

HPP Grand Project | “A Function for Every Protein”

White Paper:

In 2020, the Human Proteome Organization’s (HUPO) Human Proteome Project (HPP) celebrated its 10th Anniversary with major achievements resulting in the high stringency blueprint of the human proteome. The HPP detailed the detection of over 90% of all predicted human proteins, and has increased this effort to 92.8% in 2021. Coming 20 years after the release of the first draft of the Human Genome, these efforts by international consortia have provided substance to the collection of human genes and highlighted proteins that are extremely difficult to reliably detect by any current technology platform.

With these unprecedented developments providing rich volumes of data and resources to interrogate the proteome, we now turn our focus to understanding the proteome in its fullest with the formation of the “HPP Grand Project”. This project will focus on the exploration of the human proteome by understanding proteins in their network environment and will enable the elucidation of its biological significance, and ultimately its function. Here, we present the HPP Grand Project: “A function for Every protein” to the community. By partnering with the significant enabling initiatives worldwide to provide resources that will enhance participation by interested parties, we look towards the community to self-associate and propose HPP projects that advance the knowledge of proteins and their network of networks to provide rich biological information on their actions and ultimately their function.

Concept

The HPP is a collective membership of voluntary researchers wanting to contribute to the knowledge of the human proteome, and has recently produced the draft of the human proteome at over 90% completion. The HPP has delivered significantly on the knowledge of the human proteome and provided resources for the entire community to access and utilize in their own interest outside of the HPP. These include knowledgebases such as neXtProt and resources of the chromosome-centric, and biological/disease focused projects. The HPP has organized itself into specific focus groups that span discovery of proteins and provide credible evidence for their spatial existence. The HPP has developed a framework to disseminate and provide focused biological knowledge to understand various aspects of human biology and disease. These encompassing efforts provide an ever-expanding set of knowledgebases that is the first in the world and provides goalposts as well as community metrics for data integrity and biological relevance. Given this background the HPP has developed over the last 20 years, starting off with the Human Plasma Proteome project, and the milestones achieved recently, it is time for the Human Proteome Organization, through the HPP, to focus its efforts to collectively contribute to addressing important biological problems on a “Grand scale”.

To this end, the HPP Grand Project will provide a framework for the HPP, and its various initiatives and pillars, to join forces in order to integrate and direct their various proteome focused efforts to collectively contribute to a grand program important to human health and well-being. The goal of the HPP Grand Project is to advance our understanding of a complex biological problem in a consortia framework where individuals, or groups of individuals, can propose various work plans to contribute to the grand project and access available resources as well as support grant applications at their domicile.

The HPP Grand Project | “A Function for Every Protein”

Over the last decade the HPP has demonstrated its capacity to muster significant resources and firepower to collectively work on significant biological programs and to tackle the understanding of complex processes at the molecular level. The HPP Grand project will build on the achievements of the HPP and involve interested new members to launch a new, long term grand challenge in biomedical research. During 2021, the HPP conducted a number of discussion sessions to define the HPP Grand Project upon advice from the HPP SAB. In 2020, the HPP SAB charged the HPP to integrate its efforts and the HPP Grand Project meets this challenge and provides a new and exciting direction that brings forward all of the HPP efforts.

Goals of the HPP Grand Project

The HPP Grand Project “A Function for Every Protein will enable the deciphering and integration of networks to enable the understanding the underlying biology” allows the following:

- Status of proteins (quantitation, isoforms, PTMs etc.) to build networks/interactomes that can be perturbed whether by variation amongst individuals, disease or specific binding interactions, including comprehensive profiling (MS, Abs, or other technologies), protein complex formation and their functional relevance, analysis of specific diseases at the single cell level, broad disease applicability (response to infection and diseases (cancers, physiological disease, protein dysfunction (metabolic etc.).
- Illuminate the functional basis of the disease by building off the principles of disease manifestation from a genomic viewpoint and applying proteomics knowledge to define protein interactions and their roles.
- Pathology - measure dynamics of disease; these include early-stage disease manifestation, therapeutic response once stratified, aberration of protein networks after intervention, and possible next therapeutic steps.

As the HPP EC members coalesced around the idea of a “A Function for Every Protein” project, a discussion around the utility and capabilities proceeded. To make the project compelling there will need to be specific projects proposed with short term goals to make the overall “Grand Project” viable and be able to direct the knowledgebase of networks that are studied with specific context of health and disease. The Pathology pillar plays an obvious role to propose specific clinically focused projects with direct therapeutic benefit.

The next steps are to identify specific projects under the “A Function for Every Protein” project umbrella and to begin to identify resources for members to tap into to support a project of this type.

The HPP Grand project must be a broadly applicable project yet remain focused to deliver on a staged program in a short timeframe to be relevant to the community. Obviously, there will be a large discussion on the selection of a project, but the underlying goal is to provide inclusivity to members and to realize what resources are available as well as how we can collectively garner new resources.

For resources, many individuals already have the desire and potential than can be applied to a project of this size. In addition, by combining with external consortia, the HPP can obtain new resources such as reagents to target significant numbers of proteins, e.g., the Human

Protein Atlas antibodies, the Structural Genomics Consortium Target-2035 small molecule libraries, and others. Coupled with the assay resources of each individual and the computational resources of HUPO, a project of the size of a Grand Project will enable collaborative efforts to significantly advance the knowledge of the project focus but also advance the HPP beyond its current status quo.

Unique advantages of HPP Grand Project

Over the last two decades life science research has been profoundly changed with its comprehensive analysis in various 'omics, and to some extent dominated by the technologies and outcomes of the human genome project. Carrying forward crucial concepts of genomics, including systematic, quantitative, and sensitive molecular analyses coupled with the integrative analysis of the ensuing datasets to proteomics, opens enormous new opportunities. Some of these have been realized over the last decade by the HPP and the research of individual groups supporting the HPP. Yet, most of the biologically relevant information contained in the proteome remains to be mined. Specifically, the link between molecular entities and function, the exploration of the full complexity of the proteome such as each proteoform, post-translational modifications, protein:protein interactions, and protein structural considerations are areas of proteomic research that are now technically within reach and provide unique selling points for such a Proteomics Grand challenge.

Organization and mode of operation of the HPP Grand Project

The HPP now presents a road map towards achieving these goals. It also provides direction and guidelines and will identify resources available. The HPP also provides a worldwide community forum where the results, goals and directions of the project are discussed and refined and where high impact achievements are communicated to the wider research community.

Robert Moritz
Chair, Human Proteome Project
Human Proteome Organization