CytoSorbents™

Burn and Smoke Inhalation Injury

BURN INJURIES ARE ONE OF THE MOST COMMON FORMS OF TRAMUA INJURY. Approximately 2.4 million burn injuries are reported in the United States per year.[1] Burn injuries are often associated with smoke inhalation injuries and can occur from multiple sources: fire or flame, scalds, hot objects, electricity, chemicals, radiation, cold or friction. Burn patient treatment options are dependent many factors such as burn depth, location, and percent of total body surface area (TBSA). Aggressive modern management of burn injuries has led to significant improvements in survival. However, better therapies are needed to reduce the mortality in patients with severe burn injuries (>20-30% TBSA), reduce the risk of organ failure (particularly acute respiratory distress syndrome and acute kidney injury), improve healing and rehabilitation, and reduce complications (e.g. infection and sepsis) and hospital length of stay for all patients.

CYTOKINE STORM DRIVEN MULTI-ORGAN FAILURE AND SEPSIS ARE MAJOR CAUSES OF DEATH. Aggressive modern management of burn injury has led to significant improvements in survival to ~95% on average in leading burns centers such as the US Army Institute of Surgical Research (USAISR) Burn Center in San Antonio, TX.[2] However, better therapies are needed to reduce the mortality in patients with severe burn injury (>20-30% total body surface area [TBSA]), decrease the risk of organ failure (particularly acute respiratory distress syndrome and acute kidney injury), improve healing and rehabilitation, and reduce complications (e.g. infection and sepsis), and hospital length of stay for all patients.

One of the major driving factors leading to organ injury and adverse outcomes in burn injury is the poorly-controlled systemic inflammatory response syndrome (SIRS). In severe burn injury, there is a massive unregulated production of cytokines – small proteins that help to stimulate and regulate the immune response. This "cytokine storm" can cause or exacerbate numerous problems, including:

- Shock and hypotension, resulting in inadequate oxygen and blood flow to critical organs
- Acute respiratory distress syndrome and smoke inhalation injury, resulting in hypoxia
- Acute kidney injury (AKI), which occurs in ~25-35% of severe burn casualties, and is a major risk factor for death [3]
- Capillary leakage resulting in tissue edema, intravascular depletion, and fluid balance challenges
- Hyper-metabolism leading to massive protein and fat degradation and catabolism – yielding an increased risk of infection, impaired healing, severe weakness, and delayed rehabilitation
- Immune dysfunction, causing a higher risk of secondary infections (wound infections, pneumonia), and sepsis
- Direct apoptosis of cells and activated neutrophil-mediated organ injury, leading to organ dysfunction and failure

Up to a third of severe burn patients develop multiple organ failure and sepsis that can often lead to complicated, extended hospital stays, and even death. Broad reduction of cytokine storm, not previously feasible, represents a novel approach to prevent or treat organ failure. This may manifest itself by faster weaning from mechanical ventilation, reduced risk of AKI, prevention of shock, and reversal of the hyper-metabolic state. The goal is to improve survival, help patients recover faster, and reduce hospital costs.

CytoSorb® – A NEXT GENERATION "ACTIVE" THERAPY FOR BURN AND SMOKE INHALATION INJURIES.

CytoSorb® is the only specifically approved extracorporeal cytokine adsorber in the European Union. It is designed to help reduce deadly cytokine storm, maladaptive systemic inflammatory response syndrome (SIRS), and rhabdomyolysis in wounded soldiers with thermal or chemical burns, smoke or chemical inhalation injuries, and sepsis. The heart of the technology is a biocompatible, porous polymer bead, roughly the size of a grain of salt, designed to capture cytokines, inflammatory mediators, and myoglobin in its pores based on size and surface adsorption, while letting larger or smaller substances pass around or through. Treatment is very similar to hemodialysis. As blood is repeatedly pumped out of the body and through the CytoSorb® cartridge using standard hospital dialysis machines or small portable hemoperfusion pumps, cytokines and other toxins are captured by the beads and removed from blood. The "purified" blood is then returned to the patient. No dialysate or other fluids are needed. CytoSorb® can be used either alone or in series with continuous renal replacement therapy (CRRT), which itself has demonstrated encouraging improvements in mortality and hemodynamic stability in the treatment of patients with greater than 40% total body surface area burns with acute kidney injury when compared to closely matched historical controls.[4] Presumably, the two technologies could be synergistic, as CRRT does not remove cytokines well.

