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Athersys' MultiStem Has Enormous Potential In Trauma Treatment

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In the wake of the COVID-19 pandemic excitement, R&D and clinical development programs unrelated to COVID-19 and acute respiratory distress syndrome have been overlooked by investors. Athersys Inc., a regenerative medicine company focusing on developing its flagship product MultiStem, a highly scalable and allogeneic adult stem cell therapy, for the treatment of acute injuries and diseases in the critical care medicine area, is launching a phase 2 trial for the treatment of trauma with MultiStem.

Ticker:	(NASDAQ: ATHX)
Stock Price:	$1.93
Market Cap (M):	$381
Enterprise Value (M):	$337
Dividend/Yield:	None
Shares Outstanding (M):	197.4
3 Month Average Daily Volume (M):	13.0

The trial is being conducted at a leading trauma center in the U.S. Trauma, along with other acute medical conditions such as ischemic stroke and ARDS, has been a very difficult condition to successfully treat due to the heterogeneity of the underlying injuries coupled with the subsequent complex storm of biological cascades. We believe that stem cells, which act through multiple mechanisms of action, may have advantages in critical care conditions by affecting multiple biological pathways simultaneously, to induce a potent effect in a short amount of time.

We also believe that Athersys' MultiStem, consisting of multipotent adult progenitor cells (MAPCs), has distinct advantages over immune-modulating small molecules and monoclonal antibodies because stem cells can simultaneously and dynamically modulate multiple biological pathways. We also believe that MultiStem has distinct advantages over other stem cell therapies such as the commonly studied and poorly patent-protected mesenchymal stem cells (MSCs), as MAPCs are generally more potent and scalable, and MultiStem generally is given in higher doses, among other details.

Thus, we view the commencement of this clinical indication as highly promising, albeit mid-to-early-stage, and given the anticipated competitive positioning of MultiStem compared to other therapies, we are comfortable not derisking the program, but assigning a higher market penetration.

Our discounted cash flow, sum-of-the-parts valuation of ATHX shares takes into account the commercialization of MultiStem in the USA and Japan, assigning relatively high market penetration rates, due to the severity of the medical conditions and the lack of high-quality competing products, which we believe will drive demand for the product. Factors such as tax rates and anticipated commercialization in other geographical areas such as Europe are not included. Nonetheless, we believe shares are significantly undervalued.

Please refer to important disclosures on page 36

Athersys' MultiStem Has Enormous Potential In Trauma Treatment

In a prior article, the value proposition of Athersys' allogeneic stem cell therapy, MultiStem, in treating the holy grail of acute injury, ischemic stroke, was discussed. Since the publication of that article, Athersys and its partner Healios have made great strides in MultiStem-related clinical and strategic initiatives, including but not limited to receiving Fast Track Designation from the FDA for MultiStem in acute respiratory distress syndrome (ARDS), strengthening its ties with Healios who received Orphan Designation for ARDS (from the PAFSC), unveiling the SIFU, an ingenious next generation and cryogenic storage system with full "track and trace," informatics, security, and simple cell thawing and dispensal, allowing Athersys to have full control of its stored inventory in all potential hospital locations.

In this report, we will explain our perspective on Athersys' phase 2 severe trauma trial at UTHealth, for which the FDA just authorized initiation:

1. I believe Athersys' Multistem has great potential to treat severe trauma and it will ameliorate the complications post-trauma, as already shown in other studies (e.g. stroke, ARDS).
2. Furthermore, we believe that MultiStem is an optimal therapy for trauma as a systemic anti-inflammation and healing therapeutic; MultiStem is an anti-inflammatory therapy that potentially doesn't disrupt the inflammatory response against infection, possibly even aiding the fight against pathogens.

While those are the key takeaways to keep in mind while reading through this thesis, there are many other topics that will arise. But first, let's take a look at why trauma has flown under the radar.

Introduction: Recent Excitement

Even as Athersys' commercialization partner in Japan, Healios K.K., approaches completion of its pivotal ischemic stroke and ARDS clinical trials with Athersys' MultiStem, recent market excitement has materialized based on MultiStem's potential to treat ARDS due to COVID-19. In January of 2019, Athersys announced positive results from its phase 2 study of MultiStem in ARDS with extremely encouraging signs of strong efficacy, showing that MultiStem could potentially decrease ARDS mortality by about 50%. Even though effective treatments for ARDS, a multi-billion dollar market and a large critical care indication with unmet medical needs, have failed to be developed for decades, these quite amazing results were apparently overlooked by "the market" as Athersys' share price rose by a measly 20% that day, the equivalent of a yawn given the large opportunity and Athersys' quite small market capitalization.

The rise of the COVID-19 pandemic and associated news hysteria has, fortunately for Athersys, brought much needed attention to the concepts of SARS, "cytokine storm", and ARDS, which fell on deaf ears prior to the pandemic. Now, investors finally seem to be waking up to the fact that Athersys is the world leader in therapy development for ARDS, a deadly condition not only relevant for those infected with COVID-19, but with those affected by other issues such as influenza/pneumonia, sepsis, inhalation of harmful substances, pancreatitis, massive blood transfusions, burns, and major physical trauma. Despite all news headlines focusing on COVID-19, Athersys is in the catbird's seat to ameliorate the deadliness of not just COVID-19, but inevitable future pandemics as well as the current tremendous unmet need of ARDS due to other causes.

The Forgotten Dark Horse: Trauma

However, lost in the news hysteria is the phase 2 trial of MultiStem in severe trauma (MATRICS-1), another great unmet medical need in the critical care field. Athersys' trial, partially funded by MTEC, has great potential to become a standard of care in this quite delicate and heterogenous indication of severe traumatic injury. In fact, trauma is a leading cause of death in the US and worldwide, with an estimated cost to the world economy of $518 billion annually. As trauma is a cause of ARDS, and Athersys has shown potential efficacy in ARDS as well as preclinical efficacy in resolving hematomas in another "bleeding" indication—hemorrhagic stroke—investors have a glimpse into the potential efficacy of MultiStem for trauma, which can involve the systemic hyperinflammation involved in stroke and ARDS, without obstructing clotting and healing pathways that are so important while patients are in critical condition. These concepts will be discussed in the article below. MATRICS-1, long awaited but recently ignored, could become a smashing success for Athersys.

