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## PERSPECTIVE

### What are Proteome Atlases good for?

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#### Abstract:

The technological advances in mass spectrometry and associated computational tools have enabled the development of proteome atlases and comprehensive catalogs of proteome snapshots that have gradually transformed biomedical research. These proteome catalogs in specific biological contexts, which focused initially on model organisms, have now expanded their scope to encompass diverse organisms, tissues, and experimental conditions. These atlases, such as the Human Protein Atlas (HPA), Peptide Atlas, and Global Proteome Machine Database (GPMDB), etc. provide invaluable insights into protein expression, subcellular localization, interactions, modifications, and functions. They aid in understanding biological processes, identifying disease biomarkers, and discovering novel therapeutic targets. Despite their potential, proteome atlases face challenges like data completeness, integration with other omics data, and ethical considerations. Addressing these challenges is vital for further progress. Proteome atlases serve as indispensable resources, driving biomedical discovery and innovation.

**Keywords:** Proteome atlas, Proteoforms, Systems biology, Interactions, Mass spectrometry, Biomarkers, Drug target, Therapeutics.

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## 1. INTRODUCTION

The technological advancements in mass spectrometry-based proteomics have immensely contributed to the development of model organism proteome catalogs [1 - 5], which spurred the development of organellar and subcellular proteomes. These resources have delivered great value not only in providing deeper biological insights but also in biomarkers and the development of therapeutic strategies [6].

The “proteome atlases” are comprehensive catalogs of proteins profiled in a biological context that serve as valuable reference guides for research. These are powerful tools providing detailed insights into the proteins that govern cellular functions, pathways, and disease mechanisms [5]. Proteome atlases index thousands of proteins, orchestrating various biological processes and enabling the discovery of complex molecular mechanisms [7] underlying health and disease using big data [8].

Pioneering the concept of proteome atlas, the Human Proteome Project [9] evolved to include the protein mod-forms, isoforms, and variants, collectively called the “proteoforms” [10]. The proteome atlases have become more dynamic resources that incorporate diverse organisms, organelles, tissues, cell types, and experimental conditions. In this era of systems biology and precision medicine, these are indispensable tools for decoding the molecular basis of disease inception and progression [8].

Here, we describe the applications of these atlases and their immense yet underutilized information potential for furthering research.

### 1.1. Proteome Atlases: Knowledge Resources for Modern Biology

The proteome atlases provide comprehensive maps of protein expression and subcellular localization across different model organisms, tissues, cell types, and biological conditions. For example, the Human Protein Atlas (HPA) enables the exploration of tissue-specific protein expression patterns, helping in the understanding of organ functions and disease mechanisms [4]. Similarly, the Human Proteome Map portal

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houses a detailed resource on proteins expressed by the human body, providing important insights into the underlying biological mechanisms and exploring the interactions and roles of proteins within cells, tissues, and organs. The Peptide Atlas [1] plays a central role in advancing model organism biology, including microbes (*C. elegans*, *Candida albicans*, *E. coli*, yeast, etc.), humans, animals (mouse, rat, drosophila, chick, cow, pig, etc.) and plants (*Arabidopsis thaliana*, *Zea mays*, etc.). These organism-specific atlases allow the interpretation of experimental data by providing information on peptide and protein expression patterns.

Global Proteome Machine Database (GPMDB) is an enormous collection of mass spectrometry-based proteomics data used to decipher protein-protein interactions and post-translational modifications, and uncover important proteins associated with specific biological processes or diseases [11]. The Protein Abundance Database (PAXdb) facilitates comparative analysis of proteomes across species, which uncovers evolutionary conservation and divergence in protein functions [12]. The Mass Spectrometry Interactive Virtual Environment (MassIVE) database allows researchers to store, share, and analyze their experimental results [13]. An easily accessible platform for the dissemination of large-scale proteome datasets and results, MassIVE simplifies the challenges of collaboration and reproducibility within the scientific community. It facilitates the development and validation of computational algorithms for data analysis.

