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How to Solve Complex Scientific Challenges with Comprehensive Proteomics and Bioinformatics means - HUPO Brain Proteome Project

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HUPO - How it began

Since more than a decade proteomics is the method of choice for the life science sector as genetics could not cure all human diseases. Unfortunately, the world of proteins is far more complex than the genome; and a proper analysis can be extremely expensive and time consuming. In addition, the need of standards, standard operation procedures (SOPs) and common rules is obvious. Therefore, the Human Proteome Organisation (HUPO, www.hupo.org) was founded in 2001 aiming at the optimisation, the spreading of proteomics techniques and demonstrating its potentials. In order to focus the expertises of the participating scientists, tissue-related initiatives got together under the roof of HUPO that voluntarily analysed one distinct human organ with proteomics means. The very first initiatives were the HUPO Plasma Proteome Project (HUPO PPP or HPPP), the HUPO Brain Proteome Project (HUPO BPP/HBPP) as well as the HUPO Liver Proteome Project (HUPO LPP/HLPP). During the last seven years, several initiatives were added (as to end of 2007), namely the Human Antibody Initiative (HAI), the Mouse Models of human Disease (MMHD), the Human Disease Glycomics/Proteome Initiative (HGPI), the HUPO Cardiovascular Initiative (HUPO CVI), the Proteome Biology of Stem Cells Initiative and the Proteomics Standards Initiative (HUPO PSI, www.psidev.info), defining proteomics controlled vocabularies as well as common standards. HUPO has developed criteria for new initiatives to be found at HUPO´s homepage.

The HUPO Brain Proteome Project and the challenges

The prevalence of neurodegenerative diseases especially in Western societies increases steadily - and so does the costs for comprehensive scientific proteomics studies. This is due to immense expenses for equipment and consumables as well as the high number of repetitions to fulfil the statistical imperative. At the same time, techniques become even more complex, while suitable samples are scarce, especially when thinking of the human brain. What is the consequence?

As indicated above, the Brain Proteome Project (BPP) is one of the initial initiatives of HUPO aiming solving these problems. The HUPO BPP started its operational work in early 2003. An administration and bioinformatics group was initiated at the Medizinisches Proteom-Center in Bochum, Germany. It became clear soon that common standards and defined parameters were missing as most scientists defined their own thresholds, parameters and specifications, mostly due to different analysis set-ups. However, these different criteria led to different results, so that studies can not be compared easily. During the 1st HUPO BPP Workshop at Castle Mickeln, Germany, two pilot studies were initiated, also inspired by the experiences of the HUPO PPP colleagues. The aims and results of these two studies are described in detail in the special edition *The HUPO Brain Proteome Project – Concerted Analysis of the Brain* [PROTEOMICS, volume 6, issue 18]. The studies lasted more than two years as data generated in single labs was collected in a Data Collection Center and was bioinformatically analysed centrally afterwards. Especially the participating lab scientists and the bioinformatic task force, greatly supported by the HUPO PSI, did an outstanding job. Due to the combined effort of 18 laboratories world wide a huge amount of data sets with current proteomics technologies were gained and analyzed. Only very few of the identified differentially expressed proteins could be found combined effort of 18 laboratories world wide a huge amount of data sets with current proteomics technologies were gained and analyzed. Only very few of the identified differentially expressed proteins could be found by many or all of the participating groups, although each of the individual laboratories could show to have detected several dozens of reproducible differences. The yield of an individual protein is depending on the conditions for sample preparation, i.e. salt concentration, pH, detergents, temperature, etc. Every little change will result in a different sample composition and thus another protein set. Here, once again the need for standards became obvious when thinking of sample handling or parameters for search engines in mass spectrometry, but also the power of synergistic work of different analysis strategies. Moreover it is important to repeat experiments independently several times to show their reproducibility as it was already suggested in many articles before - but this is often unconsidered despite the own experiences.The subsequent consolidation phase has been accompanied by several workshops dedicated to the spreading of the standard concepts and to the collection of existing approaches within brain proteomics. Concerning the criteria that have to be fulfilled in successful proteomics it was stated that:

- methods have to be robust, so that e.g. the same system can be run several times

- methods have to show a high sensitivity, so that e.g. low abundant proteins can be detected

- methods should be available at reasonable cost (for academic institutes) allowing independent biological repetitions

- each laboratory has to show the reproducibility of every result

It is therefore clear that high performance has to be estimated higher than high throughput.

The work on bioinformatics standards is now carried on also by the HUPO PSI as well as the Proteomics Data Collection – ProDaC, an EU funded consortium (www.psidev.info and www.fp6-prodac.eu).

Redundant Telephone Lists

Many, probably disease-unspecific proteins are identified in numerous studies, superposing the key player proteins of neurodegenerative diseases we are interested in. A lot of protein expression changes are usually reported in numerous models or human tissue studies, ending up with protein lists that resemble each other. Only a few of them seem to be disease-specific regulated proteins or genes. Klose and his colleagues from the Charité Berlin, Germany, propose that the observed protein changes might partially be explained by a proteomic network response. They consider a class of *balancer* proteins within the proteomic network, defined as proteins that buffer changes within the protein stoichiometry. The loss or the change in the amount of essential proteins will lead to a disturbance of the protein composition. This may cause a system malfunction that can be compensated partly by the expression of other, disease-unspecific proteins. These proteins are named as *balancer* proteins, also showing significant regulation, but being probably not involved in the development of the disease. The expression of these proteins could be regulated in a defined manner, compensating the changed overall protein amount in the cell or cell compartment. However, the triggered effect could have a high influence by increasing or decreasing the amount of some *effector* related proteins, controlled by protein regulatory networks which underlie these mechanisms of *resilience* biology. The *balancer* proteins might essentially contribute to the overall network entropy and can be named hubs of these protein regulatory networks. By comparison and integration of all data available from those studies it may turn out that most of the reported proteins/genes are found in many of those different investigations, in other words they are not specific for the particular study and disease, respectively. Only large scale analyses as the HUPO BPP, integrating many different quantitative research fields, will distinguish between real *effector* proteins as disease biomarkers and *balancer* proteins. Therefore, one has to look on a variety of diseases to discriminate if a protein is disease-specific. The integration of all available scientific fields including proteomics, genomics and molecular biology will allow achieving essential insight about how cellular activities are regulated.

Outlook

The era of post identified information has begun, focusing on bioinformatics and systems biology. Large consortia as the HUPO BPP are necessary for such complex interdisciplinary research to overcome the problem of the necessary amount of data for biological interpretation in a *system* biology driven way. The gained complementary result lists as a part of the telephone book will be interpreted by systems biological means to overcome static identification lists. These efforts have to be based on comprehensive differential analyses using complementary methods and common standards. Only by combining several techniques (MS, ISH, ProteinBiochips etc.) and results from several Omics an understanding of e.g. complex brain diseases will be possible in the near future. The HUPO BPP and HUPO itself will elaborate suitable standards to collect data of many laboratories to build the mandatory fundaments of systems biology driven approaches and will help actively to realise these insights. However, the academic scientific research today needs barrier free data and publication access beside money, courage and self-criticism to bear new outstanding ideas.