It is very significant that Athersys is partnered with MTEC in the trauma trial. MTEC's mission is:

> *"To be the partner of choice for private industry, academic institutions, government agencies, and other research organizations seeking to accelerate the development of medical solutions that prevent and treat injuries and restore America's military and veterans to full health."*

Their self-described purpose is:

> *"The Medical Technology Enterprise Consortium (MTEC) is an enterprise partnership in collaboration with industry and academia to facilitate research and development activities, in cooperation with the U.S. Army Medical Research and Materiel Command (USAMRMC) and other Government agencies in the biomedical sciences (including but not limited to drugs, biologics, vaccines, medical software and medical devices) to protect, treat and optimize the health and performance of U.S. military personnel."*

The military has great interest in MultiStem to potentially be used for traumatic battlefield injuries. The possibilities for future military stockpiling of MultiStem is exciting, and this would likely mean plenty of additional DoD funding to Athersys as well. When one adds both the civilian and military trauma applications for MultiStem, there is a big time blockbuster in the making.

A Brief Recap on Athersys and MultiStem vs. Other IV Stem Cell Therapies

For those not acquainted with stem cells' diverse mechanisms of action, which may vary between cell types, or for those not acquainted with MultiStem's potential substantial competitive advantages over other stem cell therapies, a brief review is helpful before diving into trauma pathophysiology and the rationale for MultiStem administration for severe trauma.

MultiStem's Potential Mechanisms of Action

In the setting of ischemic stroke and other injuries, stem cells such as MultiStem can have a broad range of biological activity, which may include some or all of the following, but are not limited to:

- Prevention of the hyperinflammatory reaction and spleen regulation
- Production of anti-inflammatory and anti-apoptotic cytokines (paracrine)
- Cytoprotective mechanisms: component transport via extracellular vesicles (exosomes), connexins, and tunneling nanotubes. These components can range from miRNA to mitochondria.
- Enhanced endogenous neuronal stem cell migration mediated by MMPs
- Production of pro-angiogenic cytokines
- Immune cell phenotype polarization via stem cells being phagocytosed
- Homing to a site of injury

Some of these potential mechanisms of action were outlined in a prior article, Athersys Is Poised to Snatch the Holy Grail of Acute Injury, last year. The main takeaway is that *stem cells exhibit many mechanisms of action and most likely cannot even be emulated, even by a cocktail of drugs.*

MAPCs (MultiStem) Are Likely Superior To MSCs In Acute Critical Care Indications

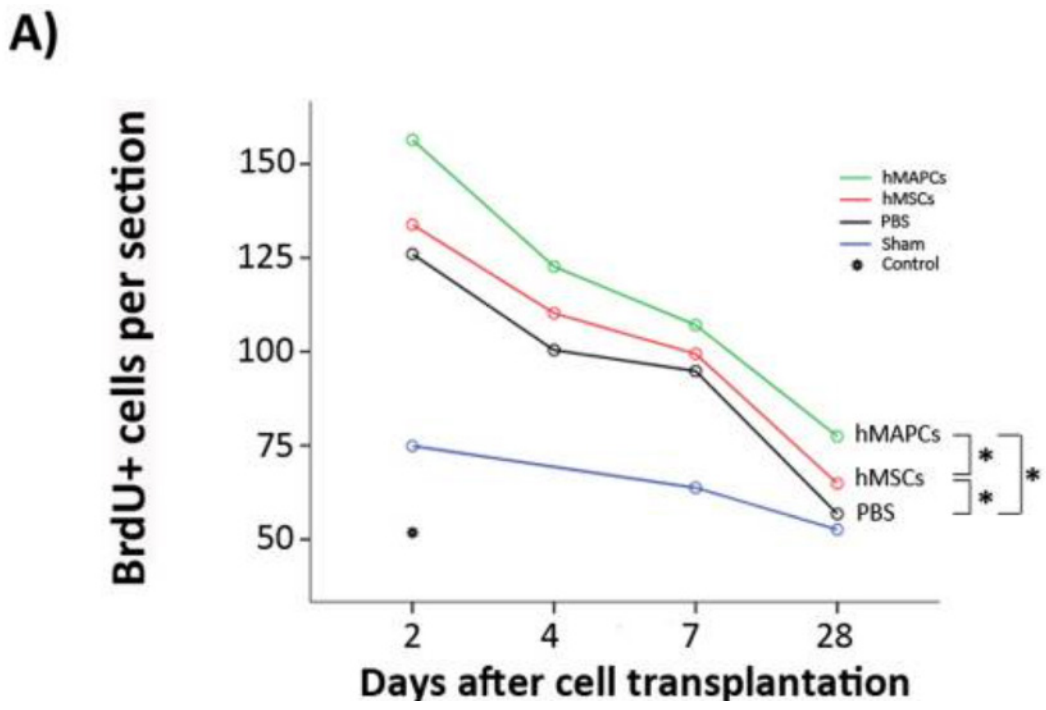
Athersys' multipotent adult progenitor cells (MAPCs) are often compared to bone marrow-derived mesenchymal stem cells (BM-MSCs) such as Mesoblast's (MESO) remestemcel-L as they exhibit similar potentials and actions, and both are considered allogeneic and immunoprivileged, lacking MHC complexes similar to Type O- blood. However, in somewhat direct comparisons, MAPCs, which makeup the product known as "MultiStem," have been shown to have a higher ability to be expanded (mass manufactured) while retaining potency and viability. Therefore, MAPCs make a more attractive product for commercialization. These distinct MAPCs have also been shown in various models to have greater therapeutic efficacy than MSCs as MAPCs arguably have stronger effects in forming new blood vessels, decreasing inflammation, preventing scar tissue, and, in the context of brain injury (TBI and stroke), enhancing neurogenesis.

