PRIME-XS, a European Infrastructure for Proteomics

Reinout Rajmakers*, Jesper V. Olsen†, Ruedi Aebersold§, and Albert J. R. Heck***

The PRIME-XS consortium is a pan-European infrastructure for proteomics. As a prologue to this special issue of Molecular & Cellular Proteomics on the research activities of the PRIME-XS consortium, we, as the guest editors of this issue, provide an overview of the structure and activities of this consortium, which is funded by the European Union’s 7th Framework Programme for Research and Technological Development. Molecular & Cellular Proteomics 13: 10.1074/mcp.E114.040162, 1901–1904, 2014.

The availability of complete genome sequences initiated a new era in biomedical research. Since the first draft of the human genome was published in 2001, the emphasis has shifted from interpreting genome sequence and variation to understanding the biological functions of gene products: proteins. Amid this shift, the thriving and rapidly evolving field of proteomics has emerged. The technologies required in order to analyze proteins on a global scale require significant investment and expertise, which are not always readily available to those researchers whose work would benefit from them. Over the past 10 years, many proteomics facilities and consortia have been established to provide the necessary technologies for users. These facilities and consortia have facilitated enormously the application of proteomics to modern life-science research.

Although local initiatives often can relieve researchers’ basic proteomics needs, continued provision of state-of-the-art proteomics technology requires a continuous investment of funding and expertise, which is feasible at only a few sites. Furthermore, the demand for access to these technologies is growing. In light of this trend, the 7th Framework Programme was proposed, of which 104 were approved and being executed at six European facilities (see Fig. 1). The proteomics research infrastructure (instrumentation and personnel) at the six sites is largely funded by national sources, not directly by the EU. Therefore, many sites are incorporated in national roadmap programs for large-scale research infrastructure. The EU funding of €7.5 million is used for three different programs: open access to the research facilities, joint research initiatives, and training and networking activities. Among the technologies offered are advanced peptide separation methods, many of the latest generations of mass spectrometry platforms, the newest targeted analysis approaches, and state-of-the-art bioinformatics tools.

Open Access to the Research Facilities—All researchers in Europe can access PRIME-XS facilities. The consortium website has an application system, through which all research proposals are evaluated by independent reviewers and, if approved, linked to selected access sites.

The public call for proposals was distributed in July 2011, and since then applicants have submitted new proposals continuously. As of January 2014, 128 projects had been proposed, of which 104 were approved and being executed at the access sites. The map in Fig. 2 shows that these projects have come from 21 different European countries, illustrating that researchers throughout Europe need access to state-of-the-art proteomics technology. The projects vary: Sometimes guest researchers stay for a single day; others are embedded at a site for weeks or months. Some users are proteomics novices; others are experienced researchers who want training and access to novel or specialized technologies that are unavailable locally. The PRIME-XS funding covers, to some extent, the costs of operating the sites, including salaries, consumables, and support services.

Prior to the founding of PRIME-XS, proteomics in Europe was already well established, with several top-notch research laboratories and several proteomics facilities operating at the local and national levels. However, the European proteomics community was not well organized. In response to the call in the 7th Framework Programme, a major effort was made to organize the community and establish a coordinated program to provide the European life-science research community with access to top-of-the-line facilities. The resulting program, coordinated by Albert Heck at Utrecht University and begun in 2011, was named “Proteomics Research Infrastructure Maximizing Knowledge Exchange and Access” (PRIME-XS). PRIME-XS is a consortium of 12 European research institutes. It includes experts in proteomics and provides access to proteomics technologies at six European facilities (see Fig. 1). The proteomics research infrastructure (instrumentation and personnel) at the six sites is largely funded by national sources, not directly by the EU. Therefore, many sites are incorporated in national roadmap programs for large-scale research infrastructure. The EU funding of €7.5 million is used for three different programs: open access to the research facilities, joint research initiatives, and training and networking activities. Among the technologies offered are advanced peptide separation methods, many of the latest generations of mass spectrometry platforms, the newest targeted analysis approaches, and state-of-the-art bioinformatics tools.

From the *Biomolecular Mass Spectrometry and Proteomics Group, Utrecht Institute for Pharmaceutical Sciences and Bijvoet Center for Biomolecular Research, Utrecht University, Padualaan 8, Utrecht, 3584 CH, The Netherlands; †Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3b, DK-2200 Copenhagen, Denmark; §Department of Biology, Institute of Molecular Systems Biology, ETH Zurich, 8093 Zurich, Switzerland; ¶Faculty of Science, University of Zurich, 8093 Zurich, Switzerland
Received April 4, 2014, and in revised form, April 4, 2014
Published, MCP Papers in Press, June 23, 2014, DOI 10.1074/mcp.E114.040162
Author contributions: R.R., J.V.O., R.A., and A.J.R.H. wrote the paper.
extent, the expenses of the guests as well as consumables and site costs. Although proteomics research often has relatively long-term aims, PRIME-XS projects already have yielded several publications. Some are in this special issue.

Joint Research Initiatives—PRIME-XS researchers have established four joint research activities (JRAs).¹ These focus on developing new technologies and the standardization of operating procedures.

Bioinformatics for High-throughput Proteomics—This JRA aims to establish the bioinformatics support necessary to streamline data generation, management, analysis, and dissemination within the consortium. The software developed is open source and available to all interested parties.

Enabling Technologies for the Analysis of Protein Interaction Networks and Protein Localization—This JRA focuses on the development and implementation of methods to characterize protein interaction networks based upon functional aspects of their behavior and the development of methods to determine the dynamics of complex components. Additionally, this JRA involves the development of methods for mapping these protein interaction networks to subcellular locations and characterization of the dynamics of protein complex trafficking.

