

## Review

## Novel model organisms and proteomics for a better biological understanding

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## ABSTRACT

The concept of « model organisms » is being revisited in the light of the latest advances in multi-omics technologies that can now capture the full range of molecular events that occur over time, regardless of the organism studied. Classic, well-studied models, such as *Escherichia coli*, *Saccharomyces cerevisiae*, to name a few, have long been valuable for hypothesis testing, reproducibility, and sharing common platforms among researchers. However, they are not suitable for all types of research. The complexity of unanswered questions in biology demands more elaborated systems, particularly to study plant and animal biodiversity, microbial ecosystems and their interactions with their hosts if any. More integrated systems, known as « holobionts », are emerging to describe and unify host organisms and associated microorganisms, providing an overview of all their possible interactions and trajectories. Comparative evolutionary proteomics offers interesting prospects for extrapolating knowledge from a few selected model organisms to others. This approach enables a deeper characterization of the diversity of proteins and proteoforms across the three branches of the tree of life, i.e. Bacteria, Archaea, and Eukarya. It also provides a powerful means to address remaining biological questions, such as identifying the key molecular players in organisms when they are confronted to environmental challenges, like anthropogenic toxicants, pathogens, dietary shifts or climate stressors, and proposing long-term sustainable solutions.

**Significance:** In this commentary, we reevaluated the concept of “model organisms” in light of advancements in multi-omics technologies. Traditional models have proven invaluable for hypothesis testing, reproducibility, and fostering shared research frameworks. However, we discussed that they are not universally applicable. To address complexities such as biodiversity and understand microbial ecosystems and their host interactions, integrated systems like “holobionts,” which encompass host organisms and their associated microbes, are gaining prominence. Comparative evolutionary proteomics further enhances our understanding by enabling detailed exploration of protein diversity across organisms. This approach also facilitates the identification of critical molecular players in organisms facing environmental challenges, such as pollutants, pathogens, dietary changes, or climate stress, and contributes to developing sustainable long-term solutions.

### 1. Broadening the scope of model organisms in biology

Widely studied model organisms have been instrumental in uncovering fundamental cellular and molecular processes. Indeed, models play a central role in biology, providing simplified systems to test

hypotheses quickly, enabling reproducible experimental measurements, and facilitating knowledge-sharing across the scientific community (Fig. 1). While model organisms have been central to numerous biological and medical breakthroughs, they also come with certain limitations. For example, the basic principles of protein synthesis—a vital

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cellular function for life—were largely derived from studies of the *Escherichia coli* enteric bacterium for its ease of growth and manipulation [18], where translation typically initiates at an AUG initiation codon, with occasional use of GUG or UUG. Genome annotation software pipelines have long relied on these rules. But are these principles valid for the entire Tree of Life? Surprisingly, no! In *Aeropyrum pernix* K1, a crenarchaeon strain, UUG is the primary codon for translation initiation [39]. Even more unexpectedly, some bacteria, such as members of the Deinococcaceae family, use alternative codons like AUC to initiate the synthesis of important proteins, as shown by systematic N-terminomics [3]. It should be evident to everyone that expanding our understanding of diverse molecular systems must be done cautiously when extrapolating insights beyond model organisms and acquiring a more comprehensive view of life's complexity.

With the considerable progress made in omics technologies over the last two decades, the concept of « model organisms » has been re-evaluated [2] and further extended for being more inclusive [8]. Findings from model organisms are often extrapolated to a broad range of species on the basis of evolutionary conservation. However, these results should be reasonably double-checked with additional representative models before being considered irrevocably correct for all organisms (Fig. 1). Besides, emerging technologies now offer even more possibilities to include sophisticated models in biological studies. For example, the development of organoids —3D structures with different cell lines that better mimic the complex structure and functionality of whole organs- and their microfluidic extensions - organ-on-a-chips – now enables scientists to investigate specific parameters under reproducible conditions more closely resembling in vivo physiological conditions [40]. Similarly, models that simulate microbial ecosystems are gaining ground, even though they still fall short of reproducing the true biodiversity and complex dynamics found in natural environments like soils, plants and animal hosts [22].

