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EXPERT INTERVIEW

Perspectives on Multi-Omics and Omics Applications in Biomedical Research: an Interview with Dr. Biswapriya B. Misra

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Dr. Misra holds an Assistant Professor position at the Center for Precision Medicine, Department of Internal Medicine, Section on Molecular Medicine at the Wake Forest University School of Medicine in Winston Salem, North Carolina, USA. Dr. Misra conducts biomedical research leveraging the power of high resolution mass-spectrometry driven metabolomics (GC-MS, LC-MS), alongside other omics (genomics, proteomics, and large scale clinical data sets) to understand human metabolic disorders (cardiovascular, obesity, and Alzheimer's disease) and health-cum-wellness (in respect to diet, aging, microbiome, and exposures) in the era of individualized/ personal/ precision medicine. Using big data from diverse -omics data sources, combined with open source tools and reproducible bioinformatic workflows to conduct research using FAIR practices. He develops robust non-invasive biomarkers from human and non-human model organism biofluids and tissues through these multi-omics/ integrated-omics efforts.

This interview was conducted by Dr. Roland J.W. Meesters, Editor-in-Chief Journal of Applied Bioanalysis.

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What began your interest in the field of omics?

An Indo-Swiss research exchange program sponsored trip to ETH, Zurich, Switzerland during my PhD at IIT Kharagpur where I worked for four months in the group of Professor Wilhelm Gruissem, Plant Biotechnology Laboratory and mentored by PD Dr. Eva Vranova exposed me to 'high-throughput' omics research where large scale DNA, protein, metabolite, and RNA isolation/ analysis was very 'routine'. Also an early exposure to GENEVESTIGATOR, the tool and its developer (Dr. Philip Zimmermann working on the same floor!) who were busy developing tools for high throughput microarray data analysis set the tone and invigorated that interest in –omics to a great level of motivation. Coming back, I would try to replicate those efforts in

my PhD in a non-model woody tree system, sandalwood, but without much success for all sorts of reasons. However, continuing with my Postdoctoral opportunities that started with the rubber genome sequencing (see: https://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-14-75) project in Malaysia, and single cell-type proteomics and metabolomics in canola, I never looked back or attempted to go back to single-gene single-protein one function type of studies (though are very important for discovery of functions and validation of –omics based findings).

Why specific this (these) field(s) of omics and not a different field(s) within omics?
Metabolomics- yes, because, it is the closest to phenotype as Professor Oliver Fiehn (WCMC Core, UC Davis, see: https://link.springer.com/article/10.1023/A:1013713905833) would say; defines the health/ wellness and diseases status the best in terms of the metabolic input and output. And given the challenges in their interpretation, diversity, data structure, complexity of chemical annotation, this field would "secure my job for the next two decades" easily. Therefore, yes, for (a) biological relevance, (b) challenges in the field and (c) job security has kept me and move along in "metabolomics.

What are the main technological challenges used in the field of omics you are working in?
Everything! From (i) quantification, to (ii) metabolite identification, to (iii) reproducibility, to (iv) data sharing all are challenges. Moreover, because, even if a lot of resourceful and well man-powered labs are able to cope up with dealing the above three areas, majority of laboratories around the world would not be able to do it, simply because of the lack of awareness and lack of resources. Also, the recent efforts that revealed concerns with usability, installability, and archival stability of software tools and resources used in computational omics is a big challenge (see: https://www.biorxiv.org/content/10.1101/452532v2), the means to call such scientific fraud (either intentional or unintentional fabrication) and lack of reproducibility (see: https://www.biorxiv.org/content/10.1101/757070v1?rss=1) in –omics/high throughput research efforts have started to police the current practices in omics practices.

