

Multi-Organism Proteomes (iMOP): Advancing our understanding of human biology

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1. Introduction

A major objective of the Human Proteome Organisation (HUPO) is to promote and support the area of proteomics as it relates to human health and disease. HUPO activity is based on thematic initiatives, work groups and hosting of international conferences [1]. In 2011, a new HUPO initiative on Model Organism Proteomes (iMOP) was established to support an action in which principles, protocols, and data standards developed for human proteomics, could be readily disseminated to proteome researchers working with a wide range of model organisms [2]. In the past four years, iMOP members have hosted international workshops, iMOP sessions under larger international conferences, and actively liaised with proteomics communities outside the sphere of HUPO [3-5]. These exchanges have aided in the evolution of iMOP from an initiative aiming to bridge the research on model organisms and human proteomics to one that embraces the full diversity of the countless organism proteomes that impact human health. These include most significantly species important for agriculture and food production, and bacteria that are indeed of major significance for human health. It soon became clear that the iMOP initiative covered communities that go far beyond what is commonly thought of as model organisms. As a consequence, in 2014 the initiative underwent a self-re-evaluation, to embrace a broader perspective, and re-named the *Initiative on Multi-Organism Proteomes (iMOP)* to better reflect and support the needs of scientific communities working with non-human proteomes.

Proteome research of non-human species has multiple levels of relevance to human health. The study of simpler organisms such as bacteria, invertebrates, animals and plants are used to further our knowledge of human biology. The decreased complexity of many of these organisms enables unique experiments and approaches to be undertaken and developed. Indeed, resources for many of the reference or model species (e.g. Arabidopsis, yeast, and mouse) are considerably more advanced and integrated than some areas of human research [6-8]. While many of these species also have obvious associations to human health through an involvement in homeostatic and pathogenic processes, many are also important agricultural species essential for food production, thus impacting human nutrition as well as the environment at large [9]. Considering the complexity of how multiple species interact with each other and the environment, in the future it will become increasingly important to incorporate complementary analyses, such as bacterial metagenomics, into clinical research programs as we progress towards personalized medicine [10]. However, despite the knowledge acquired from non-human organism communities, both at the level of analytical

techniques and of biological principles, scientific interactions and tangible extrapolations to human research remain challenging. The same holds true for the interaction of different organism communities, which often fail to find a common language, resulting in an inability to decipher common (biological) principles.

Consequently, in an effort to harmonize knowledge across communities, the iMOP program was developed to facilitate the exchange of knowledge in the area of proteomics between the researchers working with non-human species, and those focused on human proteomics research. This manuscript aims to present highlights from the recent communications and discussions that have shaped the current iMOP community. The strength of iMOP is the inclusive community, which facilitates exchange between diverse proteomics communities, bridging a currently fragmented proteome research domain. A common theme during workshops and informal discussions has been to address how non-human proteomics contributes to our understanding of human biology. This commentary will attempt to outline the importance and relevance of non-human proteomics for the understanding and potential contributions to human life. Finally, we will also discuss the future organization, objectives and goals of the iMOP initiative in the context of these discussions.

2. iMOP activities in 2013 and 2014

To facilitate active exchange and engagement between HUPO and non-human proteomics researchers, the iMOP coordinators organized sessions at international conferences and workshops.

HUPO World Congress, Yokohama, Japan (2013)

At the annual HUPO meeting in 2013, iMOP hosted a separate session, inviting speakers who work with a wide variety of species. Talks included studies of high-throughput identification of post-translational modifications in yeast and bacteria. Marc Wilkins (University of New South Wales, Australia) talked about examination of the yeast methylproteome network and the discovery of a new lysine methyltransferase [11]. Brian Tate Weinert, (University of Copenhagen, Denmark) talked about quantitative studies of the lysine acetylation dynamics in *Escherichia coli* [12], and Paola Roncada (University of Milan, Italy) presented her groups work on examination of the secretomes from both *Listeria monocytogenes* and *Lactobacillus lactis*, exploring inhibitory roles of lactic acid bacteria during growth and its role in food production [13]. The scientific session was followed by an open discussion, which made clear that the groups interested in iMOP need this initiative to focus on a far more diverse selection of species than what is generally understood by the label “model-organisms”. Moreover, a re-organization of the iMOP structure was suggested to improve inclusion and representation of a broader diversity of non-human proteomes. It was suggested to include multiple co-chairs who are in direct communication with the separate biological research communities. Finally, a change of chairman was addressed, as Michael Hengartner (University of Zurich, Switzerland) wished to step down due to his new appointment as the University president. Emøke Bendixen (Aarhus University, Denmark) was nominated as the incoming iMOP chair [14].

