Title: Effect of Glutamine on HSP-70 Expression in ICU patients

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Heat shock protein 70 (HSP-70) is a highly conserved protein known to be vital in cellular and tissue protection against stress and injury. Enhancement of the HSP response following experimental critical illness has been shown to protect against tissue injury, metabolic dysfunction, and improve survival. Presently, laboratory methods utilizing chemical or gene therapy based mechanisms of enhancing HSP expression are impractical for clinical application. Thus, this very powerful tool that could possibly significantly improve outcome in our critically ill and injured patients has yet to be clinically applied.

Our laboratory has shown that glutamine (GLN) can enhance tissue HSP expression following experimental models of critical illness. Data from our laboratory and others reveals that GLN can also improve survival in experimental critical illness and can lead to improved outcome in clinical trials of critically ill patients. We have found that a single dose of intravenous glutamine can mediate this beneficial enhancement of HSP-70 and improved outcome. Further, we recently showed in a pilot study of critically ill patients that GLN could enhance serum HSP-70 levels after one-week of therapy. Serum HSP-70 was used as a surrogate for tissue HSP-70 levels, however, the effect of GLN on actual tissue HSP-70 expression and its potential to improve outcomes in critically ill patients has not been explored. GLN has been safely administered to many groups of critically ill patients and been shown to reduce morbidity and mortality in these patients without a clear understanding of the protective mechanism.

The overarching hypothesis of this proposal is that pharmacologically administered GLN can enhance HSP-70 expression in healthy volunteers and critically ill patients. This enhanced HSP-70 expression may lead to improved outcome in critically ill/stressed patients. To address this grant's hypothesis, we propose three interrelated specific aims.

Specific Aim #1 Determine the effect of pharmacologic GLN administration to healthy volunteers on HSP-70 expression following stress. We hypothesize that administration of GLN to healthy volunteers will enhance HSP-70 and HSF-1 phosphorylation following mild heat stress. This is to determine if HSP-70 can be pre-induced to improve outcomes prior to surgery or other major stress. To address this specific aim, serum and whole blood for isolation of human blood mononuclear cells will be collected. These samples will be analyzed for HSP-70 expression and cellular HSF-1 phosphorylation state.

Specific Aim #2 Determine the effect of pharmacologic GLN administration on HSP 70 expression in critically ill patients. We hypothesize that GLN administration will enhance HSP-70 content and HSF-1 phosphorylation following onset of critical illness. To address this specific aim, a randomized, controlled, double-blind trial of GLN in critically ill patients we will collect serum and human mononuclear cells in drawn blood from surgical ICU patients.

Specific Aim #3 Determine if GLN mediated-enhancement of HSP-70 expression is correlated with improved outcome in critically ill patients. We hypothesize that administration of GLN in pharmacologic doses to critically ill patients in the surgical intensive care unit will (i) shorten ICU length of stay, (ii) decrease infectious morbidity, and (iii) improve survival.
References: