

May 11, 2008

Dear SSAT Board of Trustees:

It is a pleasure to provide an interim progress report for our grant “Adipokines and obesity in the development of acute pancreatitis” supported by the SSAT Career Development Award.

Obesity is a worldwide epidemic, and obesity has clearly been shown to be an independent risk factor for increased severity of acute pancreatitis. The mechanisms underlying this association, however, remain completely unknown. Evaluating the pathophysiology of acute pancreatitis from novel angles such as obesity offers the potential to identify unique, targeted therapy which is desperately needed.

The first 10 months of grant support have been fruitful. We have established a model of acute pancreatitis in congenitally obese mice that mimics the human situation (obese mice sustain more severe acute pancreatitis than lean wild-type animals). The manuscript resulting from these experiments has been provisionally accepted for publication in the American Journal of Physiology (Zyromski NJ, et al: A MURINE MODEL OF OBESITY IMPLICATES THE ADIPOKINE MILIEU IN THE PATHOGENESIS OF SEVERE ACUTE PANCREATITIS). In these initial experiments, we observed that circulating concentrations of the adipokine adiponectin, a strong anti-inflammatory agent, inversely mirrored the severity of acute pancreatitis. Further experiments were therefore designed to evaluate the impact of adiponectin on the severity of pancreatitis.

Data from these experiments showed for the first time a differential expression of adiponectin receptors in the obese murine pancreas (Wade TE et al: ADIPONECTIN RECEPTOR-1 EXPRESSION IS DECREASED IN THE PANCREAS OF OBESE MICE) – manuscript accepted for publication in the Journal of Surgical Research. We have also shown that administration of adiponectin modulates the chemokine and cytokine milieu during acute pancreatitis (Zyromski NJ, et al: ADIPONECTIN ADMINISTRATION MODULATES THE CHEMOKINE AND CYTOKINE MILIEU IN ACUTE PANCREATITIS), and that administration of the cannabinoid receptor CB-1 antagonist increases circulating adiponectin concentration and decreases the severity of acute pancreatitis in obese mice (Zyromski NJ, et al: CANNABINOID RECEPTOR CB-1 BLOCKADE ATTENUATES ACUTE PANCREATITIS BY AN ADIPONECTIN MEDIATED MECHANISM).

Data included in the latter manuscript will be presented as a poster at this year’s SSAT meeting, as well as at the Pancreas Club, and the latter two manuscripts are prepared for submission to the Journal of Gastrointestinal Surgery at this year’s SSAT meeting. We have also presented data from experiments supported by the SSAT award at meetings of the American Pancreatic Association, the Association for Academic Surgery, and the Society of University Surgeons.

Participation in the SSAT/DDW meeting of 2007 resulted in meeting/collaboration with Giamila Fantuzzi, PhD of the University of Illinois Chicago. Dr. Fantuzzi is a worldwide authority on obesity and inflammation. We have now collaborated in preliminary experiments utilizing a rare breed of adiponectin knockout mice developed by Dr. Fantuzzi, and she has generously provided an adiponectin generating adenovirus vector for use in current experiments.

In addition, the award supported the investigator's travel to the laboratory of Dr. Michael Steer in Boston, MA. Dr. Steer has a longstanding interest in the pathogenesis of pancreatitis, and was gracious to share with us a technique to induce pancreatitis in a murine model (retrograde injection of the mouse pancreatic duct) that more closely approximates the human situation of acute pancreatitis. Preliminary experiments are encouraging.

Current experiments are directed toward upregulating the production of adiponectin as well as understanding the impact of fat character (i.e. "good" - fish oil vs "ugly" - butter fat) on the inflammatory response in acute pancreatitis. This will allow us to complete the second set of specific aims proposed in the SSAT grant.

Data generated from experiments supported by the SSAT award comprise the bulk of an application to the NIH for funding by the R01 mechanism (submitted 2/5/2008).

It has been my tremendous fortune to be mentored by Drs. Henry A. Pitt, Keith D. Lillemoie, and Michael G. Sarr,. These individuals' contributions to our society need no extra recognition. Their societal leadership notwithstanding, it would be remiss of me to not acknowledge their stimulus, facility, and continued motivation to continue this work.

In summary, the 2007 SSAT Career Development Award has supported experiments critical to the development of a basic science program, facilitated dialogue and collaboration with scientists from other institutions, and provided support for proposal of extramural funding. It is a privilege to hold this award.

Respectfully,

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