UniProt is the most comprehensive resource for protein sequence and function information that consists of UniProtKB/Swiss-Prot, a manually curated and annotated protein sequence compendium with detailed information on protein structure, function, sub-cellular localization, and interactions [14]. Additionally, it contains UniProtKB/TrEMBL, comprising computationally predicted protein sequences. It boasts of extensive data coverage and easy access to information for facilitating protein sequence analysis, functional annotation, and biological interpretation of proteomic data. A human-focused version neXtprot is available to facilitate studies on human biology and diseases [15].

The Human Skin Atlas [16] assembled about 10,000 proteins across distinct layers and cell types of the skin, highlighting their spatial organization and functional roles. It bridges the gap between basic science and clinical application by offering a rich resource of mass spectrometry-based proteome data, methodically collected from both healthy and diseased skin samples. The ImmProt (Social Network Architecture of immune Cells) is a powerful atlas for immunobiology analysis that provides in-depth insights into the interactions between immune cell types [17]. High-resolution mass spectrometry-based proteomics was employed to thoroughly characterize 28 primary human hematopoietic cell populations in their resting and activated states, to create the extensive atlas of over 10000 immune proteins. The researchers can study the intricate network of immune cell types, to understand how these cells communicate to safeguard against diseases. Protein copy numbers were analyzed to reveal specialized immune cells that express ligands and receptors important for orchestrating immune functions. It is an open, accessible proteomic atlas that serves as a reference for

identifying altered immune-cell communication patterns associated with pathological conditions.

PhosphoSitePlus is a useful atlas for phosphorylation events across species [18]. A vast array of information is curated for phosphorylation sites, motifs, kinases, and substrate proteins, collating information from literature, high-throughput studies, and public databases. PhosphoSitePlus offers various options for in-depth analysis of phosphorylation sites, surrounding motifs, experimental conditions, and functional consequences. It also helps researchers in data analysis, visualization, and integration with other biological databases. Besides phosphorylation, the role of other Post-Translational Modifications (PTMs), such as ubiquitination, methylation, and acetylation, are also important in cellular signaling, regulation, and disease [19, 20]. The atlas covers these resources, and the wealth of curated PTM data and user-friendly interface make this a useful resource for illuminating the complex landscape of protein modifications.

