Editorial

Diagnostic Proteomics: Will this impact the clinic?

Sascha Sauer

Over the last decades we have witnessed enormous progress in the life sciences in terms of in-depth knowledge but less in the development of groundbreaking new concepts. Modern life sciences are dominated by application of the very successful reductionist research paradigm of experimental physics and chemistry [1]. However, experimental manipulation and simple mechanistic interpretation may turn out to be inadequate in biology when dealing with interconnected and inherently non-separable processes, leading to technical or even fundamental limitations due to biological uncertainty of the various states of interacting molecules [2].

Recently, systematic data driven approaches were introduced to generate in a largely unbiased fashion hypotheses, and in the ideal case to monitor the expression and regulation of all relevant molecular key players such as proteins. However, complexity may in particular arise from causality structures [3], which cannot be easily deduced from the "parts of the sum" of single molecules and mechanistic interaction of a few key players. It seems that network-based interaction of molecules results in the important redundancy, plasticity and flexibility of biological systems including homeostatic regulation of the proteome, which would otherwise be too vulnerable to environmental perturbation or stochastic events [4].

The advent of new methodologies in the life sciences including proteomics raised hope to provide efficient tools for diagnosis and for monitoring of complex disease (treatments) [5]. But the transition of proteomics-based research to clinical practice is in general still inefficient. Clinical proteomics as other fields of the life sciences dealing with complex issues may benefit from developing innovative approaches, i.e. to adequately grasp the etiology and causality of diseases to eventually develop fruitful approaches and tools for efficient diagnostics and medication of diseases. In this Focus Issue on "Diagnostic Proteomics", a number of concepts, methodologies and promising results are presented to advance the field of clinical proteomics.

In a viewpoint, Ulrich Stelzl (contribution in this issue, pp. 727–732) discusses the importance of molecular networks for interpreting various large data sets including genetic variation and proteomics data, to better understand fundamental biological organisation principles and to comprehensively analyse disease processes [6].

During the last years, biological mass spectrometry based methods have been introduced for various potential clinical applications. For example, mass spectrometry based imaging methods have become promising tools to analyze on the molecular level the pathology of tissue samples [7]. Jeremy Norris and Richard Caprioli (contribution in this issue, pp. 733–738) provide a concise update on these methods and discuss future applications. Furthermore, protein-based diagnostic markers can be identified in discovery-driven approaches using high-throughput mass spectrometers [8]. In this context, Bruno Domon and co-workers (contribution in this issue, pp. 739–747) discuss newest developments in the field of (targeted) mass spectrometry (also [9]) to validate potential protein-based biomarkers for final application in diagnostic test systems such as ELISA.

Clearly, all these endeavours in clinical proteomics and related fields would be useless without making well-organised efforts in standardising clinical samples for biomarker development and validation using genomics, proteomics or other modern methodologies [10]. In a Standardisation & Guidelines paper Gil Omenn (contribution in this issue, pp. 748–755) describes current efforts to establish solid grounds in this crucial field. Furthermore, it is well known that many research and diagnostic methods heavily rely on the use of well-validated protein binding molecules such as antibodies [11]. In a review, Mike Taussig and co-workers (contribution in this issue, pp. 756–766) give a thorough overview to guide the readers through the world of protein binders, which are key components of many diagnostic technologies.

Recently, facile, robust and standardized mass spectrometry based methods have been successfully implemented in hundreds of microbiology laboratories. In particular MALDI-TOF

mass spectrometry profiling for the detection of bacteria has become one of the diagnostic methods of choice during the last the years, replacing conventional but more expensive biochemical methods for identification of bacterial (sub-) species [12]. In a review, Markus Kostrzewa and co-workers (contribution in this issue, pp. 767–778) discuss the additional application of MALDI-TOF MS for detecting (antibiotic) resistance, a challenging daily problem in the hospital. Furthermore, Harald Mischak and colleagues (contribution in this issue, pp. 779–793) explain in a review the usefulness of capillary electrophoresis coupled to mass spectrometry for analysing complex biological material by making use of several protein markers and detecting efficiently diseases such as bladder cancer.

