypertensive effects of natural honeybee products: A review**

Zeliha Selamoglu, Omer Halisdemir University, Turkey

Title: **Expression of genes involved in taxol biosynthetic pathway in *Taxus baccata L.* and application of magnetic- and carbon-based nano-adsorbents for pre-purification of taxol**

M. Naghavi, University of Tehran, Iran

Title: **APC as an entry point to study small molecule regulation of the cell cycle**

Nubia Barbosa Eloy, Max Planck Institute, Germany

Title: **Mapping the *Arabidopsis* metabolic landscape by untargeted metabolomics at different environmental conditions**

Si Wu, Max Planck Institute of Molecular Plant Physiology, Germany

Title: **Cholinergic microRNA-132 sheds new light on the links between psychological stress and metabolic impairments**

Hermona Soreq, The Hebrew University of Jerusalem, Israel

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Anne-Marie Delort et al., Biochem Mol biol J, 3:2
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Modulation and resilience of the metabolome of *Pseudomonas graminis*, a cloud bacterium, facing H_2O_2 atmospheric stress

Anne-Marie Delort[1,2], Nolwenn Wirgot[1], Marie Lagrée[1,2], Mounir Traïkia[1,2], Isabelle Canet[1], Martine Sancelme[1], Cyril Jousse[1,2] and **Bernard Lyan[2]**

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In cloud waters, microorganisms are metabolically active although they are exposed to very strong stresses, especially due to the presence of reactive oxygenated species, including H_2O_2 and radicals. In order to understand how microorganisms can modulate their metabolism facing H_2O_2 stress, we have investigated by a metabolomics approach the response of a *Pseudomonas graminis* strain, isolated from cloud waters, to hydrogen peroxide exposure. For this purpose *P. graminis* cells were incubated in microcosms containing artificial cloud waters in the presence or absence of H_2O_2. Metabolites were extracted at two time points (50 min and 24 h) that were important regarding the evolution of ATP cellular content and H_2O_2 degradation over time. These bacterial extracts were analysed by LC-MS and 1H-NMR using the Metabolic Profiler® facility (Bruker). Metabolic profiles were converted into matrices and statistical analyses (PCA, PLS-DA) were performed; key markers of this oxidative stress were identified by 2D NMR and LC-MS-Orbitrap. At time 50 min, when H_2O_2 was still present in the incubations, the bacteria adapted and modulated their metabolome facing this stress. The major metabolic pathways of *Pseudomonas graminis* (13b-3) impacted by the presence of hydrogen peroxide were the carbohydrate pathway, glutathione, energy, lipid and amino-acid metabolisms. Unexpectedly, the concentration of a few dipeptides containing mainly Ala, Val, Leu (Ile) was also highly modified in the presence of H_2O_2. These dipeptides are reported here for the first time as biomarkers of oxidative stress. Interestingly, at time 24 h, when H_2O_2 has been completely biodegraded by the cells, no more significant difference was observed between the metabolites of exposed and non-exposed cells to H_2O_2. This shows the resilience of this bacterium metabolome after H_2O_2 stress exposure. These results are discussed in terms of impacts on cloud chemistry.

Biography

Anne-Marie Delort is a Senior Scientist at CNRS. She is working at Institute of Chemistry of Clermont-Ferrand in France. In addition to a general background in chemistry and molecular biology, her expertise covers Microbiology and Metabolomics. She specifically studies microbial metabolism in relation with the environment. She has been a pioneer in studying the microbial population in clouds. Recent studies concern the adaptation of microorganisms to atmospheric stresses and the role of microorganisms in atmospheric chemistry and physics. This includes the transformation of organic matter, interaction with oxidants and formation of ice nuclei and cloud condensation nuclei (biosurfactants). Her group is part of MetaboHUB, the French national infrastructure of excellence in metabolomics and fluxomics.

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Zeliha Selamoglu, Biochem Mol biol J, 3:2
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Antihypertensive effects of natural honeybee products: A review

Zeliha Selamoglu
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Oxidative stress is associated with increased generation of oxidizing molecules parallel to a significant decrease in the endogenous total antioxidant capacity. It represents an important pathological hallmark in several disorders, including cardiovascular conditions such as hypertension, and atherosclerosis, and neurodegenerative diseases such as Parkinson's disease, and Alzheimer's disease. Naturally occurring antioxidants are largely used as dietary supplements to attenuate oxidative stress in human disease. Honey bee products have attracted clinical interest due to their favorable pharmacological and biological properties, including anti-aging, anti-tumoral, antimicrobial, antioxidant, anti-inflammatory effects. The presence of several important phytochemical classes, such as flavonoids, aromatic acids and phenolic components has been attributed to the beneficial effects of these products. This review evaluates current findings on the antihypertensive properties of honey products and their therapeutic relevance to the clinic.