European Proteomics Association (EuPA), Saint-Malo, France (2013)

Within the framework of the EuPA 2013 Congress held in Saint-Malo (France), the iMOP consortium organized a full day session, comprising of eight presentations. The number of attendees, on average around 150 people were in the audience, reflected the immense interest of the proteomics community in this HUPO initiative. Eric Deutsch (Institute for Systems Biology, USA) started the session discussing recent developments in the Peptide Atlas and PASSEL [15, 16], two important tools for the comparative analysis of proteomes derived from different organisms. Willy Bienvenut (CNRS, France) presented data dealing with the

analytics and biology of *N*-acetylation in plant chloroplasts [17], followed by Ludovic Bonhomme (INRA, France) dealing with the analysis of maize phosphoproteomes in response to drought conditions [18]. Paola Roncada (University of Milan, Italy) discussed the role of bacterial secretomes in cheese production and its implication in food safety [13]. A related topic was presented by Véronique Monnet (INRA, France) who outlined a study on the proteolytic activity on the cell surface of lactic acid bacteria [19]. Jean Armengaud (CEA, France) presented a fascinating plenary talk about the emerging field of proteogenomics [20], which will be certainly of the major fields of action of the iMOP in the future. The session was completed by a talk by Angel Diaz (Vigo, Spain) presenting latest data about the combination of genomics, transcriptomics and proteomics data derived from bivalves, and finally, Ana Varela Coelho (New University of Lisbon, Portugal), presented research examining the regeneration of nerves and tissues in the starfish (*Marthasterias glacialis*) [21].

INPPO World Congress, Hamburg, Germany (2014)

The inaugural meeting of the International Plant Proteomics Organization (INPPO) [22] was hosted by the University of Hamburg (Germany) in September 2014. This well attended meeting marked a growing awareness and maturation of the proteomic research in plants. A brief information session about iMOP was organized by Andreas Tholey. A lively discussion highlighted opportunities, gain and challenges of including plant proteomics research in iMOP and HUPO. While generally supportive of the idea to further the interactions with HUPO, several plant community members indicated that the plant proteomic community should be careful not to lose its identity in this important and expanding research area.

HUPO World Congress, Madrid, Spain (2014)

The 13th annual Human Proteome Organization World Congress in 2014, Madrid, Spain, provided the opportunity to host a separate iMOP session, as well as to present iMOP within the context of the Human Proteome Project. The iMOP scientific session highlighted the array of research currently being undertaken in non-human systems in the field of proteomics. This included a fundamental study of metabolism and obesity in the vole, an herbivorous rodent that displays natural decreases in body mass under short days. The vole genome is not yet sequenced, thus proteome studies present a considerable bioinformatics challenge. Fabrice Bertile (Université de Strasbourg, France) presented studies of high fat diet induced obesity and metabolic adaptation, including differential expression of proteins controlling mitochondrial function and oxidative stress [23]. Dorothea Rutishauser (Karolinska Institute,

Sweden) presented an overview of insect-plant interaction research, which focused on examination of the adaptation of caterpillar saliva proteomes to the diet of the insect. This study demonstrated that caterpillar saliva contains chemosensory proteins, which likely serve to sensor both microorganisms and plants which are essential for the caterpillar's nutrition and health [24]. The session included an open discussion of the primary challenges that many iMOP partner-labs have in common. Lack of well-annotated genomes is a particularly challenging aspect of working with non-human proteomes. It was suggested that iMOP should establish a community effort to improve essential search databases, and make available a more standardized proteome analysis pipeline. In particular, a standardized workflow for how to convert expressed sequence tag (EST) libraries and next generation DNA and RNA sequencing data into applicable search databases will be addressed by a work group within the iMOP community. This will significantly increase data quality and reduce the burden of working with the proteomes of uncommon species in the near future.

