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# HUPO's Effort to Define the Liver Proteome

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The Human Proteome Organisation (HUPO) (www.hupo.org) was established in 2001. Within its first year, the organisation decided to launch international initiatives around organ systems and biological fluids that have disease relevance. Plasma and Liver were first selected, followed shortly after by Brain. Beside the fact that the liver is the largest organ in the body, probably second only to the brain in organ complexity, the strongest and most compelling argument for a proteome initiative that focuses on the liver is the essential and multi-function role of the liver in human health and disease. The liver displays the main digestive function for the metabolism of most substances but also undertakes a myriad of functions beyond digestion, such as production of red blood cells during embryonic development, production of numerous plasma proteins, and detoxification of xenobiotics. The liver is the most effective site for phagocytosis of solid material and the guardian interposed between the digestive tract and the rest of the body.

The human liver proteome project (HLPP) was officially launched in October 2002, under the leadership of Professor Fuchu He, Director of the recently-established Beijing Proteome Research Center, during a workshop held in beautiful Fragrant Hills outside Beijing. Co-chairs from Europe and the United States joined Prof. He in leading this initiative: Professor Christian Bréchot, then Director of the “Institut National de la Santé et de la Recherche Médicale”, France, replaced in 2007 by Dr. José Mato, Director of CIC BioGUNE, Bilbao, Spain; and myself, Full Member in the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center in Seattle. In July 2003, I organized the second HLPP workshop in Bethesda, with the sponsorship of two NIH Institutes, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Standards and Technology (NIST). Representatives from 6 other NIH Institutes, the National Cancer Institute (NCI), the National Institute of National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on drug Abuse (NIDA), the National Institute of Environmental Health Sciences (NIEHS) and the National Institute on Aging (NIA), participated to the workshop, reflecting the substantial interest in a liver proteome initiative at NIH. The NIH-sponsored workshop summary and recommendations are available at the HUPO website (http://www.hupo.org/research/files/HLPP_Bethesa_Workshop_Summary_July_2003.pdf; http://www.hupo.org/research/files/HLPP_Bethesa_Workshop_Summary_July_2003.pdf). These 2 inaugural workshops aimed at sketching out an action plan for the initial phase of this international liver proteome initiative. Overall, the consensus was that the study of normal liver proteome is an obligatory step to build basis for current and future research. Once the scientific basis of the

liver proteome is known, then that knowledge can be expanded to study liver diseases. Mapping and identifying the proteins in the human liver may be the key to many diseases.

Since 2003, the commitment of China to support, in a major way, such an initiative has not faded away. The Chinese Human Liver Proteome Project (CNHLPP) was initiated in 2004 by the Ministry of Science and Technology and 11 laboratories participated in the expression profiling analysis of a Chinese Liver Reference Sample. This effort was conducted in parallel to the expression profiling analysis of a French Liver Reference Sample. Both data sets are now reported in this Liver Proteomics special issue and to date, more proteomic knowledge has been assembled about the liver than any of the other organs in the human body. At the 2005 HLPP workshop held at the Airlie Center, Virginia, in conjunction to an American Association for the Study of Liver Diseases – sponsored conference entitled “Exploring the functional Genomics and Proteomics of Liver in Health and Diseases” and co-organized by Dr. T. Jake Liang from NIDDK and myself, 3 main targets for HLPP were identified, as follows: 1- identification of 5,000 individual proteins in the normal human liver; 2- availability of antibodies against these 5,000 proteins; 3- determination of the presence of these 5,000 proteins in plasma. These targets once reached will generate sufficient knowledge of the normal liver and resources to allow the study of liver diseases and biomarker discovery. A major achievement has now been made with the construction of the human normal liver proteome expression profile, with over 6,000 proteins identified in the Chinese as well as in the French Liver reference samples.

Fundamental biological questions need now to be addressed. For example, it is important to define the proteome range in “normal” liver and to determine the relationship between protein dynamic in blood and protein synthesis and processing in the liver. There is currently no information on the biological variations of the liver proteome (protein changes occurring in healthy individuals of different sex, race, age or with different diet or activity habits). Issues related to genetic polymorphisms and to liver proteome model systems have not been tackled yet. New projects should be directed as the study of the contribution to the liver proteome of each cell type (hepatocytes, stellate cells, Ito cells, Kupffer cells, endothelial cells and biliary cells). Integrative studies using proteomics and basic cellular biology or other growing fields such as imaging and mouse models will contribute to our understanding of the liver biology. Efforts to determine the presence of liver proteins in plasma using mouse models are ongoing. The rodent liver has often been used as a resource for proteomics technology development and major achievements were made on the construction of the mouse liver proteome expression profiles with extensive data sets generated in particular by Matthias Mann's and my groups. These large data sets are currently being integrated by Eric Deustch at the Institute of System Biology, Seattle, using common standard tools within PeptideAtlas for data capture and analysis. To reach further depth in the rodent liver proteome, several groups have used an organelle approach. Of particular interest, a membrane proteomics initiative (MPI) using mouse liver as the sample source was launched in 2005 by Asia Oceania HUPO (AOHUPO). Another important rodent liver subproteome, the secretory-pathway proteome, was characterized by John Bergeron with spatial information on the relative presence of each protein in the rough and smooth ER, Golgi cisternae and Golgi-derived COPI vesicles. These studies represent major breakthrough because of their comprehensive nature, providing the building blocks of the

liver proteome. The next phase is to use this information to further understand the biological functions of the liver and their regulation. To that end, groups of proteins associated with specific functions (e.g. detoxification, ER stress, lipid metabolism, liver development, liver regeneration) remain to be characterized in greater details. Such studies are emerging. For example, several groups have recently used proteomics approaches to analyze the highly homologous cytochrome P450 enzymes responsible for the oxidative metabolism of many xenobiotics and organic endogenous compounds.

HUPO initiatives such as HLPP, CNHLPP and AOHUPO MPI have generated over the past 6 years extensive information on the normal liver proteome, laying foundation for future studies. The linchpin is now to further coordinate data sets analysis and further develop a site for database management that would assure that the tremendous amount of data and resources could be put into use by the research community for a multitude of liver-related projects. The liver proteome will be studied for many decades to come. The hope is to stimulate that research now.