For instance, regarding angiogenesis:

> *"The cells express distinct cytokine profiles which may explain the observations that MAPC can induce tube formation by HUVEC cells in in vitro assays while MSC lack this pro-angiogenic effect (Lehman et al., 2012). Moreover, MAPC are able to induce functional blood vessels in vivo when the cells are implanted in a Matrigel plug with VEGF and bFGF under the skin of nude mice, where vessels induced by MSC appeared leaky (Roobrouck et al., 2011a). [...] In a recent study, intracranial injection of human MAPC and human MSC 2 days after induction*

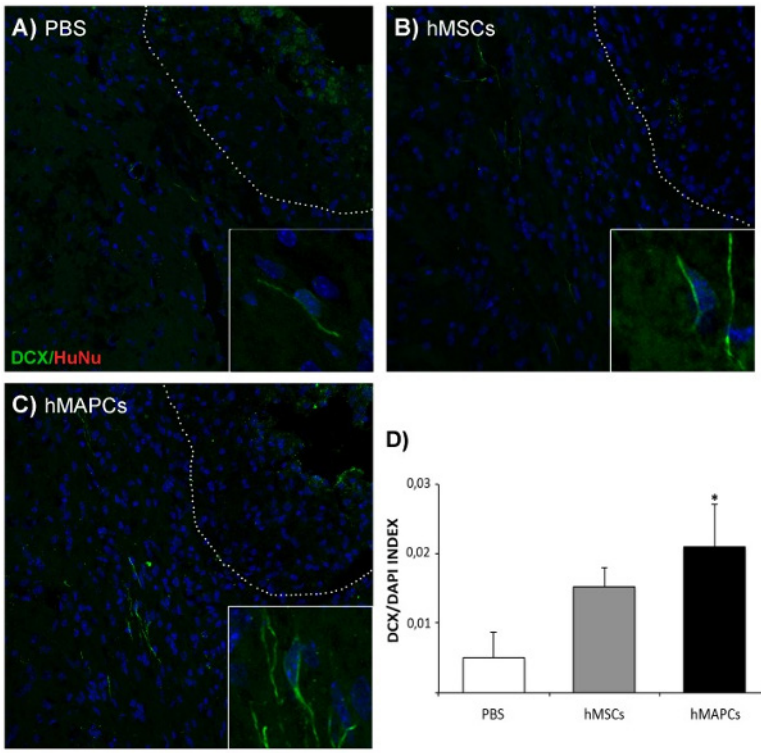
> *of stroke revealed that MAPC had a stronger effect on the attenuation of the inflammatory response and had more potency to promote endogenous tissue regeneration than MSC (Mora-Lee et al., 2012)"*
> (Vaes, B et al. (2012). Application of MultiStem® Allogeneic Cells for Immunomodulatory Therapy: Clinical Progress and Pre-Clinical Challenges in Prophylaxis for Graft Versus Host Disease. *Frontiers in Immunology, 3.)*

Furthermore, in a preclinical stroke study, MAPCs exhibited a stronger effect on neovascularization and inhibition of scar formation, the latter of which is especially important for long term recovery in ARDS (ensuring that oxygen transport across alveolar-capillary boundaries is not impaired by scar tissue) and stroke (as scar formation promotes neuronal die-back and prevent healing in that area in the long term), for example. Findings suggested that enhanced endogenous neurogenesis in the long term does not contribute to stroke recovery with MAPC treatment. However, it is possible that the reduced amount of scarring demonstrated with MAPC treatment does allow improved healing and neurogenesis in those areas over time. Therefore, it has been suggested that cell therapy increases neurogenesis in the short-term only and that scar formation (fibrogenesis) prevention allows more healing in the long term. In fact, with MAPC transplantation (as opposed to IV administration) and measurement, findings suggested that enhanced neurogenesis does play a role in recovery for both MAPCs and MSCs, and like MAPCs effects on enhanced angiogenesis, neovascularization and decreasing inflammation, MAPCs also most likely promote neurogenesis more than MSCs, as detailed below:



From: Mora-Lee, S et al. (2012). Therapeutic Effects of hMAPC and hMSC Transplantation after Stroke in Mice. *PLoS ONE, 7(8).*

The above chart shows the subventricular zone neuroprecursor proliferation from the stroke model, a sign of endogenous repair, as these cells can travel to damaged sites and replace dying neurons. The neuronal precursor cells were able to travel and survive in the damaged area, by the scar formation, in higher amounts when dosed with MAPCs, as shown below.



From: Mora-Lee, S et al. (2012). Therapeutic Effects of hMAPC and hMSC Transplantation after Stroke in Mice. *PLoS ONE, 7(8).*

In addition, MSCs such as those manufactured by Pluristem (PSTI) are placenta-derived (PD) and these cells can have different properties than BM-MSCs. PD-MSCs have also been reported to be partially immunogenic and also less immunomodulatory than BM-MSCs. Thus, Athersys may have the most powerful, (possibly) the most immune privileged, and the most mass-manufacturable allogeneic stem cell therapy.

Next, trauma pathophysiology will be examined in an attempt to speculate why MultiStem may be a game-changer in trauma treatment. Major trauma is a leading cause of death, especially in young people, worldwide, and therefore requires a therapy that can be produced and distributed at scale.

