January 1st, 2017

2016-2017 Kenneth W. Warren Fellowship Progress Report #1

Re: Therapeutic Use of Human Adipose-derived Stromal Cells in a Murine Model of Severe Acute Pancreatitis

Dear IHPBA Research Committee,

I would like to express my gratitude to the IHPBA Research Committee for awarding me the 2016-2017 Kenneth Warren Fellowship. This grant supports my study entitled "Therapeutic Use of Human Adipose-derived Stromal Cells in a Murine Model of Severe Acute Pancreatitis" under the mentorship of Drs. Nicholas J. Zyromski and Keith L. March at Indiana University.

Acute pancreatitis represents both human and financial burdens. Its incidence has increased over the past decade with over 300,000 hospitalizations in the United States annually, representing the second highest cost in hospital stays with 2.6 billion dollars. Despite promising results of experimental and small clinical studies, no therapy has been shown to modulate the course of acute pancreatitis, and current treatment is limited to supportive care. While most patients have a mild, self-limited course, up to 20% develop severe acute pancreatitis with associated systemic inflammatory response and multi-organ failure, most prominently acute respiratory distress syndrome and acute kidney injury, and a steady mortality around 20%. As the inflammatory cascade is already established at presentation, the need for therapeutic that can mitigate inflammation early and limit organ injury is crucial.

The functional plasticity of adult mesenchymal stem cells allows them to reprogram in a new environment, and enhance differentiation/proliferation of endogenous progenitor cells for the new organ site. Owing to this regenerative potential, mesenchymal stem cells have previously been used to treat myocardial infarction. Another property of mesenchymal stem cells is their immunomodulation activity, which has proved to inhibit inflammatory injury in conditions such as Crohn disease, rheumatoid arthritis and graft-versus-host disease. Adipose-derived stem cells are clinically advantageous, as they are readily available by minimally-invasive liposuction (which permits autologous treatment), and do not require ex vivo expansion due to their high abundance (100,000 adipose-derived stem cells/g adipose tissue). These characteristics are important as it permits rapid translation to clinical medicine. No therapeutic study using adipose-derived stem cells in the setting of severe acute pancreatitis has been reported.

Two models of acute pancreatitis have been developed and validated by our team: moderate acute pancreatitis (using 6 hourly intraperitoneal injections of cerulein) and severe acute pancreatitis (using intra pancreatic duct retrograde injection of sodium taurocholate) (**Figure 1.**)

Some preliminary studies have shown that stem cells work via a paracrine effect. Paracrine signaling is defined as a form of communication between two different cells using chemical mediators released in the secretome. It has been suggested that the protective effect of administered adipose-derived stem cells in mice with acute respiratory distress syndrome was mediated primarily by paracrine action of adipose-derived stem cells. Several groups have demonstrated that adipose-derived stem cells-conditioned media increased endothelial cell survival and their proliferation in vitro, and concluded that the vasculo-protective effect of adipose-derived stem cells was due to their ability to interact with endothelial cells by

complex paracrine actions, which are able to protect and regenerate damaged vasculature in acute kidney injury significantly.

Based on those findings, the aim of our study was to assess the efficacy of intravenous adipose-derived stem cells or adipose-derived stem cells secretome in ameliorating the course of acute pancreatitis, and secondarily to evaluate the ability of adipose-derived stem cells or adipose-derived stem cells secretome to rescue lung and kidney structure and function in acute respiratory distress syndrome and acute kidney injury, respectively.

Thank you for your support, and I look forward to presenting the completed study at the 2018 IHPBA meeting in Geneva, Switzerland.

Happy New Year!

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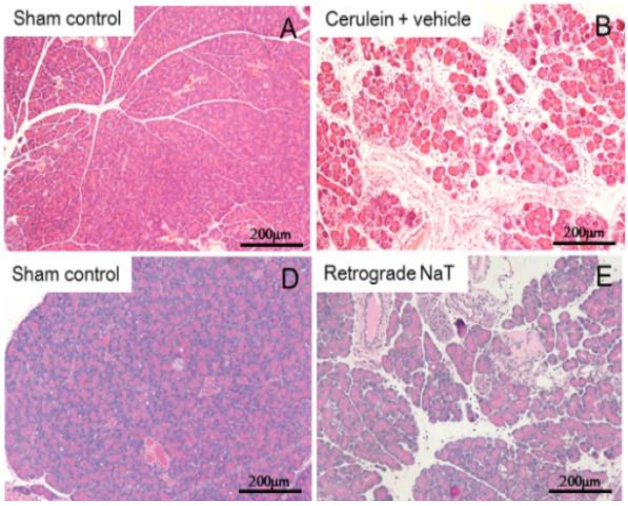

Figure 1. Acute pancreatitis murine models (moderate B, severe E)

References

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