3. The multi-organism proteome research contributes to our understanding of human biology.

Human health is closely connected to presence and health of countless organisms, including mainly food species, environmental bacteria, pathogens, and not the least the presence of at least 5,000 different microorganisms, mainly living in the human gut, and greatly outnumbering their human host; 10 times by cell count, and at least 100 times by their contribution of functional genes, which are essential for human physiology and health [25, 26]. Thus, knowledge about biological processes in plants, microorganisms, microbial communities, parasites, viruses, and higher animals have immediate importance for the understanding of human biology and its response, as will be discussed in more details below. In this perspective, the study of each organism can collectively deliver, together with the elucidation of fundamental biological processes, significant information on how these factors are influencing human health.

Human health: relevance of metagenomics and metaproteomics

A balanced composition of the gut microbiota and interaction between host and its commensal organisms is mandatory for the wellbeing of humans. As a result, perturbed balance can have severe consequences for human health. Thus, the human body can be seen as a holobiont, in which single organisms are in steady exchange [27]. Non-microbial commensals or pathogens, e.g. single or multi-cellular parasites influence the biology of humans, either as pathogens, or by becoming tolerated parasites during evolution [28]. Together with the viral communities, which are also still far from being characterized, this adds further levels of complexity to the function of the human body.

Human wellbeing: balancing food production, farming and environmental challenges

Feeding a growing population is one of humanities major global challenges, and one that most significantly determines human health and welfare at a broad scale. Industrialized farming methods are mandatory for meeting the increased demands for food, but establishing sustainable farming methods that can balance the need for productivity and the need for environmental care needs renewed research focus to solve new challenges. A very clear example is the close link between antimicrobial resistance to antibiotics (AMR), and the use of antibiotics in farming. With around 80% of global antibiotics being given to farm animals, current food production methods are by far the major cause of dramatic rise in antimicrobial resistance to antibiotics. According to the World Health Organization (WHO), AMR is a

significant challenge to human health and is predicted to cost more human lives than cancer by 2030 [29]. Proteomics and mass spectrometry analyses play a key role in elucidation of the mechanisms of antibiotics resistance in microbial pathogens [30], as well as being used to understand host-pathogen responses in farm animals [31] and humans [32].

Human nutrition: the role of dietary plant fibers

The role of dietary fiber in the human diet is now recognized as an essential aspect of human health and vitality [33]. A relationship has now been clearly established between plant dietary fiber (carbohydrate matrices) and properties of the gastrointestinal tract, for example, the ability to modify the microbiome [34] and in effecting rates of nutrient absorbance [35]. Plant dietary fiber is mainly comprised of starch and cell wall material, the former also comprising a major source of energy in human diets. Proteomics and mass spectrometry approaches have contributed significantly to the investigation of starch biosynthesis and deposition within the cereal grain [36, 37]. The characterization of compartments and complexes involved in plant cell wall biosynthesis by proteomics has revealed essential and novel enzymes involved in the construction of these carbohydrate matrices [38, 39]. The identification of key enzymes in these biosynthetic processes is enabling the manipulation of these structures within the plant. This development of functional foods targeted at improving and enhancing human nutrition will require collaborative efforts between plant biologists, mammalian researchers and microbiologists to better understand the role of dietary fiber within the gastrointestinal tract. Understanding these complex interactions will require multi-organism programs and highlights the future direction of research required to address the complexities of human biology.