CytoSorb® ADVANTAGES

- **Broad spectrum device** – Specifically designed to remove a broad range of cytokines, toxins and myoglobin, making this the most logical strategy to treat cytokine storm and the maladaptive SIRS response in decompensated burn victims
- **Efficient cytokine removal** – Capable of removing a broad range of key cytokines in critically-ill patients with sepsis & multi-organ failure
- **Efficient myoglobin removal** – Capable of removing greater that 90% of myoglobin *in vitro*
- **Excellent safety profile** – No serious device related adverse events in more than 14,000 human treatments with good tolerability
- **Positive human clinical data –** European Sepsis Trial showed the safe reduction of cytokines and demonstrated preliminary but encouraging improvements in mortality and organ dysfunction in high risk sepsis patients
- **Easy to use** – Minimal learning curve, uncomplicated set up, and high ease of use
- **Works with existing hospital dialysis equipment or portable, small hemoperfusion pumps** – No new equipment needed
- **No extra fluids or dialysate needed** – Makes treatment logistically simple
- **Compatible with both heparin and regional citrate anti-coagulation** – Systemic anticoagulation is not needed if contraindicated
- **ISO 10993 Biocompatible** – Biocompatible, hemocompatible, no genotoxicity/cytotoxicity, no acute sensitivity or complement activation
- **Massive capacity** – A single cartridge has more than seven football fields of surface area to bind cytokines
- **Long Shelf Life** - No biologic components such as antibodies or cells means excellent storage and logistics – three years at room temp
- **High Quality US Manufacturing –** CytoSorbents manufactures CytoSorb® at its ISO 13485:2012 manufacturing facility in New Jersey

BURN INJURY TREATMENT OPTIONS. To date, CytoSorb® has been used to help stabilize multiple patients with severe burn injury caused by thermal burns or electrocution. These are predominantly case report studies, while large scale randomized controlled studies in burn injury patients still need to be conducted. CytoSorb® has been used safely in more than 14,000 human treatments without serious device related adverse events. The vast majority of these treatments have been in critically-ill patients in the ICU, where the therapy has been well-tolerated.

Because the inflammatory response may be helpful and protective in early burn injury, we recommend to initiate CytoSorb® treatment only after organ dysfunction begins to develop, indicating a maladaptive SIRS response. Although CytoSorb® therapy in burn patients with advanced multiple organ failure has been successful in a number of cases, this is considered late usage, with subsequently less predictable outcomes.

Another potential use of CytoSorb® therapy is to promote faster and more complete wound healing and physical recovery in patients undergoing rehabilitation. CytoSorb® may help to reduce the persistent hyper-metabolic state following severe burn injury that is driven by systemic inflammation and results in extensive protein and fat catabolism. Currently, nothing is done to reduce this hyper-metabolic state, that when left unchecked, can inhibit healing, strength rebuilding, and physical recovery for up to a year.

US ARMY PHASE I & II SBIR GRANTS. CytoSorbents was awarded ~$1.65M in Phase I, II, and Phase II enhancement SBIR contracts managed by the U.S. Army Medical Research and Materiel Command to further develop its technologies for trauma, hyperkalemia, and burn injury in porcine models under Contract No W81XWH-12-C-0038.

30-PATIENT HUMAN PILOT STUDY FUNDED BY THE US AIR FORCE. The U.S. Air Force is funding a 30-patient randomized controlled pilot study using CytoSorb® to treat trauma patients with rhabdomyolysis with CRRT versus CRRT alone. Severely burned service members are also at high risk of developing rhabdomyolysis due to the extensive tissue destruction in severe burn injury that can release massive amounts of myoglobin into the bloodstream.

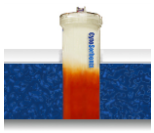
SUMMARY. CytoSorbents has developed a hemocompatible, blood purification technology with the potential to protect and preserve American lives in the face of a number of growing health threats. CytoSorb®, the company's flagship product, is now approved in the European Union as a broad, extracorporeal cytokine filter, designed to help fight "cytokine storm" in critical-illnesses such as sepsis, trauma and burn injury that can cause severe inflammation, organ failure, and often death in our wounded warriors. CytoSorb® has the potential to revolutionize critical care medicine. Case series and case reports can be found at the CytoSorb® website: www.cytosorb.com.

CytoSorb® is approved in the European Union but is not yet FDA-approved.

CytoSorbents™

NASDAQ: CTSO

For more information, contact:
Dr. Phillip P. Chan, MD, PhD
CEO and President
7 Deer Park Drive, Suite K
Monmouth Jct, NJ 08852
O (732) 329 – 8885 ext *823
C (908) 307 – 0367
F (732) 329 – 8650
pchan@cytosorbents.com
www.cytosorbents.com
www.cytosorb.com



SELECT REFERENCES

1 Medical Care Guide: Burn Statistics." Burn Survivor Resource Center. Journal of Burn Care & Rehabilitation. 14 Oct. 2008.
2 White, CE., Renz, EM "Advances in surgical care: Management of severe burn injury." Crit Care Med 2008;36(7 Supp):S318-S324.
3 Stewart, IJ, et al. "Association of AKI with adverse outcomes in burned military casualties." Clin J Am Soc Nephrol 2012: 7:199-206.
4 Kellum, JA, et al "Hemoadsorption removes TNF, IL-6, and IL-10, reduces NF-KB DNA binding, and improves short-term survival in lethal endotoxemia", Crit Care Med 2004, 32(2): 801-805.