Biography

Zeliha Selamoglu is a Professor in Medical Biology department of Ömer Halisdemir University, Turkey. She completed her PhD in Biology from Inonu University. She has published over 70 peer reviewed journal articles with over 500 citations and many technical reports. She is a member of Society for Experimental Biology and Medicine. She has served as an Editorial Board Member for many Journals.

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Mohammad Reza Naghavi et al., Biochem Mol biol J, 3:2
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Expression of genes involved in taxol biosynthetic pathway in *Taxus baccata L.* and application of magnetic- and carbon-based nano-adsorbents for pre-purification of taxol

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This work was undertaken to elucidate the consequences of some environmental cues (i.e. day length, temperature, hours of sunlight and relative humidity) on the expression patterns of TXS, DBAT, BAPT and DBTNBT genes contributed to the taxol biosynthetic pathway. Our results indicated that environmental cues have synergistic or antagonistic regulatory roles on transcription activity and taxanes accumulation in yew, though DBAT activity is less influenced, could be accordingly a rate-limiting enzyme. Furthermore, a modified analytic hierarchy process (AHP) approach based on refinement assay of non-dominated alternatives was employed to monitor the most reliable callus maintenance media of *T. baccata* callus cultures in terms of five criteria. Our results connoted that L-glutamine-based feeding appears to generate more significant results either for calli growth continuously or taxanes production, while, for stems, both amino acid supplies had fairly equal worth. Meanwhile, considering decolorization efficiency, purity of taxol, recovery and reusability of adsorbents, Fe3O4NPs@GO (50 g/L) in dichloromethane was selected as the best medium for pre-purification of paclitaxel. Finally, based on RSM data, the optimum conditions to simultaneously acquire the maximum EPPR (94.0%) and ETP (11.4%) were recorded as adsorbent dosage of 37.7 g L^{-1}, sorption temperature of 30.7°C and agitation power of 153.1 rpm; and the predictive results were confirmed using experimental rechecking survey.

Biography

Mohammad Reza Naghavi is an academic member at University of Tehran, Iran. He has published more than 140 research articles in the field of Plant Biotechnology. He has been serving as an Editorial Board Member of four international and national journals.

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APC as an entry point to study small molecule regulation of the cell cycle

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The anaphase-promoting complex/cyclosome (APC/C) is a multi-subunit E3 ubiquitin ligase that plays a major role in the progression of the eukaryotic cell cycle. This unusual protein complex targets key cell-cycle regulators, such as mitotic cyclins and securins, for degradation via the 26S proteasome by ubiquitination, triggering the metaphase-to-anaphase transition and exit from mitosis. The identification of the complete set of genes encoding subunits of the APC in *Arabidopsis* suggests that the basic processes controlled by proteolysis mediated by ubiquitin in plants are similar to those of other organisms. However, results from several groups indicate that the APC has other specific functions in the regulation of plant development. During the last years, several molecular-biology tools have been extensively used in scientific research for identifying new function of proteins and metabolites. Still, the identification of metabolites, specially which control the cell cycle is not trivial and is characterized by piecemeal progress, especially in plants. In this seminar, we will discuss the methodologies that we are using to identify and characterize metabolites that bind to the APC in the model plant *Arabidopsis*, and to potentially define their roles in plant development.

Biography

Nubia Barbosa Eloy has her expertise in Plant Development and Cell Cycle, especially in improving the ways to have better crop and production. During her academic life, she has published several peer reviewed papers about plant growth and development. Her main interest is to study the plant growth to better enhance crop productivity, using cutting edge techniques to achieve her goal.