Trauma Pathophysiology

According to the National Institute of Health (NIH), physical trauma is defined as a serious injury to the body, and there are two main types: blunt force and penetrating trauma. Even surgery can cause what is considered physical trauma—this is sometimes referred to as a "controlled injury." In the sections below, some details of physical trauma pathophysiology will be examined, but there are a few overarching details worth keeping in mind (from the NIH website):

- Research reveals that inflammation plays critical and complex roles after injury. It is needed for healing, but it can also lead to many life-threatening complications.
- Scientists have found links between the brain and the system that controls inflammation throughout the body.
- Internal organs often suffer damage after a serious injury. When faced with a life-threatening injury, the body redirects blood to try to save the brain and heart. This may rob the intestines and lungs of oxygen and other vital substances.

Endogenous Responses to Trauma: A Delicate Balance

Regarding the first bullet point above, the main problem with targeting inflammation with immunosuppressants in the context of trauma is that the complement system (part of the innate immune system that "complements" the adaptive immune system) "cross talks" with the coagulation cascade, and both the coagulation and inflammatory responses need to be balanced during critical injuries—clotting, preventing infection, and immune mediated healing mechanisms all need to function properly, and this delicate balance can go awry in the context of hyperinflammation. As an example of lack of inflammation and coagulation balance, it is becoming mainstream knowledge that COVID-19 can "cause" strokes; this is due to coagulopathy, or overactivation of the coagulation cascade due to hyperinflammation:

> *"The dysregulation of the coagulation cascade and the subsequent formation of intra-alveolar or systemic fibrin clots are prominent findings in coronavirus infections associated with severe respiratory disease, and have been demonstrated in both humans and animal models. They can be attributed to the prothrombotic response, which attempts to prevent diffuse alveolar hemorrhage, but can instead result in overt clot formation with detrimental effects in patient recovery and survival."*

A hypothesis is that these "microclots" dislodge and eventually make their way up to the brain area, causing a stroke. Nonetheless, as physical trauma patients bleed, it is important not to completely immunosuppress a patient, but balance the patient's immune system. In our opinion, therapies like MultiStem, which respond through many mechanisms of action, are best suited for healing without compromising the patient's health (by promoting or interfering with coagulation and other healing mechanisms or interfering with the immune response to infection).

But before discussing the solution to post-major trauma hyperinflammation, it is necessary to take a brief dive into more trauma pathophysiology, which is very complex and involves many different aspects.

Major and Multiple Trauma

All trauma results in a local inflammatory response; however, major or multiple trauma results in a systemic response that is stronger and more biologically complicated than a simple or minor trauma:

> *"A local inflammatory response always occurs in relation to trauma. Severe injury or multiple trauma evoke a systemic inflammatory response. This systemic inflammatory response to major injury is caused by hormonal, metabolic and immunological mediators, and is associated with a haemodynamic response. Accidental unanaesthetised trauma is also to a larger extent associated with ischemia, ischemia/reperfusion (I/R) injury, hypovolemia and the immunological reactions secondary to blood transfusion. The systemic inflammatory response is required for tissue repair and has evolved in all mammals to optimise the healing potential of an organism. In uncomplicated trauma patients the systemic inflammatory response is temporary, predictable and well balanced between pro- and anti-inflammatory mediators. If the patient is exposed to severe major trauma an initial exaggerated proinflammatory response may be observed."*
> Brøchner, A., & Toft, P. (2009). Pathophysiology of the systemic inflammatory response after major accidental trauma. Scandinavian Journal of Trauma, *Resuscitation and Emergency Medicine, 17 (1).*

Before examining the immunological response to trauma, it is beneficial to review the body's other responses to major trauma, which will be briefly outlined below.

> *"Severe injury or multiple trauma evoke a systemic inflammatory response. This systemic inflammatory response to major injury is caused by hormonal, metabolic and immunological mediators, and is associated with a haemodynamic response. Accidental unanaesthetised trauma is also to a larger extent associated with ischemia, ischemia/reperfusion (I/R) injury, hypovolemia and the immunological reactions secondary to blood transfusion."*

The main takeaway is that MS would prevent systemic hyperinflammation after resuscitation/transfusion/damage control surgery, making the common surgery or procedures required later after a major traumatic event less risky, as there would be no exhaustion of the immune system, less risk for secondary complications, and improved repair overall:

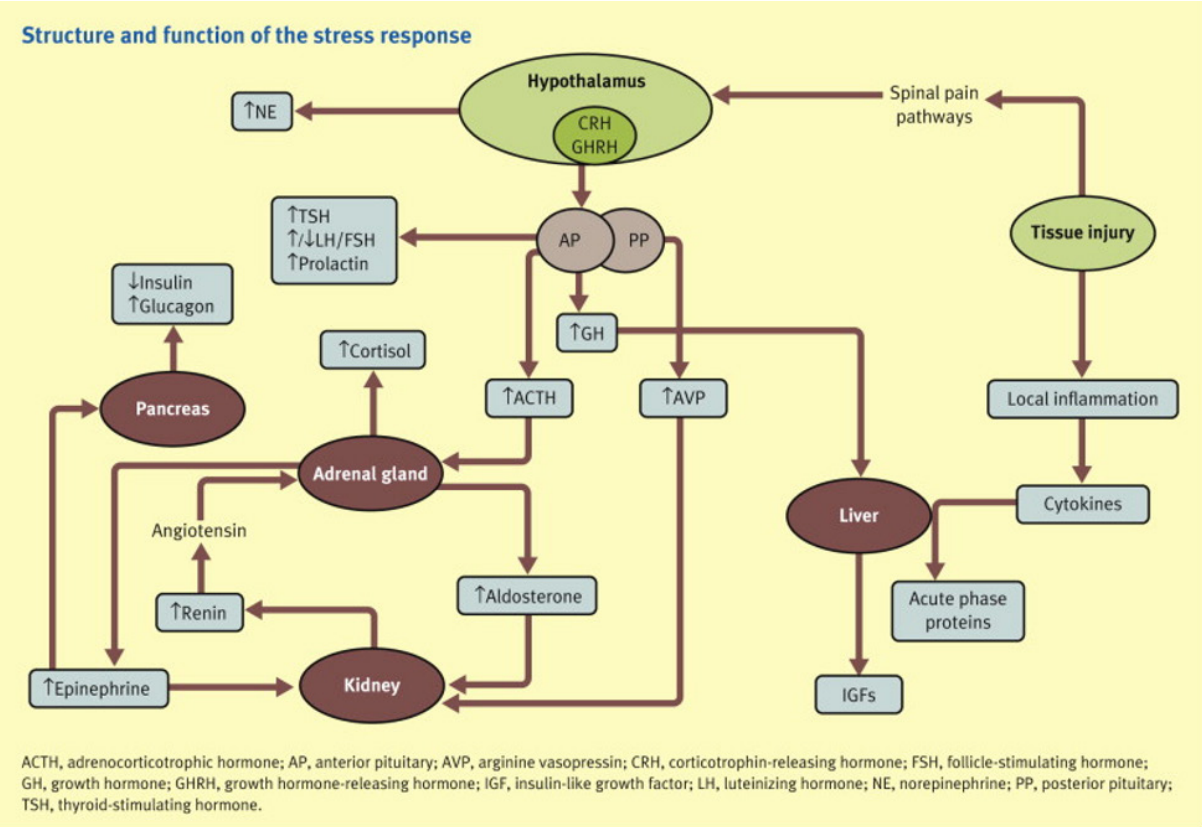
> *"In contrast to the scheduled surgical patient, the trauma patient is exposed to several events or hits. The first hit is the trauma and the second the necessary damage-control surgery. In response to these hits the immune system might be exhausted with increased risk of infection and sepsis. The final reconstructive surgery is often postponed to avoid the detrimental triad of hypothermia, acidosis and coagulopathy, but also to avoid another hit to the immune system. The timing of the final surgery is widely discussed."*

