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Neutralization *In Vivo* of Particulate iNOS with Humanized Anti-iNOS MAbs Rescues Mice from Death by Sepsis

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Background: Studies on an *in vitro* diagnostic for sepsis were conducted on plasma samples obtained over a period of days from ICU patients with sepsis or at risk for developing sepsis. We discovered particulate inducible nitric oxide synthase (iNOS) in the plasma of patients with sepsis and those who became septic within the next 48 hours – iNOS was not found in controls or in ICU patients who were not or did not become septic, such as trauma patients. After analyzing more than 1200 plasma samples, we hypothesized that particulate iNOS was partially responsible for the pathology of sepsis and that its neutralization might improve the outcome of septic patients.

Methods: To test our hypotheses, a mouse model of sepsis was developed that utilizes particulate iNOS isolated from induced DLD-1 cells and LPS to initiate septic-like pathologic symptoms and that tests the ability of our anti-iNOS monoclonal antibodies (MAbs) to rescue challenged mice from death. Three chimeric human/mouse anti-iNOS MAbs, DSX-A, DSX-D and DSX-I, were genetically engineered by incorporating a mouse anti-iNOS binding domain into a human IgG1 backbone. Each was investigated as a potential therapy *in vivo*.

Results: The three chimeric anti-iNOS MAbs were tested for their ability to protect challenged mice by neutralizing *in vivo* the lethal affects of particulate iNOS. When administered IV prior to a lethal dose of particulate iNOS, all were found to rescue some mice from death. However, DSX-I was superior when compared to the other two chimeric human/mouse anti-iNOS MAbs. The *in vivo* neutralization of particulate iNOS by the DSX-I MAb could rescue up to 60% of the challenged mice from death by sepsis, and its affect was dose dependent.

Conclusions: We concluded from these experiments that particulate iNOS does contribute to the pathology of sepsis and that its neutralization *in vivo* with a chimeric anti-iNOS MAb is protective and can rescue challenged mice from death. Treatment of human septic patients with anti-iNOS MAb may prove to be an effective therapy.