

PLOS Science Wednesday: We're Karim, Martin and Tim, trauma surgeons who edited and contributed research to the new PLOS Medicine Special Issue on traumatic injury – Ask Us Anything!

PLOSScienceWednesday¹ and r/Science AMAs¹

¹Affiliation not available

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Abstract

I am Karim Brohi, a trauma surgeon and director of the Centre for Trauma Sciences at Barts Health and Queen Mary University & London. The Centre for Trauma Sciences has a broad research into all areas of trauma care. My research especially focuses on how the body responds to critical injury and how this understanding can lead to new survivors. And I'm Martin Schreiber, MD, the Chief of the Division of Trauma, Critical Care & Acute Care Surgery at Oregon Health & Science University. I am the head of the Trauma Research Laboratory at OHSU and we focus on resuscitation, novel blood transfusion strategies and cellular therapies in trauma. We (Karim and Martin) recently co-edited the PLOS Medicine Special Issue on Trauma. In the collection we also published a paper on how the body's immune system responds to critical injury in the first 2 hours after injury. This is a difficult time window to study in trauma but we found it holds very specific signatures of how the body responds in the early activation of inflammation (which is the first stage of healing). We also found that some patients had a different response in certain cell death and survival pathways that were associated with them developing organ failure later in their clinical course. Organ failure is a common complication of trauma patients with a high associated death rate in its own right. It appears this immediate post-injury period is critical to understanding the response to trauma and therefore is likely to be a critical period for interventions that may improve survival and reduce complications. And I'm Tim Billiar, Chair of the Surgery Department at the University of Pittsburgh and current President of the SHOCK Society, USA. My research focuses on how trauma, which induces a sudden and massive activation of the immune system, leads to an abnormal immune response in some individuals. This is important because this dysregulated immune response after severe injury has been linked to dysfunction of organs such as the lungs and an increased susceptibility to infections. My colleagues and I (Tim) recently published a perspectives article titled "Time for Trauma Immunology" in PLOS Medicine as well as the results of a study in humans and mice titled "IL33 Mediated ILC2 Activation and Neutrophil IL5 production in the Lung Response After Severe Trauma: A Reverse Translation Study from and Human Cohort to a Mouse Trauma Model" in the same journal. In the perspectives piece we make the argument that trauma should be viewed like many other major disease processes that result from a dysregulated immune response (e.g. autoimmunity); as a specialized area under the broader field of immunology. We posit that this way of looking at trauma would bring the tools and expertise of the rapidly advancing field of immunology to the study of severe injury. In our experimental study, we reverse translate observations made in a large cohort of injured humans into mice genetically engineered to study the IL33-Innate Lymphocyte Cell type 2 axis. We show that an immune pathway discovered for its role in allergic airway diseases appears to contribute to acute lung injury after trauma. This study supports the idea that the study of trauma is ripe for sophisticated immunologic studies based on observations made in injured humans. We will be answering your questions at 1pm ET – Ask Us Anything!

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PLOSSCIENCEWEDNESDAY [R/SCIENCE](#)

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CORRESPONDENCE:

How do the immunomodulatory effects of trauma, sepsis, and blood transfusion differ from one another? do you think the inciting events and regulatory events differ from one another, or do they represent a convergence of foundational pathways?

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[jwis](#)

From Tim: All three can be immunosuppressive but there are major differences and the three should not be lumped together. Trauma and sepsis are too often viewed as similar insults. The trauma response is abrupt in onset resulting from tissue destruction with or without hemorrhagic shock. Sepsis is more of a syndrome and is now defined as infection with life-threatening organ dysfunction.

Typically, sepsis comes on over several hours or days. In fact, unlike trauma where the onset can be easily identified by the traumatic event, the onset of sepsis is often not known. There is overlap in the responses. For example, some of the same pattern recognition receptors of the innate immune system are involved in the initial activation of the immune responses for both. I can't say that we know enough to say there is a convergence but the body uses many of the same regulatory and mediator systems during the response to trauma and severe infection. However, experimental studies have shown that modulating a pathway in a model of sepsis can have a very different consequence than that seen in a model of trauma. A lot to learn.

Thank you for doing the AMA! I also have a few questions.