4. A new iMOP organizational structure

The main objective of the iMOP initiative is to bridge a current gap between human and non-human proteome research. Technology advancement in species-oriented proteome labs would greatly benefit from a more seamless cross-species research. Currently, a lack of adequate access to proteome technology, infrastructure and access to associated support structures e.g. bioinformatics resources, is a major shortcoming in non-human proteome research. In order to reach a wide range of proteome communities and biological research fields, the core iMOP partners have been selected to represent scientists from a broad variety of research fields and species. The iMOP chair Emøke Bendixen works in the area of farm animal proteomics, and thus co-chairs the *animal proteomics section*. Andreas Tholey is co-chair of the analytical *standards section* of iMOP. His research focuses on analytical method development and implementation of protein analysis standards adapted across a wide range of animal species and bacteria communities, which helps to assure a seamless transfer between analytical methods across human and non-human proteomics. A major advantage is the possibility of generating standards for biological material, which will help to standardize analytical methods. The *plant section* is co-chaired by Joshua Heazlewood, who focuses on plant proteomics, mainly to study the role that subcellular partitioning plays in metabolic and biosynthetic processes in plant development, including plant cell wall biosynthesis. The *microbial section* is chaired by Dörte Becher, who works in the area of microbial physiology, focusing on *in vitro* proteomics to investigate the molecular basis of infections of opportunistic pathogens, and also using metaproteomics analyses to link structure and functions of microbial communities in terrestrial, aquatic and also human environments. Kathrin Riedel took over the section for single and multicellular pathogens. It has been suggested to include an additional co-chair for a *bioinformatics section*, This role is currently vacant until a suitable candidate can be identified. Sabine Schrimpf has the role of iMOP *coordinator*, and has her expertise in comparative proteomics in *C. elegans*. Information about iMOP members, their research, and on iMOP activities can be found at the following website (<http://www.imop.uzh.ch>).

5. Future activities of iMOP

Improved bioinformatic pipelines

Enabling bioinformatics pipelines, training and open access to curated search databases for selected species is a major aim for the next few years. The iMOP initiative will aim to assist in the creation of common structures in the future. Major challenges will be to find common languages and to tackle known problems, for example, different communities use different identifiers for database entries, complicating direct communication and making it difficult to generate and elucidate common principles. The current work plan involves the establishment of a wiki page to create an interactive portal for the proteomics community at large. A primary common project is to encourage open communications, which should lead to creation of a unified and recommended workflow for how to convert EST libraries and next generation sequencing data into search databases for proteomics.

Reaching out to species oriented communities

Many research groups working with fundamental biology, are still not familiar with the gains that can be achieved by current proteome technologies. Moreover, many proteomic researchers seldom pay attention to work outside their specific species or genus of interest. Therefore, reaching new communities and expanding the scope of current proteomic researchers is a major goal of iMOP. To achieve this, the seven parallel sections have been identified (Table 1), each headed by a dedicated section co-chair from the area has been assigned. The co-chairs are responsible for communicating with their respective communities.

Increasing the awareness and opportunity of model organism diversity

Choosing the most informative animal model is of utmost importance for progress in human clinical proteomics research [40]. Knowledge about the diversity of model organisms needs to be greatly improved within the human proteome research community if cross-species synergies are to occur. iMOP aims to highlight novel model organisms that are often overlooked as opportunities for biomedical research e.g. farm animals such as the pig, which like humans are monogastric and are obvious systems for studies on processes such as nutrition [41]. Better representation of non-human species and novel model organisms in the current proteome data repositories will be a major help to raise awareness and access to a larger diversity of model animals. One example is the ongoing collaboration between farm animal proteomics communities and the PeptideAtlas project (42,43), in order to improve proteomics research of veterinary and food species.

Upcoming events

The iMOP community closely follows, and also seeks to contribute to the HUPO human proteome project initiative (HPP). An iMOP session will take place on the 30th September 2015, at the 14th HUPO meeting in Vancouver, Canada. This session will present proteomic applications in non-human systems, and provide the opportunity to discuss the building and future of the iMOP community. The iMOP team welcomes and encourages feedback from iMOP members as well as the broad proteomics research community on how to benefit from synergies between human and non-human proteomics research. In particular, contributions of expertise and suggestions from the bioinformatics domains will be crucial for building of future non-human proteomics sciences.

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Table 1. The iMOP section co-chairs and sections were developed to incorporate major areas of proteomic research.

Section	Description	Section Co-Chair(s)
Animals	Higher order mammals, farm animals	Emøke Bendixen
Microbial	Single species, microbial communities	Dörte Becher
Pathogens	Commensals, multicellular pathogens	Kathrin Riedel
Plants	Crops, reference plants, agricultural plants and fungi	Joshua Heazlewood
Bioinformatics	Standards, database structures	<i>Position vacant</i>
Standards	Analytical and proteomics standards	Andreas Tholey

Figure Legend

Figure 1. Flowchart outlining the shift in focus for iMOP.