## 2. The objectives of iMOP

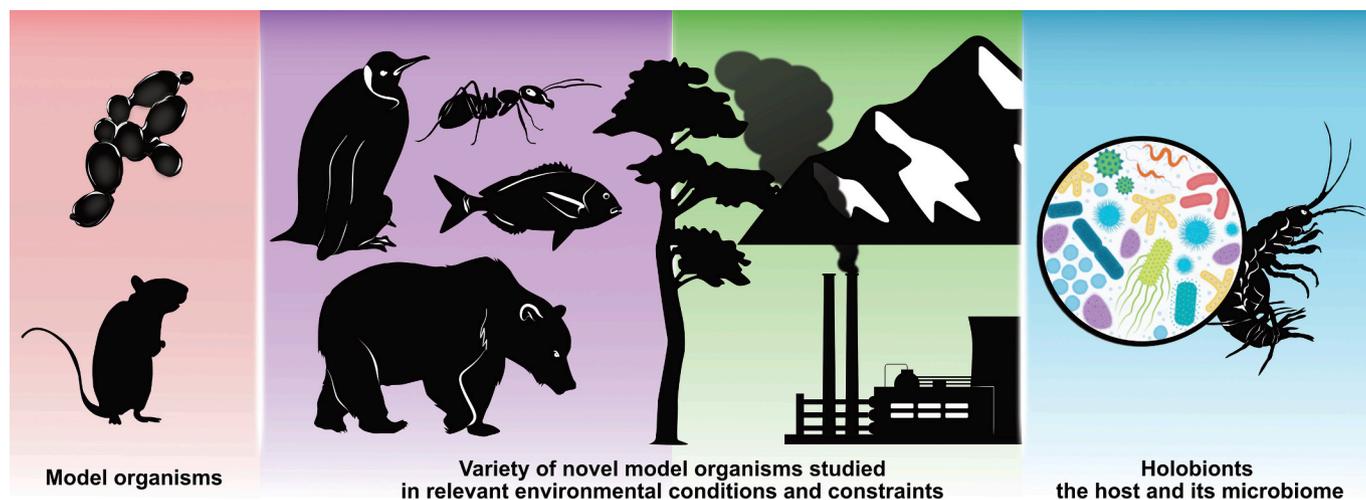
The “Initiative for Model Organism Proteomics” (iMOP), under the umbrella of EuPA and HUPO proteomics organizations seeks to promote i) the adoption of new biological models to tackle biological questions and ii) the most advanced tools and techniques to improve our knowledge of these models. Through comparative evolutionary proteomics, iMOP aims to deepen our understanding of proteins critical to human health, animal and plant welfare, and environmental sustainability, key

components of the One Health framework. By uniting expertise and resources across the scientific community, the iMOP initiative strives to explore biodiversity, select and promote the most relevant biological models, and expand our knowledge of proteins and their diverse proteoforms, as well as their dynamics and functional roles.

It is worth mentioning that EuPA and HUPO from the very beginning encouraged researchers to study animal and plant organisms in their whole diversity [19,36,37]. The Journal of Proteomics, initiated by EuPA, also promotes the study of new model organisms [10]. At the recent HUPO/EuPA joint meeting held in October 2024 in Dresden, Germany, which brought together over 1800 participants from 51 countries with a primary interest in the human proteome, we have organised an iMOP initiative session entitled « Delving into biodiversity's depths: integrating new model organisms and unraveling the mysteries of unknown proteins ». The session attracted a large audience, highlighting the scientific community's strong interest in promoting a more inclusive approach to research. Engaging discussions were initiated on the pivotal role of model organisms and proteomics in advancing transformative knowledge and applications. Below, we provide a summary of the four key themes discussed during the session, offering insights for those who were unable to attend, followed by an overview of the future directions of the iMOP initiative.

## 3. Holobionts, towards new complex but more inclusive models

Until very recently, experiments using animal or plant models overlooked the possible effect of their microbiomes. Surprisingly, several plant or animal genomic data were released and published while fully erroneous due to cross-contamination resulting from the total extraction of host DNA, but including that of the associated microbiome [30]. This error led to the publication of chimeric genomic sequences, breaching the quality measures and insufficient metrics in place. While the term ‘holobiont’ was first introduced in 1943 to describe the collective of a host organism and its associated microorganisms, a new conceptual framework has emerged in recent years, expanding the term to encompass not only bacteria, archaea, and fungi but also viruses, microalgae, and other microbes such as parasites [20]. It better represents the interdependence and co-evolution between a host and its microbiota, suggesting that together they operate as a unified ecological unit (Fig. 1). Such a view should improve our understanding of the ecosystem functions, shifting attention from individual entities to the intricate interactions and relationships within the entire microbial



**Fig. 1.** Representation of the three pillars of model organisms. These models can be either, i) classic, well-studied models (Left) such as the *S. cerevisiae* yeast or mouse, ii) new model organisms (in the centre) that can be selected among all the branches of life, from arthropods to fish, mammals and birds, as well as plants, studied in different relevant environmental conditions and constraints, and iii) model organisms considered in the framework of the holobiont concept including their microbiomes (right).

community and its host. By thinking more holistically, scientists can achieve new levels of knowledge about the functioning of complex ecosystems and gain a better understanding of their levels of resilience and evolutionary trajectories.