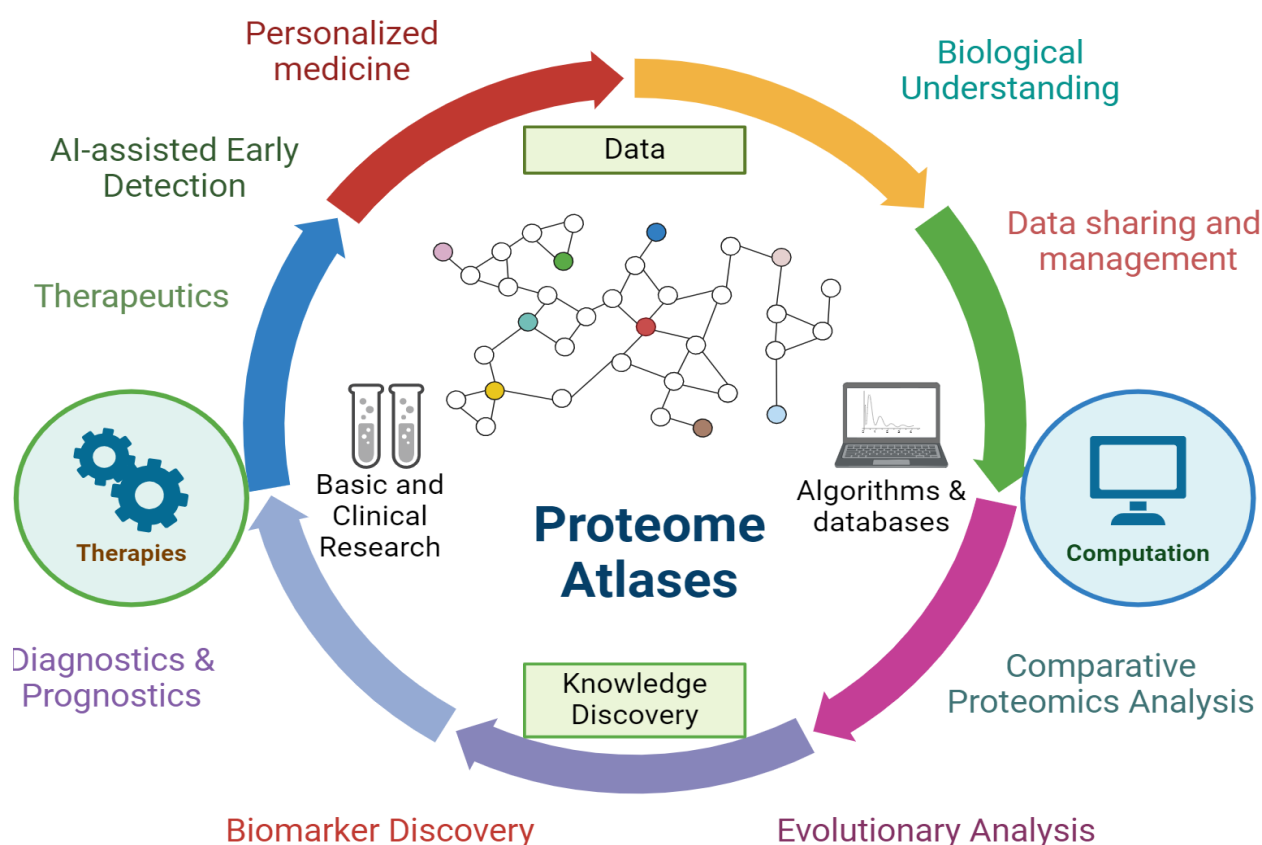
PTMCode [21] is a comprehensive resource on PTMs and their cross-talks. The PTM crosstalks are important in many diseases [22]. PTMCode has been curated by integrating experimental PTM data and analyzed using several computational algorithms. PTMCode is a powerful knowledge-base that can predict PTM crosstalk sites using machine learning techniques and sequence-based features. This assists the study of regulatory mechanisms and functional implications of PTMs and their crosstalks in important cellular processes, such as signaling cascades, protein-protein interactions, and disease pathways.

The proteome atlases enumerated above are just some examples, and many such resources exist to facilitate biomedical research. Numerous studies have been facilitated by these resources across model organisms, biological samples and cell types, subcellular localizations, and biofluids. These portals allow research advances by elucidating cellular signaling networks and the discovery of promising biomarkers and drug targets. In the next section, we list out the important use cases where proteome atlases are useful, their limitations, and a way forward in the future.

## 1.2. What are Proteome Atlases Good for?

The Proteome atlases are information-rich resources that serve the research community in many ways and have proven indispensable for advancing biological research. Such atlases house valuable information, data, and tools for researchers across diverse biological disciplines, catering to their information requirements on protein expression, subcellular localization, interactions, and modifications within biological systems. This allows multifaceted use cases described in Fig. (1) and the text below.

The proteome atlases allow the rich exploration of biological processes by providing deep insights into the cellular machinery regulating metabolism, signaling, and gene regulation. The abundance and localization of proteins and their interactors across diverse biological samples, conditions, and disease contexts provide a mechanism to interpret experimental data in the light of comprehensive information where their role in the interconnected molecular pathways becomes increasingly apparent.



**Fig. (1).** The overview of proteome atlases and their uses in biological discovery, comparative & evolutionary proteomics, biomarker discovery, therapeutics, and personalized medicine.

Biomarker discovery is an important aspect that flows out of such endeavors. Carefully curating and cataloging the protein expression patterns in healthy and disease conditions, these proteome atlases promise unprecedented ease of comparative studies that will allow for early discovery of potential biomarkers of disease. These can also be used to facilitate the diagnosis, prognosis, and monitoring of therapeutic responses to different drugs.

One of the major goals of developing proteome atlases has always been to discover potential drug targets for debilitating diseases for which there are no FDA-approved drug targets, such as non-alcoholic steatohepatitis. Uncovering potential therapeutic targets becomes more robust and easier if such catalogs are part of the analysis strategy from the beginning of studies. This obviates the need to rely on single or multiple individual studies that may have contradictory or non-conformant observations. This will also facilitate personalized medicine approaches where precision is important.