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Mapping the *Arabidopsis* metabolic landscape by untargeted metabolomics at different environmental conditions

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Metabolic genome-wide association studies (mGWAS), whereupon metabolite levels are regarded as traits, can help unravel the genetic basis of metabolic networks. Aiming to increase the discovery of true metabolite–gene associations, we applied abiotic stress to *Arabidopsis thaliana* using an integrative approach combining mGWAS and metabolite-transcript correlation-network analysis. 309 natural accessions were grown under two independent environmental conditions (control and stress) and subjected to untargeted LC-MS-based metabolomics; levels of the obtained hydrophilic metabolites were used in GWAS, followed by integration with network-derived metabolite-transcript correlations using a time-course stress experiment. Our two-condition-based GWAS for ~2,000 semi-polar metabolites resulted in the detection of numerous highly resolved mQTL, many of which environment-specific. We show increased discovery of causal genes for well-characterized secondary metabolites by applying GWAS under stress. We, moreover, discovered a large number of hitherto uncharacterized metabolite-gene associations, serving as a rich reservoir for further gene-characterization efforts. Of these, we identified 93 key candidate associations between structural genes and metabolites. We then experimentally validated-using loss-of-function mutants-eight of the novel associations, two of them showing differential genetic regulation in the two environments studied. Our study thus demonstrates the power of combining large-scale untargeted metabolomics-based GWAS with time-course-derived networks, when both approaches are performed under different abiotic environments, to facilitate the identification of metabolite-gene associations. Additionally, it also provides new global insights into the metabolic landscape of *Arabidopsis* using a strategy that could readily be adapted for other plant species.

Biography

Si Wu conducted MS-based untargeted metabolomics study to investigate the pathophysiology of complex metabolic disease – hypothyroidism and therapeutic effects of traditional Chinese medicine. She published four metabolomics-related scientific papers as the first author during the Master degree. She worked as an Intern at Agilent Technologies (Shanghai, P.R. China) to conduct Drug Quality Standard Test of Chinese Pharmacopoeia (2010 Edition). At present, she is a PhD candidate waiting for the defense at Max Planck Institute of Molecular Plant Physiology to carry on an integrative research of combining Genome Wide Association Study (GWAS) and network analysis to identify novel genes involved in secondary metabolism in *Arabidopsis*.

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Cholinergic microRNA-132 sheds new light on the links between psychological stress and metabolic impairments

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Cholinergic signaling affects both anxiety-related and metabolic disorders and is continuously subjected to epigenetic and microRNA (miR) regulation. However, key anxiety-induced microRNAs may potentiate both cholinergic-mediated suppression of inflammation and metabolic syndrome-related processes. Specifically, genomic, epigenetic and microRNA regulators of acetylcholine signaling (CholinomiRs) may implement inherited and/or acquired anxiety-prone states while acting as inflammatory suppressors, which in peripheral tissues can shift the balance towards metabolic disorders. To study the *in vivo* contributions of specific cholinergic targets to miR-mediated phenotypes, we quantified their levels in diet-induced obese mice with hepatic steatosis, diverse nonalcoholic steatohepatitis (NASH) models and LDLR-/- mice, a model for familial hyperlipidemia. All of these models displayed hepatic increases of the anxiety-induced miR-132, accompanied by variable decreases in multiple miR-132 targets and lipolysis-related transcripts, and elevations in lipogenesis-related transcripts. Furthermore, engineered mice over-expressing miR-132 presented severe fatty liver phenotype, multiple miR-132 target decreases and increased body weight, serum LDL/VLDL, liver triglycerides, and prosteatotic and lipogenesis-related transcripts. Inversely, injecting diet-induced obese and LDLR-/- mice with anti-miR-132 oligonucleotides, but not knockdown of individual miR-132 targets, efficiently reversed the hepatic miR-132 excess, hepatic steatosis and hyper-lipidemic phenotype. Our findings identify miR-132 as an upstream CholinomiR regulator of both anxiety and hepatic lipid homeostasis, which displays context-dependent suppression of multiple targets with cumulative synergistic effects; and call for interrogating cholinergic impairments as co-regulating causes of anxiety-related disorders, hepatic steatosis and NASH. Furthermore, realization of the intriguing cholinergic-mediated tradeoff between anxiety and metabolic-related phenomena may offer novel opportunities for re-classifying healthy and un-healthy anxiety- and metabolic-prone states, discriminating between causes of stress-related and metabolic disorders, and cautiously identifying novel cholinergic biomarkers and management strategies.

Biography

Hermona Soreq was trained at Weizmann Institute of Science and the Rockefeller University. At Hebrew University of Jerusalem, she holds a University Slesinger Chair in Molecular Neuroscience and is also a founding member of the Edmond and Lily Safra Center for Brain Science. Her research pioneered the application of molecular biology and genomics to the study of cholinergic signaling, with a recent focus on its microRNA regulation and on signaling changes in health and in nervous system and metabolic disease. She is the elected Head of International Organization of Cholinergic Mechanisms, served as elected Dean of Hebrew University's Faculty of Science from 2005-2008, authored hundreds of publications and won numerous awards in Israel.

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