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A protein shake-up

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Developments in proteomics could produce significant benefits in everyday healthcare, suggest EuPA's György A Marko-Varga, Ákos Végári and Thomas E. Fehniger...

Healthcare systems today are undergoing major restructuring. We envision that the future of patient care will change considerably in order to meet the shortcomings that stem from a lack of resources, while embracing targeted treatment efficiency. From the patient's perspective, expectations focusing on high-quality treatments for most common diseases – such as cancer, cardiovascular diseases, neurodegenerative diseases, diabetes, and others – have gone unmet in most countries throughout the world.

> 'The announcement of the Human Genome Project by Bill Clinton and Tony Blair on 23rd June 2000 marked a scientific milestone, allowing the public to access an enormous information sequence data set.'

In most cases, society is expected to be able to offer improved prognosis at a reduced cost to the healthcare system by early detection, with personalised treatment and evaluation of response to treatment. Many patient cases are problematic due to the multifactorial disease indications and variable disease statuses that occur in each patient. In most cases it is impossible to align a given disease diagnosis with a single molecule that is uniquely related to one disease or clinical complaint. Quite to the contrary, there are typically hundreds of such biological signals (multiple signals), which complicate the identification and selection of the important factors that lead to disease. This is hampered by the lack of tools and data available for implementing early diagnosis, modelling of disease progression and evaluation of treatment responses.

As an example, lung cancer caused by smoking often develops in a lung already beset with the chronic inflammation and reduced airway function that occur with coincident Chronic Obstructive Pulmonary Disease (COPD). Both lung cancer and COPD are further linked to coincident cardiovascular disease in epidemiological prevalence studies.[1, 2] Together these three diseases represent the leading causes of smoking related mortality wor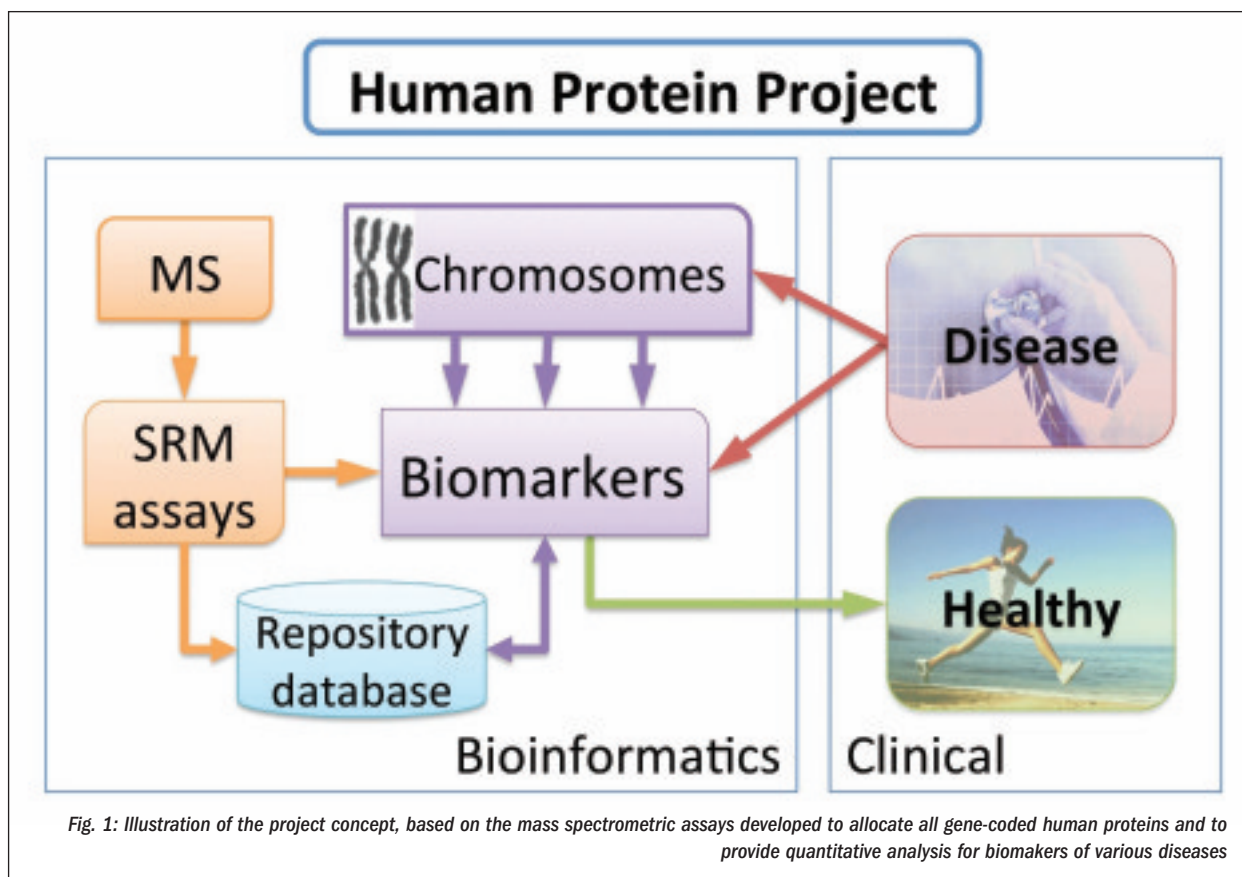ldwide.[3, 4] Lung cancer continues to be the most common cause of cancer death in men in the EU, with 178,400 deaths estimated in 2004 (27.3% of all cancer deaths), and a lifetime mortality risk of 5.5%. The cost of treatment of lung cancer in one model study in Switzerland came to around €20,000.