What have been the most exciting developments in your field of omics?
In metabolomics, I would say 'high resolution mass spectrometry' without naming specific vendors/ brands, 'ion mobility and imaging mass spectrometry applications', of course, 'nano-/micro-flow chromatography, 'open source tools and mass spectral databases aiding in metabolite annotation' (see: https://onlinelibrary.wiley.com/doi/full/10.1002/elps.201800428) , 'molecular networking approaches in spectral identification, such as Global Natural Products Social Molecular Networking (GNPS) (see: https://www.nature.com/articles/nbt.3597)', 'lab-on-a-chip' technology, 'mass spec imaging in real time i.e., 'mass spec pen', iKnife and so on.

How important are omics and multi-omics (if applicable for you) to personalized medicine?
Very important, and in order to realize the goals of precision/ personalized/ individualized metabolomics (see: https://www.degruyter.com/view/j/cclm.ahead-of-print/cclm-2019-0130/cclm-2019-0130.xml) one needs to implement all the omics platforms and workflows in healthcare/ clinics. Unfortunately, proteomics and metabolomics have failed to woo the investors in healthcare and insurance sectors (mostly due to lack of standardization and harmonization of technology, software and skilled manpower needed) to bridge technology development and clinical needs, but good to see that the next generation sequencing (NGS) genomics based methods making decent in roads into clinics, genetic counseling and healthcare decision making. It is a matter of time only when advanced practices (i.e., mass-spectrometry driven –omics) will creep into the medical system for critical health care needs and solutions.

There are a number of platforms currently working toward the system biology e.g., genomics, transcriptomics, proteomics, and metabolomics. What is to your point-of-view the main motivation for the integration of multiple omics platforms?
Motivation is that 'data are never standalone- and they interact like the biomolecules in an organism'. Hence, multiomics is the way to go forward for realization the of goals of individualized/ precision/ personal metabolomics. Moreover, the 'challenges associated with data itself' prior to integration and for integration (see: https://jme.bioscientifica.com/view/journals/jme/62/1/JME-18-0055.xml) is a big motivation for improving the current state of art in these endeavors. Eventually, from genotype to phenotype all layers of omics together in the form of a systems-biology driven trans-omics era (see: https://www.cell.com/trends/biotechnology/fulltext/S0167-7799(15)00273-5) that needs to be informative enough to provide mechanistic insights and solutions to challenges in disease, biotechnology, healthcare,and agriculture among others.

How is omics going to change the future perspective of system biology?
Through big data of course! Through large-scale data generation (possibly with wider coverage and lesser depth), mass spectrometry based metabolomics is one of the most high throughput data generation platforms in this era of big-data driven biology which can help formulate and solve hypothesis in areas of systems biology. This trans-/multi-/poly-/integrated –omics area o research would provide granular insights into biological mechanisms of action into a wide variety of diseases in the ongoing and future systems biology approaches. Few of the best examples of application of metabolomics into resolving systems biology questions in a very simple model of the bacterium, Escherichia coli can be found in the research reports coming from the laboratory of Professor Uwe Sauer (see: https://imsb.ethz.ch/research/sauer.html).

High throughput, low cost, information-rich are few benefits offered by "omics" platform. There are few private health-related companies working toward a commercial concept of multi-omics platform (i.e. genomics, transcriptomics, proteomics, and metabolomics) offering low cost and high throughput technologies. What is your opinion about the commercial future of multi-omics?
As mentioned above, the lack of standardization and harmonization of technology, software and skilled work force needed in clinical set ups guiding the physician/ surgeon are definite bottlenecks. It goes not only for –omics or multi-omics platforms but also for high throughput technologies such as 'imaging'. But given large-scale efforts (see: https://www.nature.com/articles/s41591-019-0414-6#Sec62) from well-established PIs such as Professor Michael P. Snyder, Stanford University, recently using hundreds of time-points for sampling and analysis of just two individuals (n=2; NASA Twins study, see: https://science.sciencemag.org/content/364/6436/eaau8650.abstract) led the community to very soon realize the importance of integrated omics/ multi-omics in the real world applications. If academia is making considerable progress using multi-omics efforts, industry/ commercial efforts in the form of start-ups are booming, be it those for personalized microbiome screening or those based on metabolomics-driven therapeutics such as: ReviveMed (an MIT spinoff, see: http://www.revivemed.io/). It is all happening driven by computational workflows and cloud-based solutions with the aid of artificial intelligence (AI) and machine learning (ML) mediating churning of healthcare omcis and imaging data.

