UCLA NIH/NHLBI Proteomics Center

Introduction

This UCLA NHLBI Proteomics Center consists of an international effort led by UCLA School of Medicine. The central scientific goal aims to provide fundamental information on the proteome biology of cardiovascular diseases, an essential component for the "Human Proteome Project". This Center is supported by an NIH/NHLBI award designating UCLA School of Medicine as the primary contractor, along with the following participating institutions from the US, Europe, and Asia (see list of key investigators below) including The Scripps Research Institute (TSRI), The Arizona State University (ASU), the European Bioinformatics Institute at United Kingdom (EBI/EMBL), the Royal Technology Institute at Sweden (KTH), the Karolinska Institute at Sweden, the Uppsala University at Sweden, and Zhejiang University at China.

The establishment of this International Proteomics Consortium was inspired by the UCLA campus-wide Proteomics Initiative; this collaborative effort has been encouraged by the UCLA leadership to advance our scientific and education missions via international collaborations. Our Proteomics Center has been privileged to build upon the strong foundations of cardiovascular biology and medicine cultivated at UCLA in the past three decades. Our Center thrives to support creative investigations in proteomics science and to provide a training environment for young investigators from UCLA and from the scientific community at large.

Research Synopsis

Background. Advancing cardiovascular medicine requires an understanding of cardiac function at the systems level but with molecular details. This Center application meets this challenge by identifying and overcoming limitations in our conceptual and technical abilities to study heart disease. In terms of concept, we lack the knowledge to understand how organelles in the cardiac cell such as proteasomes and mitochondria behave as integrated systems. Therefore, we have an imperfect understanding of how these organelles malfunction, causing disease. Inextricably linked to this conceptual limitation is a technical one: we lack the tools to measure individual subpopulations of organelles and to quantitatively assess large groups of proteins that are responsible for cardiac phenotypes. Together, these limitations prevent effective translation of proteome knowledge into the clinical setting.

As the leading cause of death in the developed world, there can be no doubt that cardiovascular disease is a colossal bane on human health. Transformative insights into the systems-level properties of this multifactorial disease are necessary if new treatments are to be developed. The goal of our Center is to address these challenges and fundamentally advance cardiovascular proteomics in the near term.

The intended impact of the proposed Center is to create technologies that reveal levels of understanding beyond the reach of current approaches. We will disseminate this knowledge as well as the tools used to gain it, thereby advancing the field as a whole by empowering investigators with novel approaches.

With these benchmarks in mind, we have designed a research plan of four sections; and each with specific objectives. The investigator team consists of leaders in the areas of cardiovascular biology and clinical medicine, proteomics (mass spectrometry, protein arrays, antibody-based proteomics, and protein separation), network biology and bioinformatics. This multidisciplinary approach is essential for such a project to produce meaningful results. The demonstrated commitment of the investigator team is strong evidence supporting the successful progress of research in this Center.

Central Objectives. Dysfunction of mitochondria and proteasomes is causative in the pathogenesis of cardiovascular disease. However, treatments specifically targeting these organelles are very underdeveloped in the clinical setting. A major reason for this lack of translation is the paucity of systems-level mechanistic understanding of mitochondrial and proteasomal biology. Individual molecules have been characterized in detail, but their various roles in the milieu of the organelle, and integrated function as a biological network, are unknown. We reason that novel technological approaches must be invented to reveal the properties of organelle function *in vivo*; only then will the powerful therapeutic targets reveal themselves. To tackle this long term objective, we have designed this Center

to develop tools for proteome biology that are specifically tailored to answer critical questions in cardiovascular medicine. We will develop these tools in animal models of cardiovascular disease and immediately validate them in human tissues.

The central Objectives of the proposed studies include **(i)** To develop novel proteomic approaches enabling large-scale and quantitative characterization of cardiac organelle proteomes in health and disease, including innovations in instrumentation and software development (e.g., computation pipelines and multidimensional CE-MS/MS); **(ii)** To develop technology platforms enabling spatial resolution and visualization of molecular pathways in animal and human cardiac tissues (e.g., production of quality antibodies, protein arrays, and high resolution imaging); **(iii)** To develop Wiki-like resources for the dissemination of new proteomic tools and for public access to functionally annotated proteomic datasets; to provide proteomic resources to support the cardiovascular scientific community (e.g., organelle-specific peptide spectra libraries for mouse & human myocardium, software tools to decode PTMs with high accuracy); **(iv)** To develop experimental models to characterize heterogeneity of mitochondria and proteasomes in the normal heart and to reveal changes that drive disease; to establish toolboxes to study mitochondrial and proteasomal proteome biology in the context of their phenotypes using systems perturbations (chemical perturbations, disease model perturbations, and genetic perturbations); and **(v)** To develop novel experimental approaches to examine the interactions between gene networks and protein networks; to advance our understanding of the genome-proteome interface, identifying network-level mechanisms that control cardiac function.

The NHLBI Proteomics Center at UCLA
List of Key Personnel

Updated on August 15th, 2010.

#Participating Key Investigators at UCLA, School of Medicine

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Program Director of NIH/NHLBI Proteomics Center at UCLA
Program Director of PPG on Myocardial Ischemic Injury
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#Participating Key Investigators From US (The Scripps Research Institute, The BioDesign Institute at Arizona State University), Europe (EBI/EMBL, KTH, Karolinska Institute, Uppsala University), and China (Zhejiang University).

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