While median survival for all patients with lung tumours has increased from seven to 17 months in the past few decades, much of this progress arises from improved surgical methods, combined modality treatment for locally advanced disease, improved symptom palliation, and moderate but real improvements in survival of late stage (stage IV) disease.

Benefit to society

Improving the quality and coverage of healthcare is a global effort that requires the development of both infrastructure and public awareness, but also a commitment of large-scale resources to support these endeavours. The cost of healthcare throughout the European Union is rising beyond the forecasted levels of committed funds. A combination of factors is acting here, including costs dependent upon the ever-increasing utilisation of modern medical technology, an increase in life expectancy among the public, and diminished state resources. The rising costs of healthcare could be partially addressed by systems that enable clinical data to be managed under repository of healthcare providers, irrespective of the location of the data acquisition. In recent years IT solutions to centralise medical records, so-called e-health systems, have been implemented in the EU (with Estonia being the model system).[5] Such systems act as repositories of all clinical measurements, clinical evaluations and treatment records throughout an evaluation and treatment period. An important aspect of this system is to classify disease using standardised scales of nomenclature that most accurately describe the form and stage of the disease being assessed, as well as reference to previous disease or co-morbidities of disease.

Clinical proteomics is a key research area today within the EU, with widespread activities of clinical importance, such as developing new methods for diagnosing early disease or for monitoring treatment efficacy. However, the true usefulness of these new markers needs to be evaluated and established in large-scale clinical studies of whole populations of subjects. Each measurement needs to be evaluated within the contexts of individual

Fig. 1: Illustration of the project concept, based on the mass spectrometric assays developed to allocate all gene-coded human proteins and to provide quantitative analysis for biomakers of various diseases

differences in disease presentation and in context with established clinical measurements that address disease development and outcome. An electronic e-health database that has the utility to assign the context of disease to individual patients – and combine such data in large population-based data sets – is an invaluable tool for evaluation of all clinical measurement endpoints, including clinical proteomics markers. The integration of these datasets would foster new possibilities for modelling treatment protocols to meet individual patient needs, in the mode of personalised medicine programmes already under rapid development in many clinical specialties.

‘Clinical proteomics is a key research area today within the EU, with widespread activities of clinical importance, such as developing new methods for diagnosing early disease or for monitoring treatment efficacy.’