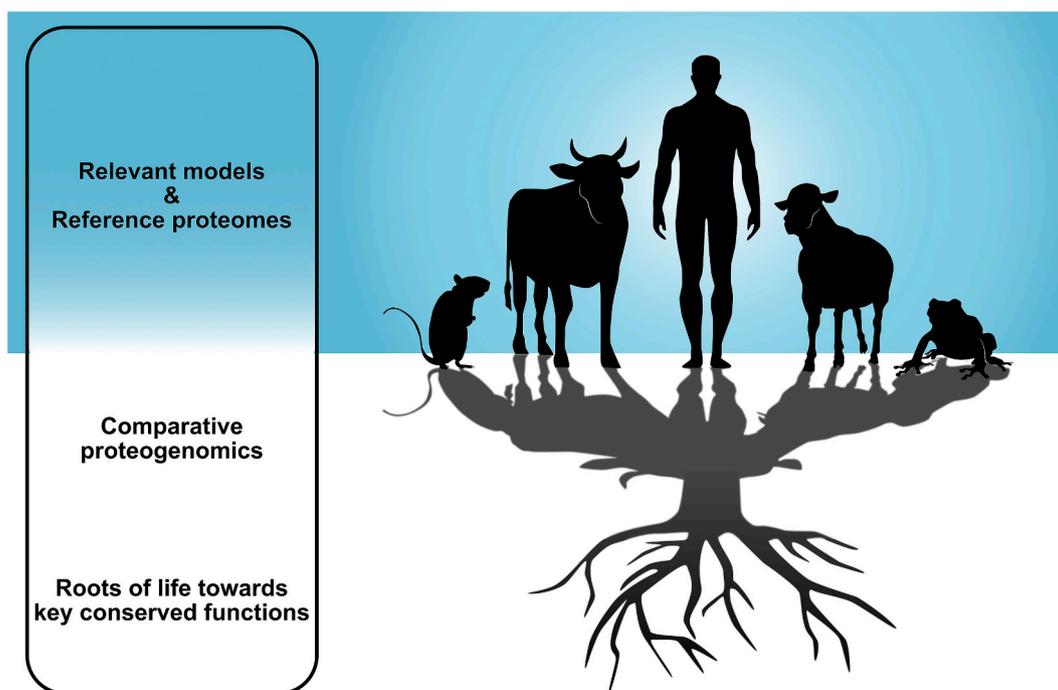
As illustrated by the physicist Richard Feynman's well-known phrase, « What I cannot create, I do not understand » [16], a core axiom for scientists is to build their own experimental biological systems with all the parameters controlled in order to gain deeper insight into how they function. In this spirit, microbiologists are increasingly experimenting with microbial ecosystems using multi-omics approaches for advancing our understanding of microbial interactions [1]. Synthetic communities are by definition simplified microbial consortia assembled from specific strains grown in a controlled environment, offering a streamlined model for dissecting these complex interactions. In these studies, combining metabolomics and metaproteomics is especially powerful: on the one hand, metabolomics allows precise quantification of metabolic products, while on the other hand, metaproteomics, through peptide sequencing and taxonomical links obtained from these peptide sequences, identifies the active pathways within each member of the community. This dual, integrative approach directly connects microbial functions with their metabolic outputs, providing insights that metagenomics alone cannot fully capture. Synthetic communities can also be customized to include specific microorganisms of interest or those with targeted functional impairments, enabling precise studies of the role of each microorganism within the broader system.

Understanding how microorganisms and environmental factors influence the health or disease states of their host presents a more complex challenge. To tackle the critical interactions involved, developing and promoting appropriate holobiont models is essential. However, creating, sharing among scientists and maintaining these models remains today a daunting, insurmountable task. Indeed, there is not yet such a model shared by researchers. The iMOP initiative likes to contribute to the definition and adoption of such models. Despite these complexities, meaningful progress in this field is attainable through the dedicated, concerted efforts of the entire scientific community.