The blue sections represent the “classic” use of model organisms in human research. The green sections outline the current and emerging focus of model organism research. The red sections outline future directions for iMOP.

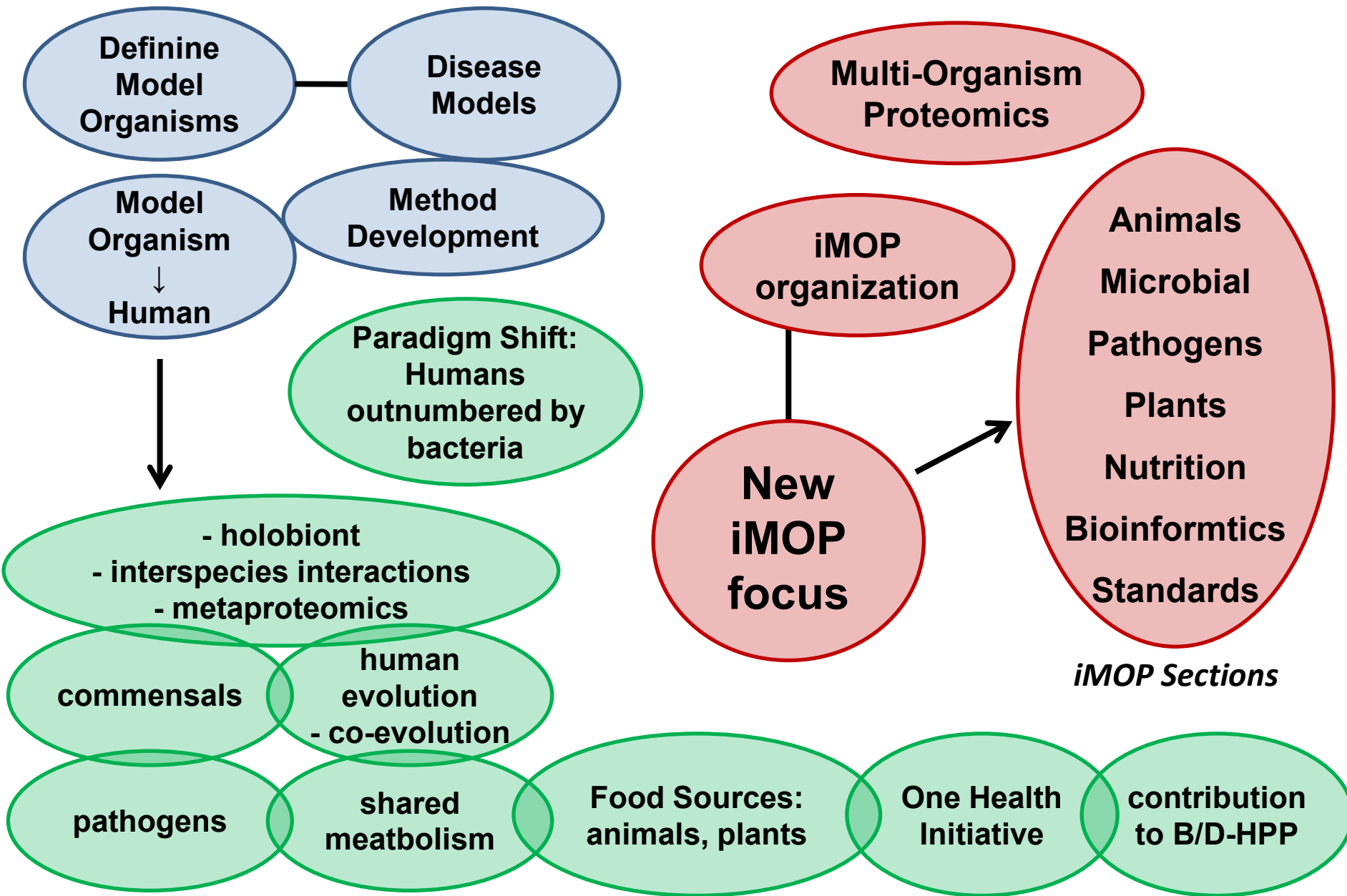


Figure 1



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