- 1) Do different patterns of trauma result in different incidences of MODS? For example, is a patient with blunt liver trauma more likely to develop this inflammatory pathway than a patient with a lacerated limb? Or, does there seem to be an exposure/response based purely on ISS?
- 2) Clearly this field of trauma research is still young but looking ahead, do you anticipate their being any future therapeutics to counter act this inflammatory pathway? Perhaps a new use for already established drugs similar to how TXA is now used in trauma? Steroids or short term immuno-suppression?
- 3) In a similar vein as Q2, in your opinion is this inflammatory pathway as significant as hypothermia, acidosis, and coagulopathy; all of which were, at one point, not understood at all in trauma. Are we going to be teaching the trauma tetrad of death in 10 years time?
- 4) Career advice request incoming, please ignore if not appropriate- I'm a British 4th year medical student who wishes to become a surgeon, with an interest in trauma surgery. My impression is that across most of the UK there doesn't seem to be such a thing as a "trauma surgeon" in the same way as there is in London MTCs or US Level 1 trauma centres. I'm told that this is due to change and there's a push for trauma to become a standalone surgical speciality in MTCs. For now, most trauma surgeons I've come across are most commonly general surgeons and occasionally vascular surgeons. For a student wanting to become a trauma surgeon, which speciality would you recommend pursuing? Also, do you have any other career advice?
- 5) Slightly cheeky to ask but I'd like to do my elective placement in trauma surgery in the USA (a level 1 centre) but many don't accept applications from overseas students. Do you know of any that do?

Many thanks

[QuestionableSam](#)

1. Interesting question. In general, the degree and prolongation of the shock state along with the degree of tissue injury will determine whether or not a patient will develop MODS. However, there are specialized situation. For instance, the independent risk factors for ARDS are pulmonary contusion, long bone fractures and massive transfusion. The development of infections can also be associated with MODS.
2. One area of trauma research that is being aggressively pursued is the administration of stem cells. In general, stem cells go to the site of injury and elaborate mediators which suppress dysfunctional inflammation. These mediators are being studied and they are a promising area for future

development.

3. Great question, the inflammatory pathway is a result of the lethal cycle. Severe injury and shock results in the acute coagulopathy of trauma which is exacerbated by fluid resuscitation. All of this produces a robust inflammatory response. 4 + 5. We plan to stick to the science.

I know in cases like spinal injuries, you can have glial scarring form after time, and that there is generally the thought that the glial scarring is one of the things that makes spinal injuries pretty much untreatable (among all of the other issues associated with neural repairs). Is there work being done on any treatments that can be done during the time period immediately following a spinal injury that might prevent/reduce this glial scarring? Are there other types of injuries where immediate intervention might improve the long term outcomes in a similar fashion?

[kero von](#)

(Marty) Once again direct administration of stem cells to the site of spinal cord injury is being studied with promising results. There is also a current trial randomizing patients to a goal MAP >85 mmHg versus normotension (65-75mmHg) in patients with ASIA A or ASIA B spinal cord injuries to see if increased perfusion results in improved long term neurologic outcomes.

Hi! Thanks for doing this AMA. This isn't exactly my wheelhouse, but I've always been interested in the intersection between immunology/trauma research and traumatic brain injury research. I currently study mild TBI in my graduate program, and I've been curious about how treatment might differ for more severe brain injuries than traumatic injuries you might incur elsewhere on the body. Have you done any research into specifically brain-based reactions to traumatic brain injuries? In light of the recent study published in JAMA about chronic traumatic encephalopathy in athletes, is there anything physicians and professionals can do post-brain injury to help prevent things like from CTE occurring?

Thanks for your time!

[Austion66](#)

(Karim) I think it's safe to say that the field of brain injury research is wide open. Brain injury care is almost entirely focused on optimising oxygen delivery to 'at risk' areas of the brain. Only recently is focus shifting to other areas such as inflammatory and coagulation changes within the brain and potential options for neuroprotection and neuromodulation. Studies like the EU funded CENTER-TBI study are an example of the beginnings of this. <https://www.center-tbi.eu/>

Thank you for doing this AMA!

The human brain has a different relationship with the immune system than a lot of other organs--are the immune responses in the brain after a traumatic injury pretty distinct from those in other organs too?

[neurobeegirl](#)

(Karim) Again not directly my field but the brain has similarities and differences in its immune responses. Again very challenging to study changes within individual organs in humans - but not impossible by any means.

Thank you for doing this AMA!

The human brain has a different relationship with the immune system than a lot of other organs--are the immune responses in the brain after a traumatic injury pretty distinct from those in other organs too?

[neurobeegirl](#)

From Tim: Traumatic brain injury is a very active area of research. Direct injury to the brain induces an intense local inflammatory response that then induces further injury to the penumbra (area adjacent to the damaged brain). This is made worse by systemic shock. So the brain responds like other organs and is susceptible to the systemic consequences to trauma.

What recent biotech advances have had the greatest impact on how you conduct your research and how?

