

REPORT

Cardiovascular Initiative of the Human Proteome Organisation, 5th Workshop October 2007, Seoul, Korea

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The Cardiovascular Initiative (CVI) of the Human Proteome Organisation (HUPO) held its fifth workshop prior to the Sixth Annual HUPO World Congress in Seoul, Korea in October 2007. The objectives of this report are as follows: to trace the (relatively brief) history of the CVI for those who may not be acquainted with it; to highlight lectures given by members of the CVI during this Workshop; and to make the community aware of the aims of this Initiative, including collaborative projects currently under consideration.

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1 Introduction and Brief History

The basic motivation behind all HUPO Initiatives has been that the Organisation could facilitate tackling biological questions too grand (in terms of sheer manpower and breadth of expertise) for individual laboratories. The Cardiovascular Initiative (CVI) was formed on the basis of this same philosophy. Cardiovascular disease – encompassing coronary heart disease, cardiac hypertrophy/failure, rheumatic heart disease, pulmonary heart disease, arrhythmias and sudden cardiac death, atherosclerosis, stroke, peripheral vascular disease and a host of genetic syndromes – is projected to cost

the United States >430 billion dollars in 2007 [1]. In 2004 (the most recent year for which comprehensive data is available), cardiovascular disease afflicted 79.4 million people in the United States and was responsible for ~870,000 deaths, as compared with ~550,000 deaths due to cancer during the same time period; similar trends are projected for 2007 [1, 2]. Worldwide, 30% of all deaths are due to cardiovascular disease (World Health Organisation (WHO) 2007. www.who.int). Perhaps more startling, the aging of the world population over the next two decades is predicted to be accompanied by a massive increase in deaths due to cardiovascular disease from 16.7 million in 2002 and 17.5 million in 2005 to a projected 23.3 million in 2030 (World Health Organisation (WHO) 2007. www.who.int and [3]). Unmitigated by significant advances in our ability to detect, treat and cure these diseases, such increases in cardiovascular disease will certainly be accompanied by a major health and financial burden.

The potential of proteomics to reveal novel biomarkers/biosignatures of disease, as well as basic insights into biological mechanisms, is well understood by readers of the

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Abbreviations: CVI, the Cardiovascular Initiative; GO, gene ontology

Journal. Because of the gravity of the worldwide epidemic of cardiovascular diseases, a collaborative Initiative to apply proteomics to these pathophysiological states has the potential to make a substantial impact on human health. To date there have been five official CVI workshops: Boston, United States (March 2006); Hinxton, United Kingdom (July 2006); Long Beach, United States (at the 5th HUPO World Congress, October 2006); Pilar, Buenos Aires, Argentina (at the 1st Iberoamerican Proteomics/Latin American HUPO Congress, June 2007); and the most recent HUPO World Congress in Seoul, Korea (October 2007). The co-chairs [4] of the CVI are Michael Dunn (UCD Conway Institute, University College, Dublin, Ireland), Peter Liu (Toronto General Hospital, Toronto, Canada) and Peipei Ping (UCLA, Los Angeles, USA); members of the CVI Executive Committee include Mario Hugo Genero (Universidad Austral, Buenos Aires, Argentina), Robert Gerszten (Massachusetts General Hospital, Harvard University, Boston, USA), Jennifer Van Eyk (Johns Hopkins University, Baltimore, USA), Pengyuan Yang (Fudan University, Shanghai, China) and Frank Vitzthum (Dade Behring, Marburg, Germany).

2 Seoul Workshop

2.1 CVI *Raison d'être*, Current Proposals and Moving Forward

The 5th CVI Workshop, held prior to the 2007 HUPO World Congress, drew ~75 attendees and included a panel discussion and four lectures: Robert Cotter (John's Hopkins University, USA), Thomas Vondriska and Sarah Warburton (UCLA, USA), Melanie White and Jennifer Van Eyk (John's Hopkins University, USA) and Michael Dunn (University College Dublin, Ireland). Dr. Cotter discussed novel MS-based methods for analysis of proteins and post-translational modifications in cardiovascular diseases. Dr. Vondriska spoke on the use of mouse models of human heart disease (such as acute myocardial infarction and cardiac hypertrophy) to investigate basic mechanisms of injury and protection in the myocardium. Dr. White reported on the development of new biomarkers for cardiac disease and highlighted the need for studies to be performed in both biological fluids (*e.g.* plasma) as well as in the tissue. Following the talks, a panel discussion, led by Dr. Dunn, allowed attendees to discuss and vote on CVI objectives. One project, proposed by Dr. Dunn, involved CVI participation in the annotation of genes associated with cardiovascular diseases as a means to facilitate proteomic research and to generate a resource for the proteomics (and *non*-proteomics) cardiovascular research community.