¹ The abbreviation used is: JRA, joint research activity.
Enabling Technologies for the Analysis of Post-translational Modifications—This JRA addresses fundamental challenges in global post-translational modification analyses to develop robust and facile technologies that reduce complexity and dynamic range issues. The goals are to apply superior chromatographic separations and/or affinity enrichment and to improve the sensitivity of these technologies through miniaturization.

Enabling Technologies for Biomarker Discovery—The goal of this JRA is to develop targeted, primarily peptide-specific, approaches to monitor hundreds of potential biomarkers in hundreds of samples. The approaches should be amendable to the analysis of body fluids and tissues and should be comprehensive, reproducible, robust, and cost-effective.

As we mentioned above, a portion of the work done in these JRAs has been published, and some of the latest findings are in this special issue. Moreover, the PRIME-XS website offers about 20 standard operating protocols for proteomics researchers. These include, for example, specialized protocols for phosphopeptide enrichment, affinity purification, and selective reaction monitoring.

Training and Network Activities—One of the major aims of PRIME-XS is to build a strong proteomics community in Europe. The consortium organizes an annual meeting, at which all involved researchers meet and discuss their progress and challenges (Fig. 3). In addition, JRA researchers meet several times a year, either at workshops or at international proteomics meetings. PRIME-XS plays a proactive and supportive role in training courses, such as the MaxQuant Summer School, the European Summer School in Proteomics in Brixen, Italy, the Late Summer Practical Proteomics Seminar in Vienna, and a selective reaction monitoring course in Zurich. Finally, the sites also host researchers for hands-on training.

The combined research effort of the PRIME-XS users, the sites, and the JRAs has resulted in more than 100 scientific publications so far. Some illustrative examples that reflect the impact and quality of the work are provided (1–7). Taken together, the European proteomics community and research outcomes clearly are strengthened by the consortium. Therefore, the time is right to start discussing the future of proteomics infrastructures in Europe and the links that could and should be forged among local, national, and European infrastructures.

We find it encouraging that significant recent national investments in several EU member states have recognized proteomics as a vital technology for biomedical research. This holds promise for the sustainability of the proteomics infrastructure in Europe. The recognition, combined with the positive feedback that PRIME-XS receives from users and the potential for new scientific breakthroughs at its sites, makes the PRIME-XS community optimistic about the future of proteomics in Europe.

Moreover, with the success of PRIME-XS, the consortium could be used as a model for initiatives on other continents or across continents and even could be adapted by the U.S. National Institutes of Health or the Human Proteome Organization.

We hope you will find the articles in this special series helpful for your own research.

**To whom correspondence should be addressed:** Prof. Dr. Albert J. R. Heck, http://www.hecklab.nl; Biomolecular Mass Spectrometry and Proteomics Bijvoet Center for Biomolecular Research and Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Padualaan, 83584 CH, Utrecht, The Netherlands. Tel: +31-30-2536797; E-mail: a.j.r.heck@uu.nl.

REFERENCES
1. Altelaar, A. F. M., Munoz, J., and Heck, A. J. R. (2013) Next-generation proteomics: towards an integrative view of proteome dynamics. Nat. Rev. Genet. 14, 35–48
2. Huettenhain, R., Surinova, S., Ossola, R., Sun, Z., Campbell, D., Cerciello, F.,
Schiess, R., Bausch-Fluck, D., Rosenberger, G., Chen, J., Rinner, O., Kusebauch, U., Hajdúch, M., Moritz, R. L., Wollsiefer, B., and Aebersold, R. (2013) N-glycoprotein SRMAtlas: a resource of mass spectrometric assays for N-glycosites enabling consistent and multiplexed protein quantification for clinical applications. Mol. Cell. Proteomics 12, 1005–1016

3. Low, T. Y., van Heesch, S., van den Toorn, H., Giansanti, P., Cristobal, A., Toonen, P., Schafer, S., Huebner, N., van Breukelen, B., Mohammed, S., Cuppen, E., Heck, A. J., and Guryev, V. (2013) Quantitative and qualitative proteome characteristics extracted from in-depth integrated genomics and proteomics analysis. Cell Rep. 5, 1469–1478

4. Tanco, S., Lorenzo, J., Garcia-Pardo, J., Degroeve, S., Martens, L., Aviles, F. X., Gevaert, K., and Van Damme, P. (2013) Proteome-derived peptide libraries to study the substrate specificity profiles of carboxypeptidases. Mol. Cell. Proteomics 12, 2096–2110

5. Vizcaíno, J. A., Cote, R. G., Csordas, A., Dianes, J. A., Fabregat, A., Foster, J. M., Griss, J., Alpi, E., Birim, M., Contell, J., O’Kelly, G., Schoenegger, A., Ovelleiro, D., Pérez-Riverol, Y., Reisinger F., Rios, D., Wang, R., and Hermjakob, H. (2013) The Proteomics Identifications (PRIDE) database and associated tools: status in 2013. Nucleic Acids Res. 41, D1063–D1069

6. Wagner, S. A., Bell, P., Weinert, B. T., Nielsen, M. L., Cox, J., Mann, M., and Choudhary, C. (2011) A proteome-wide, quantitative survey of in vivo ubiquitylation sites reveals widespread regulatory roles. Mol. Cell. Proteomics 10, M111.013284

7. Weinert, B. T., Schoelz, C., Wagner, S. A., iesmantavicius, V., Su, D., Daniel, J. A., and Choudhary, C. (2013) Lysine succinylation is a frequently occurring modification in prokaryotes and eukaryotes and extensively overlaps with acetylation. Cell Rep. 4, 842–851