As such, the body's other responses to the major trauma are briefly outlined.

The Hormonal Response

Major trauma first induces a metabolic and hormonal response. The hormonal response is characterized by the release of stress hormones including epinephrine (and other catecholamines), cortisol, glucagon, growth hormones, aldosterone, and antidiuretic hormone. The hormonal response's effect on inflammation and blood flow is powerful and is meant to preserve critical organs when the body is in critical condition:

> *"The CNS response to trauma is predominantly neuroendocrine in nature, and acts to preserve the CNS, heart, and kidneys. It is enacted primarily by the kidneys and adrenal glands, which collectively produce renin, angiotensin, aldosterone, cortisol, erythropoietin, and catecholamines. The kidney is generally able to maintain GFR via vasoconstriction but loses its ability to concentrate urine (and preserve volume). In most patients, the heart is well-preserved until the late stages of shock, however in elderly patients (with a more fixed stroke volume) or those with cardiac disease, cardiac function may not be responsive to fluid resuscitation and decompensation may occur much earlier [Dark PM et al. Intensive Care Med 26: 173, 2000]. The lungs, which may act as a depository for the mediators of inflammation, are often the sentinel organs for multiple organ system failure (MOSF) in traumatic shock patients [Demling R et al. Curr Probl Surg 30: 345, 1993; Horovitz JH et al. Arch Surg 108: 349, 1974]. The GI tract vasoconstricts early in the trauma/shock process, exhibits "no-reflow" phenomena (where cellular edema after a hypotensive event prevents microcirculatory flow following restoration of blood pressure) [Reilly PM and Bulkley GB. Crit Care Med 21(2S): S55, 1993] and possibly being the initiating organ in multi-organ failure. The liver is notable for its susceptibility to reperfusion injury [Chun K et al. Shock 1: 3, 1994] – if recovery of synthetic function does not occur, death is almost always imminent."*



From: Ben-Menachem, E., & Cooper, D. J. (2011). Hormonal and metabolic response to trauma. *Anaesthesia & Intensive Care Medicine, 12(9),* 409-411.

The Metabolic Response

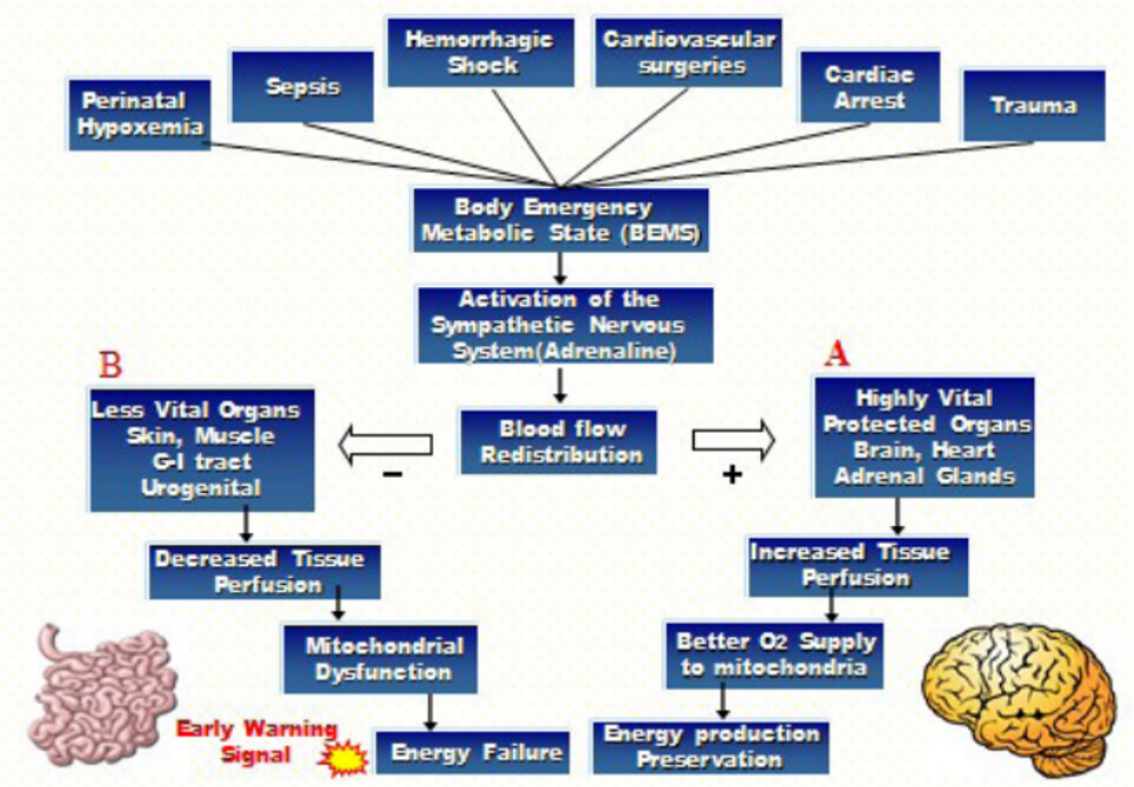
As mentioned before, major trauma also induces a metabolic response in tandem with the hormonal response, where the metabolic rate is reduced for up to a day. This is followed by a hypermetabolic and catabolic phase where catabolism of bones, muscle and fat and increased gluconeogenesis results in hyperglycemia. After major or multiple trauma, this hypermetabolic phase usually lasts less than a week in lieu of complications. This hypermetabolic response, of course, parallels heightened oxygen demand, which is why trauma patients with COPD or cardiac disease don't fare as well.