2.2 Cardiovascular Gene Ontology (GO) Annotation Initiative

General agreement was reached at the Workshop that the HUPO CVI would participate in the Cardiovascular GO

Annotation Initiative based at University College London (UCL). This group has identified >2500 cardiovascular-associated genes which it seeks to annotate with the help of the cardiovascular community. Using a controlled vocabulary and the three standard categories of GO annotation (molecular function, biological process and cellular compartment), these genes will be annotated in the specific context of cardiovascular disease. Without precise, hierarchically-related terminology to classify proteomic data in the setting of a given disease state, the large amount of data produced through disparate proteomic technologies cannot be effectively compiled, analyzed and shared. As anyone who has performed a careful proteomic investigation of intracellular proteins is aware, the actual protein product(s) of a gene are rarely restricted to the function, process and compartment predicted bioinformatically from the gene sequence. As such, GO terms assigned in the absence of rigorous, experimentally based annotation are of questionable utility. This initial project of the CVI will be to collaborate with the group at UCL to provide such experimental annotation in a resource useful to the community. This project is already underway and maintained in a wiki-based web format (<http://wiki.geneontology.org/index.php/cardiovascular>). We would encourage all individuals interested in supporting this initiative to visit the website and contribute to the annotation of these cardiovascular-associated genes.

Independent from this collaboration with the existing Cardiovascular GO activities, a need exists for protein databases specific to cardiovascular disease. The exact format of such a database is still under discussion, but should include links to relevant protein/gene databases (including SWISS-PROT/TrEMBL, NCBI, and others); again, a wiki-based approach would be ideal, in which investigators with expertise in given proteins and networks *in the setting of cardiovascular function and disease* could spearhead annotation of these molecules, including links to relevant original publications, schematic figures and (when it exists) clinical data.

2.3 Collaborative Projects and Sample Repositories

Cardiovascular disease impacts multiple organ systems and cell/tissue types; thus, there is no one clear substrate, so to speak, for proteomic dissection (as is the case with the plasma or liver proteome projects, for example). A strength of the initiative is expertise in cardiac, vascular and neural physiology in addition to proteomics technologies. Future projects will require expert communication between those developing and implementing state-of-the-art technology and the clinical colleagues collecting human samples. While there is a dearth of healthy heart, vascular or brain tissue for analyses, these tissues are readily available from patients with disease following transplantation or post-mortem. In the case of plasma, these concerns are mute, therefore making this bodily fluid one of the prime targets for biomarker discovery. This fact also highlights the natural interaction of the CVI with the Plasma Proteome Project, which is revealing (and overcoming) critical technical and conceptual hurdles associated with the large-

scale analysis of human plasma. There has been general agreement at the meetings of the CVI thus far (as articulated by Dr. White in her talk) that biomarker identification is best facilitated by analyses of both the target tissues and the bodily fluids where the markers ultimately reside for detection.

Interest has been expressed in the establishment of repositories – perhaps on different continents and at multiple individual institutions – of cardiovascular tissues to be analyzed in a collaborative manner. Such resources would doubtlessly facilitate global proteomics studies, although they also present formidable challenges. Standard operating procedures for sample collection and storage are of paramount importance in all proteomic studies and must be the subject of increased scrutiny in collaboration with clinical colleagues. Transport of samples is non-trivial in terms of preservation as well as differing international regulations. Lastly, the patient consent procedures must be approved by individual hospitals/institutions (as well as by the ultimate location of the work, if the samples are shipped to another location) and must take into account various ethical and legal issues regarding use.

2.4 Community Participation

Since the Seoul meeting we have re-vamped the CVI website which will now serve as a regular means for communication within the Initiative (www.hupocvi.org). Because the CVI is an international effort, it is not always possible for all members to attend each meeting. Our hope is that this website will facilitate communication to overcome this challenge. A key new feature of the website is a discussion area for meeting reports and other announcements. We encourage anyone interested in upcoming symposia, collaborative projects and/or joining the HUPO CVI to visit the website and contact us. Also posted on the website are the primary objectives for the

CVI proposed at the Seoul Workshop, which include expanding membership and visibility in the cardiovascular and proteomics communities, advancing interactions with other HUPO initiatives, evaluating the feasibility and scope of a pilot phase of collaborative projects to apply proteomics to diseased human tissue and to attract industrial partners.

The CVI encourages community participation and feedback on the direction of this new HUPO Initiative in the critical human health area of cardiovascular disease. There are three CVI Workshops currently scheduled for 2008: the first in March at the United States HUPO Conference in Bethesda, USA; the second in August during the 7th Annual HUPO World Congress in Amsterdam, The Netherlands; and the third in September at the Siena Meeting in Siena, Italy (please see the CVI website for additional details).

The authors have declared no conflict of interest.

3 References

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