Preclinical Studies for the Treatment of Blast-related Injuries

Targeting Complement Therapy for Improving Mortality and Morbidity of Blast Injury

Blast injury is the signature wound accounting for 70-80 percent of military casualties in the Iraq and Afghanistan conflicts (*Belmont et al. 2012*). Blast casualties commonly suffer:

- Primary injury (lung, gastrointestinal tract and middle ear injury by blast overpressure)
- Secondary injury (penetrating injury by flying objects)
- Tertiary injury (fracture, amputation, and traumatic brain injury from displacement by blast wind)
- Quaternary injury (burn and inhalation injury)
- Quinary injury (hyperinflammation by unconventional materials) (*Greer et al. 2016*)

Blast injury often causes multisystem, life-threatening injuries that represent complex triage, diagnostic, and management challenges for the health care provider. Currently, there is no specific drug therapy for blast injury.

Traumatic hemorrhage involves tissue injury, ischemia, and subsequent reperfusion. Ischemia/reperfusion injury, as well as direct tissue damage activates a multifaceted network of plasma cascades (complement, coagulation, kinin, and fibrinolytic systems) that play a major role in the systemic inflammatory response syndrome (SIRS). SIRS ultimately leads to injury-related early multi-organ dysfunction syndrome that represents the leading cause of mortality following severe trauma. The underlying immunologic disturbance is highly complex and involves early activation of the complement cascade, a crucial component of innate immunity. Researchers from U.S. Army Institute of Surgical Research (Fort Sam Houston, Texas) previously published findings that blast injury triggered early complement activation that was associated with brain injury (*Dalle Lucca et al. 2012*). They also demonstrated the beneficial effects of pharmacological manipulations of complement activity on modulating systemic and local inflammatory responses and attenuating brain damage post-blast injury in rats (*Li, Chavko, et al. 2013*).

In this study, the researchers have shown that early complement activation was present in combat casualties suffering blast injury, and correlated with clinical outcomes (brain injury, injury severity score. and mortality) (*Yang et al. 2017b, 2017a*). The team recently developed a novel clinically-relevant rat model of the battlefield polytrauma (BI combined with hemorrhagic shock), and tested the efficacy of a complement component 5 inhibitor (a clinical stage small molecular drug) in this model (Figure 1 and 2). They found that treatment with the component 5 inhibitor significantly increased survival (80 versus 30 percent), improved mean artery pressure response to fluid infusion, reduced metabolic acidosis, and mitigated multiple organ damage after blast injury and hemorrhage (Figure 3). Of note, the small molecular

adjunct component 5 inhibitor can be incorporated into small volume pre-hospital resuscitation on the battlefield because it can be carried in small vials without refrigeration and quickly reconstituted with saline. Therefore, targeting complement component 5 will present as a novel therapy for blast injury.

In summary, the utilization of component 5 inhibitor in the pre-hospital setting will lead to significant reduction in mortality and morbidity of military Service members as well as civilians who suffer blast injury.

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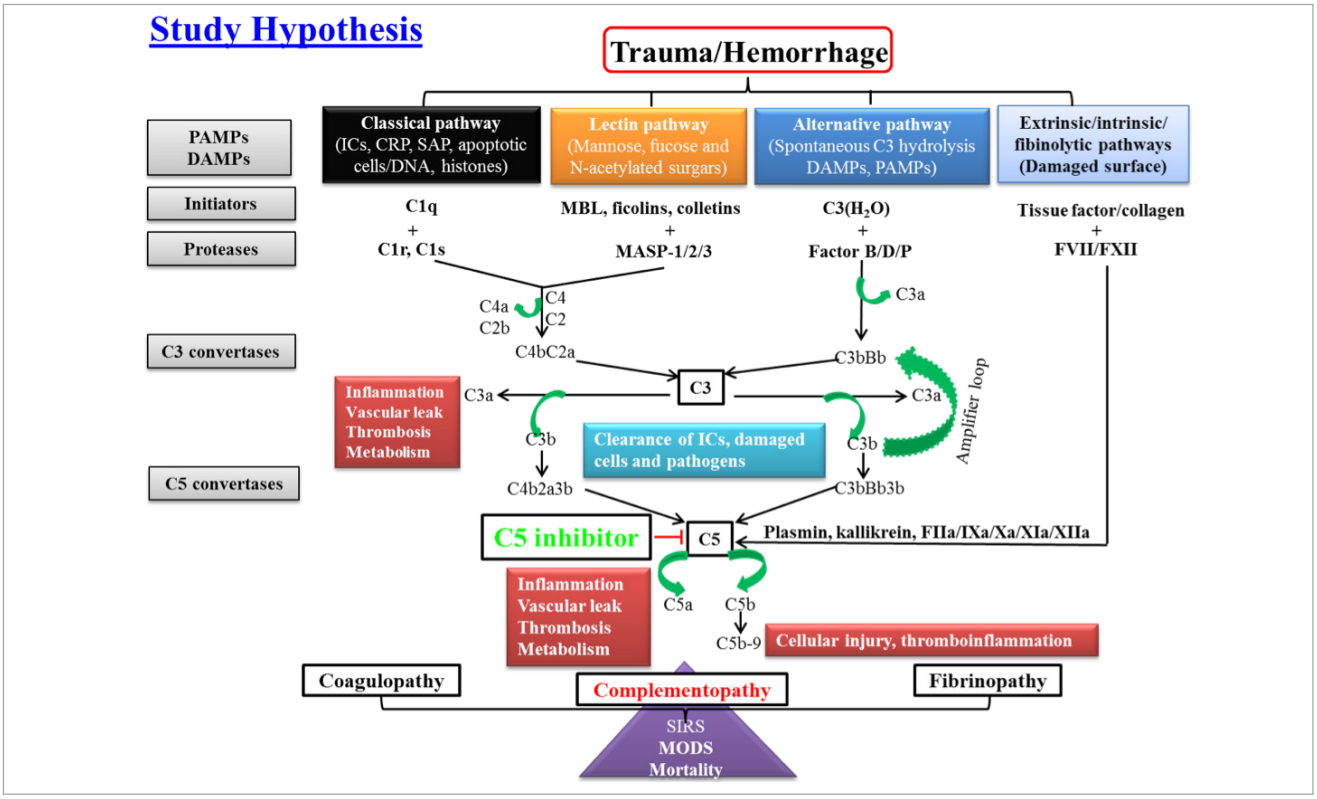