The reproducibility of omics results is a major challenge. The record of metadata, having a minimum standard to publish omics data and deposition of intact omics data are few approaches to make these study more reproducible. Do you have any comments or suggestion on the reproducibility of the multiomics data?
Vast majority of researchers (including those working in the realms of other omics such as proteomics and genomics) are unaware of metadata and data sharing/data archiving platforms dedicated for 'metabolomics' data such as Metabolomics Workbench: http://

www.metabolomicsworkbench.org/, MetaboLights: https://www.ebi.ac.uk/metabolights/ and, GNPS/ MASSIVE: https://gnps.ucsd.edu/ProteoSAFe/static/gnps-splash.jsp; though making data submission and sharing a community and global effort for Findable, Accessible, Interoperable, and Reusable (FAIR) practices in metabolomics and –omics research. There are also open source platforms that enable access, discovery and dissemination of omics datasets, such as OmicsDI (see: https://www.omicsdi.org/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5831141/).
Even though a Metabolomics Standards Initiative (MSI) was formulated by the esteemed members of the International Metabolomics Society as early as in 2007 (see: https://link.springer.com/article/10.1007/s11306-007-0082-2) those possibly needs to be updated in the light of newer advancements, i.e., lipidomics standards initiative (LSI) (see: https://lipidomics-standards-initiative.org/) among others.

The field of omics is a rapidly changing and developing research field. How does the field to your point of view change in the next years? And will it be capable of answering all the questions and challenges we have today?
The pace at which the field of omics (and metabolomics) is moving forward, least said, is phenomenal. I would expect inventions relating to diverse advances in mass-spectrometry (different sources to mass analyzers) and spectroscopy as technology platforms, sample handling/preparation, miniaturization, to cloud-based informatic solutions (see: https://www.cell.com/trends/biotechnology/fulltext/S0167-7799(16)30233-5 and https://academic.oup.com/gigascience/article/8/2/giy149/5232984), data storage and analysis are all going to be experiencing impressive growth/ change. Going forward ML and AI driven solutions to handle large-scale (i.e., population-scale, single cell, personalized medicine) omics datasets alongside reproducible automated (aka. FAIR) workflows are going to be the keys for future biomedicine and healthcare.
No, omics sciences (including metabolomics) would not be capable of answering "all" questions/ challenges, but would be well-equipped to take us closer to the answers/ ground truth. However, some of the recent studies and reviews have captured the essence of metabolomics-driven omics research and its future prospects in very impressive manner. Taking a closer look at some of the recent reviews that have summarized what a state-of the-art metabolomics study can do or not, highly recommended reads are from Professor David Wishart: https://www.physiology.org/doi/full/10.1152/physrev.00035.2018 and Professor Gary Siuzdak: https://www.nature.com/articles/s41580-019-0108-4 where an ensemble of newly discovered and relevant metabolites important to human health and pathophysiology of diseases (https://www.annualreviews.org/doi/abs/10.1146/annurev-biodatasci-011420-031537) where the role of imaging mass spectrometry enabled spatial metabolomics drive by machine learning (ML), deep learning (DL), and artificial intelligence, that promise to revolutionize biology and healthcare. ; and Professor Gary Miller (https://science.sciencemag.org/content/367/6476/392/tab-e-letters) where the role of high-resolution mass spectrometry (HRMS) in capturing human health and disease exposome are discussed. Similarly, the scope of exposomics, a new booming area of research in mass-spectrometry based –omics and its future can be found in the review of Professor Oliver Fiehn: https://www.sciencedirect.com/science/article/pii/S2468202017301389, while Professor Pieter Dorrestein (see: https://www.nature.com/articles/s41570-017-0054) has discussed a diverse array of tools and resources available to use biological mass-spectrometry data for future research in ecosystems/ environment, human health, microbiomes and plants.