Immunobiology of Trauma

Pre-Affinity Research Collaborative (pre-ARC)

Dr. Daniel Remick, pre-ARC Director

BU researchers with interests in this topic are encouraged to discuss with Dr. Remick (Daniel.Remick@bmc.org**) ideas for collaborative projects and joining this ARC.**

Traumatic injury affects millions of people annually across the world, and results in the hospitalization of thousands, Patients who survive the initial traumatic injury are at increased risk to develop infectious complications. These complications arise from multiple cellular, tissue and organ derangements and are not merely the result of a breach in barrier function, such as a break in the skin. The traumatic injury causes a maladaptive immune response such that the patient can no longer eradicate a relatively minor bacterial infection. Although trauma patients are not classically considered immunosuppressed, such as a patient with AIDS or a cancer patient receiving chemotherapy, trauma patients are functionally immunosuppressed.

The dysregulated immune system following traumatic injury extends to the innate as well as the adaptive immune systems. There are also derangements in the networked systems of complement, coagulation and fibrinolysis that collectively result in systemic coagulopathy associated with poor outcome and slow recovery, particularly after traumatic brain injury. Many molecules in these pathways are potent modulators of immune responses by virtue of their ability to interact with a spectrum of cell-based receptor systems for both activation and regulatory purposes.

All of these systems act in concert to keep the patient in the hospital and slow return to a full, functional life. From an evolutionary perspective, the responses were appropriate but modern intensive care complicates and confuses the immune response to injury. Understanding these interactions, both individually and collectively, offers the potential for improvements in both diagnosis and therapy.

The dysregulated responses may be increased or decreased, and great controversy exists concerning the direction and magnitude of the response after trauma. Some argue, with good evidence, that excessive inflammation increases organ injury, particularly in the lungs, liver and adrenal glands. They point to increased levels of circulating, activated neutrophils as well as elevated levels of plasma cytokines as evidence to support their argument. Other investigators believe that traumatic injury results in paralysis of the immune system, and provide convincing data that cells from trauma patients fail to effectively clear pathogens or produce cytokines. There is also good evidence that systemic inflammation during bacterial infection can be greatly influenced by neurological contributions, but how this operates during trauma is unknown. The immunobiology is further complicated by the frequent complication of hospital acquired bacterial pneumonia in trauma patients.

Excessive inflammation or immunosuppression, the controversy cries for clarity. We have a group of diverse investigators who intend to work collaboratively, using interdisciplinary

approaches, to understand the problem. The current team interested in examining the issues includes:

Daniel G. Remick, M.D., Professor and Chair of Pathology and Laboratory Medicine. Dr. Remick has a long standing interest in the inflammatory response in traumatic injury and formerly was the principal investigator on a program project grant to study these issues.
Peter Burke, M.D, Professor of Surgery, who has examined the role of nuclear factors and hepatic dysfunction to better understand the maladaptive response to trauma.
Ivana Delalle, M.D., Ph.D., Assistant Professor of Pathology and Laboratory Medicine is a neuropathologist who examines brain plasticity in chronic inflammatory conditions such as brain plasticity.
Thomas Einhorn, M.D., Professor and Chair of Orthopedic Surgery who studies bone healing following femur fracture.
Louis Gerstenfeld, Ph.D., Professor of Orthopedic Surgery who works with Dr. Einhorn and also examines bone healing following femur fracture.
Shinichiro Kurosawa, M.D., Ph.D., Associate Professor of Pathology and Laboratory Medicine studies the development of coagulopathy in response to infectious challenges.
Jay Mizgerd, D.Sc. Professor of Microbiology and Chief of the Pulmonary Center examines the innate response to pulmonary infections.
Deborah Stearns-Kurosawa, Ph.D., Assistant Professor of Pathology and Laboratory Medicine examines anticoagulation pathways and inflammation during infectious challenges.
Catherine Valentine, M.D., Assistant Professor of Medicine, evaluates TLR2 and TLR4 modulation during infection.

This group of investigators **will employ interdisciplinary approaches** to coalesce around a common animal model to study the immunobiology of traumatic injury in the context of secondary pulmonary infection. We intend to rapidly translate our findings from the animal model and translate the information into the clinical arena.

We will develop a polytrauma-pneumonia model which closely recapitulates the clinical setting. For this model, bilateral femur fracture and fixation will be done by the laboratories of Drs. Gerstenfeld and Einhorn. Contemporaneous with the femur fracture, mild traumatic brain injury will be induced under controlled conditions by Dr. Delalle. Outbred mice will be used, rather than inbred mice, to better mimic the human condition. Three to seven days after trauma, pneumonia will be induced in the mice by Drs. Mizgerd and Valentine. This animal model closely reproduces the clinical scenario of a patient involved in a motor vehicle accident who has suffered polytrauma, and then develops nosocomial pneumonia while hospitalized,often during pulmonary ventilator support. After polytrauma and pneumonia has been introduced, the mice will be closely followed on a daily basis for multiple parameters of injury. Using technology developed in Dr. Remick's laboratory, it is possible to do a complete blood count and differential and measure 20 different cytokines, from 20 microliters of blood. This will allow close monitoring of the individual mice as the pneumonia progresses.

After initial pilot studies to define the natural history, mice will be sacrificed at different days after the induction of pneumonia. At this point, the true power of this collaborative study will become evident. At the time of sacrifice, multiple samples will be distributed to the entire investigative team. The goal will be to provide a comprehensive examination of the changes that polytrauma and pneumonia cause, and integrate the information across disciplines to provide evidence-based criteria for prognosis, diagnosis and clinical management decisions.

Tissue/organ	**Parameter**	**Investigators**	**Affiliation (Departments and school)**
Plasma	Coagulopathy	Kurosawa, Stearns-Kurosawa	
Peripheral blood cells	Cell function	Remick	
Lung	Lung injury	Mizgerd, Valentine	
Liver	Regeneration	Burke	
Brain	Diffuse axonal injury	Delalle	
Femur	Bone healing	Gerstenfeld and Einhorn	

Submitted by Daniel Remick, M.D., June 2009