In addition to these various papers, three research articles concretely show the potential impact of using proteomics-based approaches for clinical application. Ute Ceglarek, Joachim Thiery and co-workers (contribution in this issue, pp. 794–801) developed a standardised sample pre-treatment protocol for absolute quantification of apolipoproteins in human serum using LC-MS/MS detection. The protocol shall allow the potential user to perform facile analysis of apolipoproteins in the context of cardiovascular diseases. Moreover, Jörg Hoheisel and colleagues (contribution in this issue, pp. 802–812) use high-content antibody microarrays for the analysis of plasma of patients with different B-cell lymphomas to identify classifiers, which can subsequently be useful as starting points for further validation as diagnostic markers. Finally, Thorsten Cramer, Joachim Klose and co-workers (contribution in this issue, pp. 813–824) present a study exemplifying the application of two dimensional gels for protein quantification combined with mass spectrometry based protein identification to functionally analyse emerging resistance due to targeted cancer treatment. Such studies may contribute to improve our understanding on the unwanted dramatic relapse of cancer therapies.

We hope that the various articles will give the reader a flavour on the potential of proteomics methodologies for clinical application–and in the best case inspire the reader to develop new ideas for eventually better diagnosing and treating the patient!

Sascha Sauer

Otto Warburg Laboratory, MPI for Molecular Genetics, Berlin, Germany

References

[1] Weinberg, R., Point: Hypotheses first. *Nature* 2010, *464*, 678.

[2] Meierhofer, D., Weidner, C., Hartmann, L., Mayr, J. A. et al., Protein sets define disease states and predict in vivo effects of drug treatment. *Mol. Cell Proteomics* 2013, *12*, 1965–1979.

[3] Sugihara, G., May, R., Ye, H., Hsieh, C. H. et al., Detecting causality in complex ecosystems. *Science* 2012, *338*, 496–500.

[4] Sauer, S., Protein set analyses: how could this impact the clinic? *Exp. Rev. Proteomics* 2013, *10*, 305–307.

[5] Sauer, S., Lange, B. M., Gobom, J., Nyarsik, L. et al., Miniaturization in functional genomics and proteomics. *Nat. Rev. Genet.* 2005, *6*, 465–476.

[6] Goh, K. I., Cusick, M. E., Valle, D., Childs, B. et al., The human disease network. *Proc. Natl. Acad. Sci. USA* 2007, *104*, 8685–8690.

[7] Stoeckli, M., Chaurand, P., Hallahan, D. E., Caprioli, R. M., Imaging mass spectrometry: a new technology for the analysis of protein expression in mammalian tissues. *Nat. Med.* 2001, *7*, 493–496.

[8] Michalski, A., Damoc, E., Hauschild, J. P., Lange, O. et al., Mass spectrometry-based proteomics using Q Exactive, a high-performance benchtop quadrupole Orbitrap mass spectrometer. *Mol. Cell Proteomics* 2011, *10*, M111 011015.

[9] Domon, B., Aebersold, R., Mass spectrometry and protein analysis. *Science* 2006, *312*, 212–217.

[10] Baumann, S., Ceglarek, U., Fiedler, G. M., Lembcke, J. et al., Standardized approach to proteome profiling of human serum based on magnetic bead separation and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Clin. Chem.* 2005, *51*, 973–980.

[11] Taussig, M. J., Stoevesandt, O., Borrebaeck, C. A., Bradbury, A. R. et al., ProteomeBinders: planning a European resource of affinity reagents for analysis of the human proteome. *Nat. Methods* 2007, *4*, 13–17.

[12] Kliem, M., Sauer, S., The essence on mass spectrometry based microbial diagnostics. *Curr. Opin. Microbiol.* 2012, *15*, 397–402.