[p1percub](#)

From Karim: Hi, nice question. Bringing a lot of existing technologies, like genomics, epigenetics and computational biology to trauma research is very exciting. One of the key challenges is to be able to do research in the emergency (or even prehospital) environment and so anything that makes analyzers or techniques (even preprocessing) easier or more robust is of value. Also evaluating and designing or re-designing new diagnostic tools for research and care is a promising and wide-open field. There's also real promise in cellular therapeutics and bioengineering for both treatment of acute changes and for reconstructing/rebuilding trauma patients.

What recent biotech advances have had the greatest impact on how you conduct your research and how?

[p1percub](#)

from Tim: The use of biomarkers to accurately stratify patients early in the course (even en route as mentioned) could take advantage of point-of-care diagnostics currently in development. We need to make sure that we enroll patients that are likely to benefit and include trial designs (developed by industry) such as adaptive design. Finally, therapies targeting the immune system have made major impact in other immune-mediated diseases and many of these could be useful in trauma---repositioning as already pointed out by Karim.

Asking as a paramedic in the United States, do you foresee any of your research having an effect on pre-hospital care of trauma patients? If so what sort of additions to treatment could your research bring about?

[harvard_9A](#)

(Marty) Some of the most important research currently being done is occurring in the prehospital setting. There is increasing evidence that aggressive fluid resuscitation is harmful in bleeding patients. Several studies have been done suggesting delaying resuscitation until bleeding is controlled or resuscitating to a radial pulse and normal mental status is superior to aggressive resuscitation. Also, there is increasing use of blood products in the prehospital arena to include RBCs and plasma and this is being studied. Adjuncts to resuscitation are also being studied in the field. This includes several trials of TXA for both brain injury and bleeding. We are also planning a study of prothrombin complex concentrates in the field for trauma patients in severe hemorrhagic shock. There is also a discussion of studying REBOA in the field. All of this research is critical because early trauma deaths from

hemorrhage are the greatest source of preventable deaths.

Asking as a paramedic in the United States, do you foresee any of your research having an effect on pre-hospital care of trauma patients? If so what sort of additions to treatment could your research bring about?

[harvard_9A](#)

(Karim) hi. As several of the articles in the Plos Medicine trauma special issue suggest, it's clear that the prehospital phase is a critical time period and must be the focus of discovery science and translational research.

Intervening early may allow us to protect cells and organs and/or take advantage of a time window where pathological processes are still controllable.

Research has already brought interventions like tranexamic acid, blood transfusions and temporary haemostatic devices to the prehospital phase of care. I'm sure this is just the beginning.

We also need to understand the effects - good and bad - of what we already do in the prehospital arena. For example the effects of anaesthesia on some of these early acute changes.

Thanks for doing this AMA! I have several questions, hope you don't mind (I really like immunology!):

1. What is typically the very first pro-inflammatory event immediately following trauma? Is it immune cells detecting cell damage via DAMP receptors, or is it damaged cells releasing pro-inflammatory cytokines or chemokines upon receiving damage (or none of the above)?
2. What interventions do you anticipate being useful to prevent organ failure in trauma patients? Would you expect more general immunosuppressant drugs, or would it more likely be targeted ones aimed at the specific pathways involved in trauma-induced hypersensitivity?
3. What type (on the I-IV classification system) of hypersensitivity response do you generally see in trauma patients? Is that classification system applicable to trauma?
4. Is there any research on trauma-induced inflammatory responses in people who are already experiencing either an infectious disease or an autoimmune condition? That is, if someone has the flu and then experiences serious trauma, is their subsequent inflammatory response likely to be more or less serious? Or if someone experiences serious trauma during, say, an SLE flare-up?
5. Is there any information on what role (if any) the complement system plays in the inflammatory response to trauma?

[rslake](#)

From Tim: All good questions.

1) It is probably all the above. There is definitely a DAMP surge shortly after injury and blocking DAMP receptors (i.e., TLR2,4, and 9) in experimental models reduces systemic inflammation and organ damage. These targets are yet to be tested in humans but would probably need to be targeted early.

2) General immunosuppressives probably would not be a good idea (these patients are already susceptible to infections and need to heal their wounds) but targeted therapies could work. However, we still need to understand how to stratify patients to identify which patients will benefit from interventions. So, the timing will be important and perhaps biomarkers to find the right patients. Prospective randomized trials will be needed

- 3) Not known and may not be applicable.
- 4) Not well studied, however older patients do not do as well suggesting the patients with altered immune systems may have more complications.
- 5) There is evidence that the complement system is activated early after injury and studies in mice show that complement deficient animals (C3) have less systemic inflammation and organ injury after hemorrhagic shock