The hormonal metabolic response is related to the inflammatory response as if the hypermetabolic response lasts more than 7 to 14 days, the trauma patient has likely developed severe systemic inflammatory response (SIRS) and infection and sepsis should probably be suspected. This suggests that, possibly, mitochondrial transfer from MAPCs to endothelial tissue may help alleviate stress from increased oxygen demand. This could be a minor or secondary mechanism of action of MultiStem in trauma treatment, if there is any effect at all regarding metabolism or mitochondrial health.

The hormonal and metabolic response to major trauma is likely not extremely important in the context of MultiStem treatment; it is included simply as an illustration of how complex the body's response to trauma is.

The Haemodynamic Response

The initial shock phase of trauma where hemorrhage causes hypovolemia is distinguished by considerable peripheral vasoconstriction (from the hormonal response), retention of sodium chloride and water, and a shift of blood flow and volume from peripheral to central vital organs, as shown below:



From: Mayevsky, A. (2018). Oxygen Balance Homeostasis and Tissue Metabolic Score (TMS) of Patients in Emergency and Critical Care Medicine. *Journal of Emergency Medicine and Care, 1(2).*

If untreated, the shock phase lasts up to about one day, but current standards of care includes blood transfusion as well as anesthetic agents that counteract vasoconstriction.

After the patient is resuscitated, the hemodynamic response moves to a vasodilated state where blood flow is increased not only to the vital organs but also to muscles and injured tissue. This vasodilated state is in tandem with the hypermetabolic phase, where increased metabolism reflects increased reparative activity. It is standard to maintain sufficient intravascular volume by administration of intravenous fluids.

The Inflammatory Response (Key Focus)

Of critical importance to improving trauma care and of most relevance to stem cell therapies is the inflammatory response to trauma. According to OpenAnesthesia:

> *"Ultimately, all trauma leads to decreased organ perfusion, cellular ischemia, and a cascade of edema and inflammation.* ***Once begun, inflammation becomes a disease process independent of its origin, and can lead to multiple organ failure and death even after a patient has been completely resuscitated."***

It is this independent inflammatory process that is of concern for late complications and death after major or multiple trauma.