#### 4. Improving the annotation of proteins in animals by comparative proteogenomics

Returning to the subject of protein translation, the mechanistic rules by which ribosomes initiate protein translation from the Kozak sequence in animals [21] have been adopted to predict and build protein sequence databases from any genome. Most proteomics studies have been conducted relying on these conservative, streamlined protein sequence databases, occasionally supplemented with alternative splicing variants and amino acid polymorphisms. Important efforts have been done by the scientific community to improve these protein sequence databases, validating predicted protein sequences with experimental evidence obtained by tandem mass spectrometry [29]. However, Kozak's early work also suggested that ribosomes could bind outside conventional mRNA sites, suggesting more complex translation patterns. With modern advances in mass spectrometry technology now making it possible to identify up to 38,000 proteins in half-an-hour [13], it may be time to re-examine this question. Indeed, evidence of non-canonical translation events in eukaryotic cells has been documented, revealing a series of non-standard proteins [11], and suggesting that these cells exhibit polycistronic behavior. While complete understanding of these phenomena and their biological significance is still lacking, we believe that it is essential to revisit translation rules in diverse animal models using modern proteogenomic approaches that analyze, without relying on prior assumptions, the full repertoire of synthesized proteins. For instance, comparative proteogenomics across various animals such as schematically represented in Fig. 2 could help cataloging conserved alternative proteins and refining translation predictive models across the Chordata phylum. In this respect, a first proteogenomic resource has been developed recently, providing users an inventory of non-canonical or alternative open reading frames for nine animal species [23].

Newly identified alternative proteins, which are often referred to as the uncharted "ghost proteome", remain largely uncharacterized in terms of function. Important structural and functional features are likely to be found for a number of alternative proteins and the multiple proteoforms with dedicated strategies [12]. The different facets of proteomics, including studies of their abundance across different



**Fig. 2.** Representation of the concept of comparative evolutionary proteomics. Four reference proteomes of selected species (e.g. mice, cow, human, sheep, frog) merge into a common proteome in form of the roots of the tree of life and function thanks to comparative proteogenomic and unreferenced level (Shadows).

physiological conditions, their protein interactions, spatial localization across tissues and organs and possible post-translational modifications in combination with the use of predictive tools and molecular and cellular biology experiments hold promise for unraveling their roles.

## 5. Comparative evolutionary proteomics to tackle key biological questions

Protecting human health requires safeguarding both animal and plant health and the environment, a principle central to the « One Health » concept [31]. Human activities are increasingly polluting the environment with toxic compounds, which will inevitably affect future generations [28]. Tackling this issue from a comparative evolutionary point of view by looking for species that are naturally resilient or able to adapt more quickly could lead to bioinspired therapeutic solutions. Similarly, although 60 % of infectious diseases have an animal origin (WHO), finding species that have evolved solutions to resist certain pathogens, and deciphering their mechanisms, is also a crucial issue that could provide new levers to combat the threat posed by the rise in antibiotic resistance. To address these and other key biological questions from an evolutionary perspective, studying various types of organisms in their environment using comparative proteomics is a promising approach [8]. Proteogenomics provides a powerful strategy for dealing with the increasing diversity of model species, in which databases of customized protein sequences generated from genomic and transcriptomic information are used to assist in interpreting proteomic data [17]. A recent open source solution, Brownotate (<https://github.com/LSMBO/Brownotate>), has been developed to expedite the process even for non-specialists. This user-friendly tool demonstrates excellent performance in generating high-quality protein sequence databases, enabling conducting straightforwardly comparative evolutionary proteomics.

Several examples illustrate that comparative proteomics, or more generally comparative omics, can be a successful approach to advance knowledge on health issues. In particular, molecular changes linked to mixtures of trace elements have been identified while macrophysiological parameters were insufficient (e.g. body condition) in Mediterranean sea bream *Sparus aurata*- [5,6], European pilchard *Sardina pilchardus*- [5,6] and Indian Ocean green turtle *Chelonia mydas*- [4], leading to a set of biomarkers of exposure for long term monitoring. Comparative proteomics has also shown that yellow gorgonians *Eumicella cavolini*- transplanted from deep waters to surface waters are able to adapt perfectly to these new environmental conditions, offering the possibility of restoring colonisation of surface waters in response to future heat waves [4,7]. Life expectancies are greatly diverse in the animal kingdom. Comparative proteomics and metabolomics of the eusocial black garden ant *Lasius niger*- have shown that the different life expectancies between the queen (up to 20 years) and workers (3 years) involves energy trade-off mechanisms linked to somatic maintenance, energy management and immunity [32,34]. Moreover, it was shown that age-related differences in workers involve several processes, including sugar fuel utilization, chemical communication, cancer risk factors and immunity [33].

Therefore, the use of comparative omics from an evolutionary perspective has the potential to address key biological questions, with the combination of multiple omics technologies likely to provide more comprehensive results by capturing multiple pieces of evidence of the same phenomenon. Fig. 2 shows a schematic representation of the concept of comparative evolutionary proteomics with four selected species merging into a common proteome to highlight the most conserved functions and associated molecular players. The diversity of situations encountered by wild animals is infinite, and studying them using comparative multi-omics [35] could be as part of the 'One Health' concept the key to improving human health, improving species conservation and better controlling environmental quality.