FIGURE 1: Simplified scheme of the complement cascade activation. The complement cascade can be activated through the four pathways (classical, lectin, alternative, and/or coagulation pathways). (Figure used with permission from the authors)

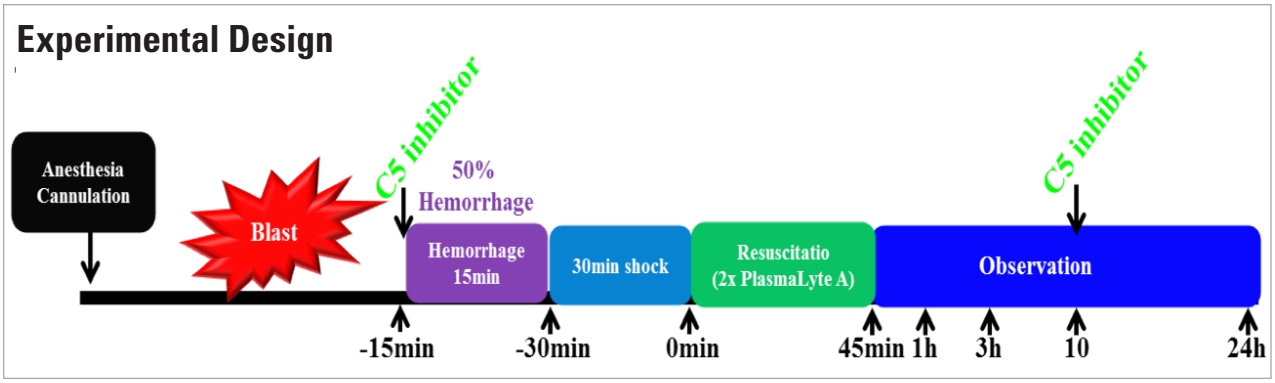

FIGURE 2: Scheme of the experimental design. All rats underwent blast injury with subsequent hemorrhage. Animals were randomized to three study arms treated with component 5 inhibitor versus Injury receiving saline alone. (Figure used with permission from the authors)

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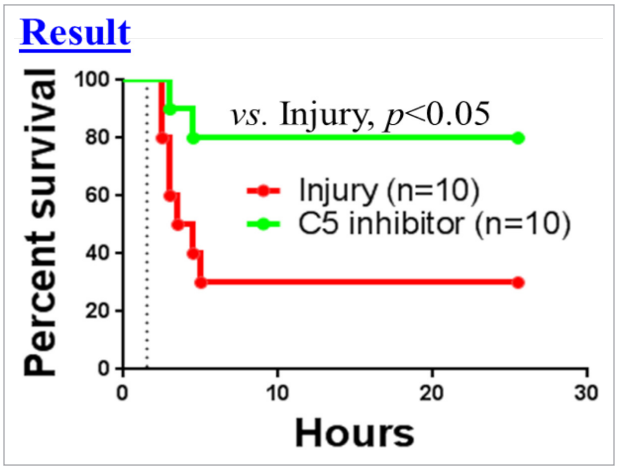

FIGURE 3: Component 5 inhibitor significantly improves survival of animals exposed to blast injury and hemorrhage (Component 5 inhibitor versus Injury, 80 percent versus 30 percent, p<0.05). (Figure used with permission from the authors)

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