Despite their immense clinical potential, it must not be forgotten that all useful information arises from fundamental information on protein structure, function, and activity, a primary goal for basic sciences. These proteome atlases are a primary source of such information-rich annotations that allow unearthing the latent connections between biomolecules,

stressing upon important mechanisms and pathways. This information can be later exploited for biomarker or therapeutic research.

Dobzhansky once remarked that “nothing in biology makes sense except in the light of evolution.” It is obvious that biological studies will also require evolutionary studies and comparative studies of proteins across the tree of life. Facilitating evolutionary and comparative analysis, some resources contribute immensely to understanding the evolutionary implications of proteome catalogs such as PhosphoSitePlus, ImmProt, and PTMCode. Comparative biology allows the discovery of conserved and divergent features of proteins.

Proteome atlases provide a bird's-eye view of biology by enabling systems biology research, in which integrating proteomics data with other omics and systems analysis of networks and pathways are employed to make sense of complex biological phenomena. It can enable data-driven research approaches to discover novel information compared to traditional hypothesis-driven research. This also makes heavy use of machine learning and deep learning algorithms to utilize such vast amounts of curated data for novel biological insights.

Last but not least, such proteome catalogs also promote

open science and foster collaborations and data sharing to enable reproducible research. This allows data scientists and bioinformatics researchers to connect the dots across disciplines and make new discoveries that the original study authors may not have envisioned. In summary, proteome atlases are essential resources that empower researchers to unravel the complexities of biology, disease, and therapeutics, driving forward our understanding and ability to address pressing biomedical challenges.

Although proteome atlases have proved to be indispensable to modern biological research, they also have certain limitations. For future progress, tackling the issues of data completeness and uniform processing to make the data quality more accurate, reliable, and robust are warranted. The atlases need to also move beyond static snapshots of the proteome. The technology has vastly improved to allow for more in-depth, spatially- and temporally- resolved proteomes enriched with diverse PTMs and interaction information. These aspects must be catered to enrich these atlases and provide more value. To fully exploit the potential of multi-omics for systems-level understanding, semantic methods for integration need to be developed and incorporated into these atlases. Then, there is the challenge of maintenance, accessibility, usability, and interoperability of the resources. Improvement of user interfaces as per modern development practices, interactive data visualization, and standardization of data formats would enhance their usability and facilitate data-driven research. There is a recent rise in concerns about the ethical and legal considerations for the use of clinical data for proteome catalogs that need to be addressed aptly, keeping data privacy, consent, and responsible sharing in the design goals.

## CONCLUSION

The proteome atlases hold immense potential for advancing biological research and addressing important biomedical challenges by mapping proteins from diverse organisms such as humans, animals, plants, and microbes. They support advancements in pharmaceuticals, biomedical research, agriculture, *etc.*

To fully harness their power, it is essential to address limitations such as data completeness, accuracy, and standardization. Advanced computational methods such as machine learning and artificial intelligence will strengthen the analysis and interpretation of vast proteomic datasets to uncover hidden patterns and generate actionable insights. Additionally, fostering collaboration among multidisciplinary teams with biologists, data scientists, and clinicians is crucial for integrating diverse expertise and perspectives, thereby enhancing the applicability and utility of proteome atlases while maintaining global ethical standards. Ensuring data privacy, obtaining informed consent, and addressing potential biases in data collection and analysis are important aspects of the appropriate use of proteome atlases.

By enhancing data accuracy, improving data acquisition and integration methods, fostering interdisciplinary collaborations, and maintaining ethical standards, we can fully leverage such atlases for significant scientific breakthroughs in biomedical, agricultural, and microbial sciences.

The proteome atlases have immense potential to advance

biological knowledge, as well as improve human and crop health through interdisciplinary collaborations and integration of data science techniques with strong ethical standards. A gradual increase in studies facilitated by proteome atlases in diverse biological areas promises to unlock their full potential in the near future.

## AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

## LIST OF ABBREVIATIONS

HPA	=	Human Protein Atlas
GPMDB	=	Global Proteome Machine Database
PTMs	=	Post-Translational Modifications

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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