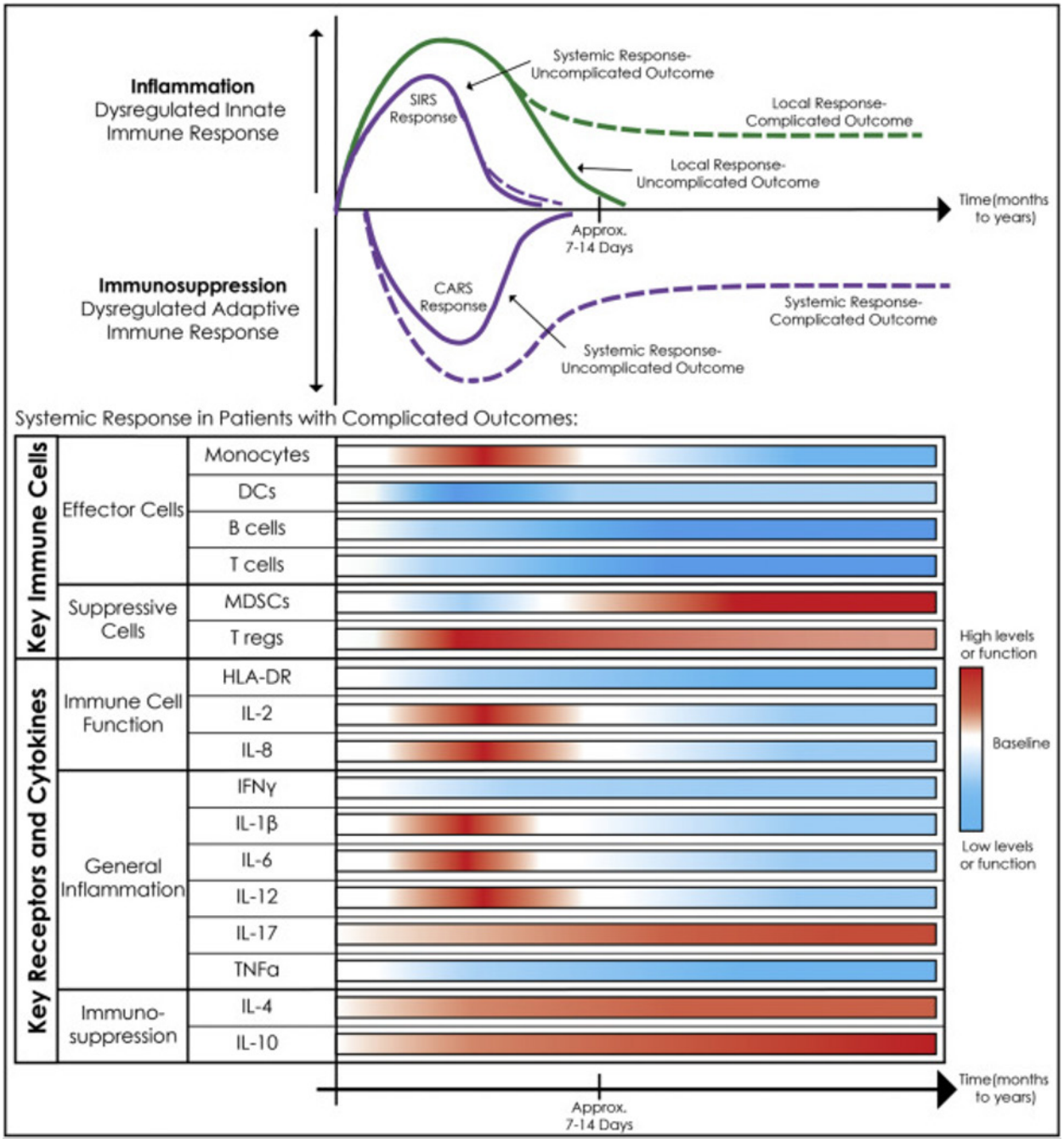
However, it is not only late complications that result in multi-organ dysfunction syndrome (MODS). Major trauma can lead to a swift substantial inflammatory response and severe systemic inflammatory response syndrome (SIRS), independent of infection, or "sterile." This is what is referred to as a "one-hit" initiation of MODS. Patients with less severe trauma may also develop MODS due to additional immune system activating catalysts such as additional surgical stress, general anesthesia, transfusion of blood products, infection, or ischemia/reperfusion injury, all of which can reactivate an inflammatory response in the exhausted immune system. This is referred to as the "two-hit" model of MODS.

Anyway, the general immune response to trauma includes the initial local response to injury that, by mechanisms partially explained above as well as via immune signaling, develop into a local and systemic immune response. Ideally, a systemic inflammatory response is balanced by an almost concurrent compensatory anti-inflammatory response to deal with pathogens, clean up debris, mitigate host vs. host tissue damage, and facilitate wound healing. In this ideal situation, the local inflammation also resolves and the patient can adequately recover.

However, when the inflammatory response overwhelms the anti-inflammatory response, multiple organ failure and hyperinflammation can lead to early deaths. On the other hand, when the anti-inflammatory response is too large, systemic immune dysregulation and systemic immunosuppression can develop and persist, leading to increased risk of infections, and also poor wound healing.

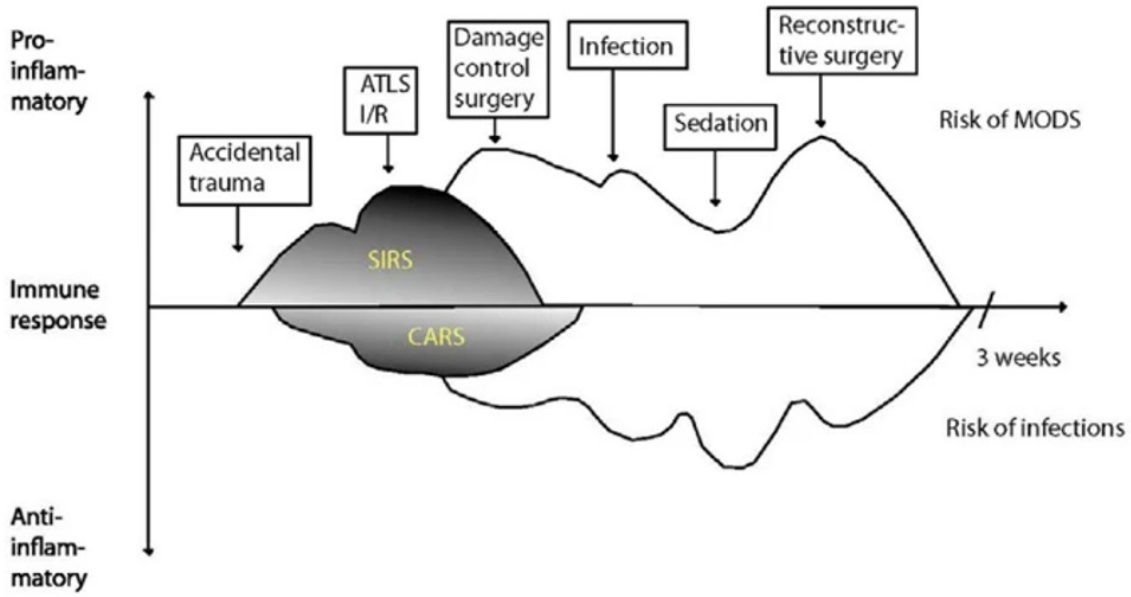
> *"Despite systemic immunosuppression, the local site of injury suffers from chronic inflammation, creating an environment not conducive to inflammation resolution and healing. This condition has been termed persistent inflammation, immunosuppression, and catabolism syndrome. Maintenance of systemic immunosuppression requires significant energy, resulting in high levels of catabolism that further suppresses immune responses by preventing immune effector cells from utilizing these resources."* (Vantucci, C. E. (2018). Immunomodulatory strategies for immune dysregulation following severe musculoskeletal trauma. *Journal of Immunology and Regenerative Medicine*, 2, 21-35.)

Below is a depiction of various local and systemic inflammatory responses to trauma—complicated and uncomplicated.