Why then would such e-health electronic data management systems be of interest to the clinical proteomics community or to clinicians? This question is most often posed as either 'what value do protein biomarkers have in clinical management?' or 'what forms of clinical presentation are associated with which specific markers?' The actual clinical importance of individual measurements (both quantitative and qualitative) of protein biomarkers as prognostic indicators can only be

evaluated by first establishing ranges of normal values in population-based studies and then aligning these scores with contexts of disease presentation, contexts with other clinical measurement devices that address structural and functional abnormalities, and with eventual clinical outcome. It is at this point that the true value of an electronic e-health database begins to be appreciated as a valuable resource, not only in clinical proteomics studies but also in other essential clinical measurement tools. An electronic e-health database has the ability to assign context to disease development in individual patients who are members of large population-based data sets that can be assessed as individuals or as populations.

Proteomics - the human proteome map
Proteins have long been the focus of disease biologists over the last century. The area of proteomics has been developing since the 1960s, long before the term itself was coined. Classical protein expression analysis has been an exciting area for scientists to study in order to understand the structure and content of proteins in a given biological system. The announcement of the Human Genome Project by Bill Clinton and Tony Blair on 23rd June 2000 marked a scientific milestone, allowing the public to access an enormous information sequence data set. Interestingly, the final gene map was presented simultaneously by two independent research consortia, utilising both a traditional gel technology, as well as a multicapillary high-throughput approach.[6, 7] Today, the study of the human genome is a common activity in laboratories, and is taught in public schools around the world daily. The human genome represents an important

catalogue that holds the basis of human health and disease. These 22,300 human genes encode all of the proteins within the 330 human cell types of our body – the human proteome.

The proteomics scientific community has, during the last two decades, been involved in a two-front scientific engagement:

■ To map the protein content in a large number of various biological samples, of both human as well as microorganism origins;

■ To develop technology tools for enabling accuracy and specificity in the measurement and identification of each of the proteins in the proteome.

It has taken the proteomics research society some time to understand and outline novel ways of achieving high resolution analytical data with thousands of unique signatures, as intact proteins or as peptides, which are the building blocks of proteins, constituted of single amino acids.[8, 9] Today, a number of protein expression and analysis platforms are available that can generate large-scale maps of proteins and their relationships in health and disease. These mass spectrometry-based technologies are used on a daily basis by thousands of research laboratories around the world. The academic sector and the pharmaceutical industry have remained as the main drivers in these developments.

'An electronic e-health database that has the utility to assign the context of disease to individual patients – and combine such data in large population-based data sets – is an invaluable tool...'

One major challenge that remains a daily problem in laboratory experiments is the need to reach a lower abundance of protein sequencing – as biological samples in most cases constitute not only a high number of proteins, but are also expressed in a wide dynamic range. This leaves the scientist faced with a dilemma, where the data output is intimately connected to the access to clinical material. For instance, the window of protein expression in blood is in the order of 10-12 orders of magnitude.

The major limitation in this respect is the lack of protein amplification technologies. Protein PCR amplification technology would be a major benefit to the proteomics field.

The recent developments and announcement from the Human Proteome Organization (HUPO) on the Human Proteome Project (HPP) is a major undertaking, in some ways similar to the Human Genome Project (HUGO).[10, 11, 12] The major difference is that each of the approximate number of 20,300 proteins encoded by the human genome will be mapped to specific locations on individual chromosomes. Protein annotations will be linked to the human genome and to specific diseases by applying both

mass spectrometry assays (see Fig. 1) and antibody-based assays.[13, 14, 15] A commitment was made on 23rd September 2010 in Sydney, at the 9th Annual World Congress of HUPO,[16] to map all gene-coded proteins within the 46 chromosomes of the human body. [17, 18] This is by no means a novel idea – it had already been discussed at the first HUPO world congress in Paris in 2002. We have entered a new era of protein science that has the potential to greatly influence our basic understanding of disease and provide useful tools for clinical decision-making.

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