## 6. Understanding life responses to toxicants: a multidimensional approach by toxicoproteomics

Chemical pollution represents an unprecedented planetary crisis, with continuous exposure of toxicants posing significant risks to both ecosystems and human health [14]. Our oceans, the largest and most vital ecosystems on Earth, are particularly vulnerable to these pollutants, which affect marine life and disrupt ecological balance, further exacerbating global environmental challenges [26,27]. From the smallest microorganisms to the largest organisms, it is crucial to deploy advanced molecular and high-throughput tools across different trophic levels to assess the health of our ecosystems and its impact on human health. There is an urgent need to understand the molecular effects of toxicants on key taxa and diversify the choice of model organisms in experimental designs to fully grasp the environmental health of our ecosystems.

Understanding the full range of environmental exposures accumulated over a lifetime— the so-called exposome — and its impact on health requires advanced tools capable of predicting adverse outcomes across a wide range of organisms. Current research primarily focuses on human health, leaving a substantial gap in our knowledge of how these exposures affect animal health. This gap is significant, as animal and human health are deeply interconnected under the One Health framework. The lack of high-throughput methods to assess the exposome's impact on animal health threatens animal welfare, food safety, and human health.

The Proteome Integral Solubility Alteration (PISA) assay is a powerful proteomics-based method for large-scale identification of protein targets of chemicals [15]. For its application to toxicology, the first requirement is to eliminate microsomal vesicles that could uptake hydrophobic compounds from the studied proteome [24]. Although this implementation has been successfully applied to identify target proteins for chemical mixtures, methodological constraints have limited its broader applicability to environmentally relevant animal species [25]. The method has been implemented by selecting a single temperature for the thermal shift assay. This ensures that significant differences in abundance between chemical-bound and unbound proteins can be achieved for a broad identification of targets. In addition, incorporating the principles for minimal proteomic sample preparation has considerably reduced the experiments' time and cost. As a proof-of-concept, the proteome-wide identification of protein targets for a toxicant at environmental concentration has been determined across various species, including human cell lines, tissues from animal models (*Mus musculus*), farm animals (*Gallus gallus*) and sentinel animals (*Mytilus edulis*). Based on the species-specific mapping of functional disturbances, differences in adverse effects can be predicted. Toxicoproteomics thus provides essential insights for predicting the toxicant impacts on health across species, supporting broader efforts to protect human and environmental health.

## 7. Perspectives

In its early days, proteomics encountered difficulties in expanding its scope beyond a limited number of model organisms. However, recent advances have highlighted its capacity to characterize proteomes and their dynamics in a wide range of organisms using draft genomes as part of a pan-proteomics strategy [9]. It even applies very well to study complex mixtures of organisms through its meta-iteration – meta-proteomics- [38]. Comparative evolutionary proteomics presents exciting opportunities to extrapolate biological insights from thoroughly studied model organisms to others. By leveraging comparative proteogenomics, comprehensive protein sequence catalogues can be established. The occurrence and roles of these proteins can be identified across the key branches of the tree of life by comparative evolutionary proteomics. Additionally, proteomics provides a powerful methodology for studying the impact of toxicants on a vast diversity of model

organisms by offering a detailed view of the molecular alterations that occur in response to exposure. The potential interactions between proteins and toxicants can be identified and characterized using advanced techniques, such as the PISA assay, which allows for a more refined analysis of protein targets under various environmental stressors. By combining PISA with other complementary approaches, researchers can gain a more comprehensive understanding of how toxicants affect biological systems at the molecular level. These integrated strategies are essential for uncovering the intricate and multifaceted responses of organisms, from the smallest microorganisms to higher trophic animals, to pollutants and play a critical role in developing innovative mitigation strategies for developing innovative mitigation strategies that protect both environmental and human health. Together, the complementary approaches employed in the iMOP initiative provide a powerful framework for advancing our understanding of the complex and interconnected biological systems that sustain life on Earth. The iMOP initiative provides a platform for the research community to explore potential synergies, encouraging the adoption and detailed characterization of innovative models such as holobionts. This effort supports the integration of cutting-edge technologies to advance our understanding of complex biological systems.

#### CRediT authorship contribution statement

**Jean Armengaud:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization. **Tristan Cardon:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Susana Cristobal:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Sabine Matallana-Surget:** Writing – review & editing, Investigation, Conceptualization. **Fabrice Bertile:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

#### Declaration of competing interest

The authors declare no conflicts of interest.

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#### Data availability

No

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