Final Progress Report DE-FG02-05ER6406

The modern practice of medicine depends on recognizing patterns that identify the patient's disease using historical data, physical examination, and clinical laboratory tests. The use of more sophisticated laboratory markers of disease has allowed the implementation of therapies that are targeted to the individual and hold the promise to introduce an era of truly individualized medicine. The overall goal of this proposal was to establish a Pediatric Clinical Proteomics Center to accelerate the progress of proteomic discovery of human disease biomarkers.

The application proposed the establishment of a Clinical Proteomics Center composed of three Laboratory Cores to focus initially on four clinical proteomics projects. The four proposed Cores were:

1. Shotgun Proteomics Core
2. Quantitative Proteomics Core
3. Small Molecule Identification and Quantitation Core
4. Gene expression Core

The pilot projects that were proposed were analysis to identify lead biomarkers in the following diseases

Project 1: Diabetic kidney disease
Project 2: Metabolic syndrome/Prediabetes
Project 3: Environmental exacerbations of asthma

Manuscripts Published from DE-FG02-05ER6406

The diabetes and pre-diabetes projects were addressed throughout the funding period (2005-2012, including two no-cost extensions. In addition to investigation of diabetes, the laboratory soon turned to very productive collaborations in the field of Alzheimers Disease. The proteomics laboratory (1-12) published twelve clinical papers during this period that applied proteomic analysis to the study of diabetes, pre-diabetes anemia, and Alzheimers Disease. As the capabilities of the laboratory increased and became more well known, we were able to provide proteomic analysis to investigators working in basic science fields including ophthalmology, nephrology, physiology and neuroscience in animal and cell culture models that examined problems in macular degeneration, diabetic nephropathy, nitric oxide synthesis, and neurodegeneration (13-29). The environmental exposures role in asthma project was discontinued due to insufficient patient enrollment.

Grants and Contracts Resulting from DE-FG02-05ER6406

The preliminary data developed in the published manuscripts led directly to the following funded grant proposals:

PI: Tongalp Tezel, M.D. Primary Mentor: Jon B. Klein, M.D., Ph.D 4/1/2005-
K08 EY016120 - NIH – Mentored Clinical Scientist Development Award 3/31/2008
"Proteomic Analysis of Age-Related Macular Degeneration"

NIH (PA-03-107) R21-HD050564-01 PI:
Mary Jayne Kennedy, Ph.D. Co-PI: Jon B. Klein, M.D., Ph.D.
"Urinary Proteomics in Aminoglycoside Treated Newborns"
This project seeks to utilize proteomic methods such as two-dimensional gel electrophoresis and mass spectrometry to identify and develop biomarkers of

aminoglycoside nephrotoxicity in newborns.

PI: Jon B. Klein, M.D., Ph.D. 4/1/2004-
R01 DK067638 02 - Joslin Diabetes Center (NIH-Sub Contract) 3/31/2009
"The Urinary Proteome and Renal Function Loss in Diabetes"
Proteomic analysis of urine from clinical diabetic samples will be analyzed in order to identify proteins associated with diabetic nephropathy.

1K01DK080951-01A1 (Michelle T. Barati, Ph.D.) 12/01/2008-
NIH-NIDDK - Mentored Research Scientist Development Award 11/30/2013
Jon B. Klein, MD., PHD – **Primary Mentor** **0.00 Calendar** TDC:
Title: "Endoplasmic Reticulum-Induced Stress and Apoptosis in the Renal Tubule" $126,383
The goal of this project is to delineate the signaling pathways regulating ER stress response and associated apoptosis in renal tubule cells during diabetes and the role of this stress response in renal function changes during diabetes, using transgenic mouse models.

NIH-R01 **R01-01DK091584-** Development & Validation of Disease Biomarkers
"Novel Biomarker Validation and dosing algorithms for anemia management in ESRD" 04/01/2011 -
PIs: Drs. Michael L. Merchant & Michael Brier, PhD 03/31/2016
Co-Investigator: Jon B. Klein, MD., PhD**.** **2.4 Cal Mos (15%)** TDC:
$2,381,244

The proteomics laboratory funded by DE-FG02-05ER6406 continues to function and has developed resources to replace the equipment originally purchased. Ongoing projects include biomarker work in diabetic nephropathy, pediatric lupus nephritis, and environmental cardiac damage.

Literature Citations

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