From: (Vantucci, C. E. (2018). Immunomodulatory strategies for immune dysregulation following severe musculoskeletal trauma. *Journal of Immunology and Regenerative Medicine, 2*, 21-35.)

Another graphic of an exemplary SIRS/CARS response and subsequent long-term immune dysregulation in response to other insults such as surgery and infection is shown below:



From: Brøchner, A., & Toft, P. (2009). Pathophysiology of the systemic inflammatory response after major accidental trauma. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 17 (1).

Recently, with the advances provided by critical care medicine, a larger portion of patients are surviving beyond the initial inflammatory reactions and developing a chronic critical illness referred to as persistent inflammatory-immunosuppressive and catabolic syndrome (PICS), which is defined in patients who have been critically ill for longer than two weeks with significant lymphopenia and chronic inflammation. PICS can last for months and increase risk for late MODS and infections, leading to mortality or increased morbidity, including manageable organ dysfunctions, poor wound healing, recurrent nosocomial infections, delirium, psychosocial stress, and prolonged rehabilitation needs with less of a chance to return to pre-trauma functional status.

Because of initial hyperinflammation and persisting chronic inflammation in response to trauma, immunomodulatory therapies for trauma have been investigated for decades. The goal has always been to rectify transient or chronic immune dysfunction to improve patient outcomes such as alleviating or preventing PICS, SIRS, or MODS, as well as improving wound healing. However, despite attempts to create proven immunomodulatory therapies for trauma for the last four decades, no established therapies exist. While some immunostimulatory therapies have been shown to improve individual aspects of the immune system, these therapies generally lack the ability to improve overall immune dysregulation. This is a primary reason why MultiStem is so promising in trauma treatment. As stated by the Journal of Immunology and Regenerative Medicine

> *"Their lack of success in modulating the immune system highlights the complexity of the interactions between different immune mediators as well as the synergistic and redundant effects of those mediators.* ***Because of this complexity, improved immunomodulatory therapeutics are needed that address more than just one component of the immune system. [...] Targeting an entire cell population or using cell-based therapeutics may have a more significant impact on the immune system compared to targeting individual molecules, receptors, or cytokines."***

Various Immunomodulatory Approaches to Major Trauma Treatment

Various immunomodulatory therapies have been tried in the trauma or trauma related setting, and there is a case to be made for both inflammatory or immune stimulating therapies and anti-inflammatory or immunosuppressive therapies as risk of infection but also hyper or prolonged inflammation persistence in the late-trauma setting can be problematic. Below is a list of therapies that have been pursued:

Therapy	Type	Intent/Outcome	Citations
G-CSF/GM-CSF	Inflammatory	Dealing with sepsis, preventing infections	[1,2,3]
IFN-γ	Inflammatory	Preventing infections	[4,5,6]
IVIG	Anti-inflammatory	Preventing infections, reducing inflammation	[7,8,9,10,11,12,13]
IL-10, TGF-β inhibitors	Inflammatory	Reversing immunosuppression	[14,15,16]
IL-7	Inflammatory	Immunostimulant, T-cell proliferation	[17,18,19]
Thymosin α1	Immunomodulatory	Restoring immune cell function	[20,21]
PD-1/PD-L1 inhibitors	Inflammatory	Restoring immunosuppression	[22,23,24,25,26]

This review also provides a list of generally anti-inflammatory therapies attempted to modulate the inflammatory response (SIRS), all with either conflicting or null results, albeit most studies were with small sample sizes.

The problem is that, in general, purely inflammatory therapies can result in impaired healing and that targeted anti-inflammatory therapies could contribute to increased risk of infection. Thus, the multimodal action of MultiStem in trauma may be of immense benefit by allowing immune regulation without increasing risk for infection. After all, in Athersys' phase 2 ischemic stroke and ARDS trials, the treatment arms trended with lower rates of secondary complications.

Where many of these therapies used are targeting immune cell function, few are anti-inflammatory medicines (high dose IVIG, thymosin alpha 1), and even those do not necessarily improve healing effects for trauma patients.

> *"Treatment strategies to improve outcomes have been difficult to develop as the immunophenotype of injured personnel following trauma is variable, fluid and difficult to determine."* (Thompson, K. B., Krispinsky, L. T., & Stark, R. J. (2019). Late immune consequences of combat trauma: A review of trauma-related immune dysfunction and potential therapies. *Military Medical Research*, 6(1).)

While caution is given to simply compartmentalize therapies in "inflammatory" or "anti-inflammatory" boxes, certainly none of these therapies are as potentially robust as MultiStem, which is pleiotropic in nature, affecting many biological pathways through multiple mechanisms of action. Thus, one can be more confident that MultiStem will yield a meaningful clinical benefit for major and multiple trauma patients without significant drawbacks.

Hope For Trauma Immunomodulation In Stem Cell Therapy

In fact, there has been recent work to treat trauma and immune dysfunction using MSCs. The anti-inflammatory effects of stem cells are well known since various stem cells, notably MSCs and MAPCs have been tested in treating graft-versus-host disease, stroke, and autoimmune diseases. This might make one think that stem cells are contraindicated in trauma where immune activation for the clearance of pathogens is so important and common. However, what is particularly interesting is that MSCs have been shown to help restore NK cell function (IFN-g secretion) in immunocompromised trauma patients.

This falls in line with the theory that stem cells are kind of like "smart medicine", where the cells react according to their environment, counteracting immune dysfunction whether it is an inflammatory reaction or an environment of immune dysfunction and immunosuppression. Can any other type of therapy both stimulate the immune system, function as a systemic anti-inflammatory, and enhance healing simultaneously?

Consistent with Athersys' ARDS phase 2 study that suggested significantly improved quality of life in a one year follow up, treating major trauma patients is not only about saving lives; patients may have improved quality of life and functional independence following MultiStem treatment.

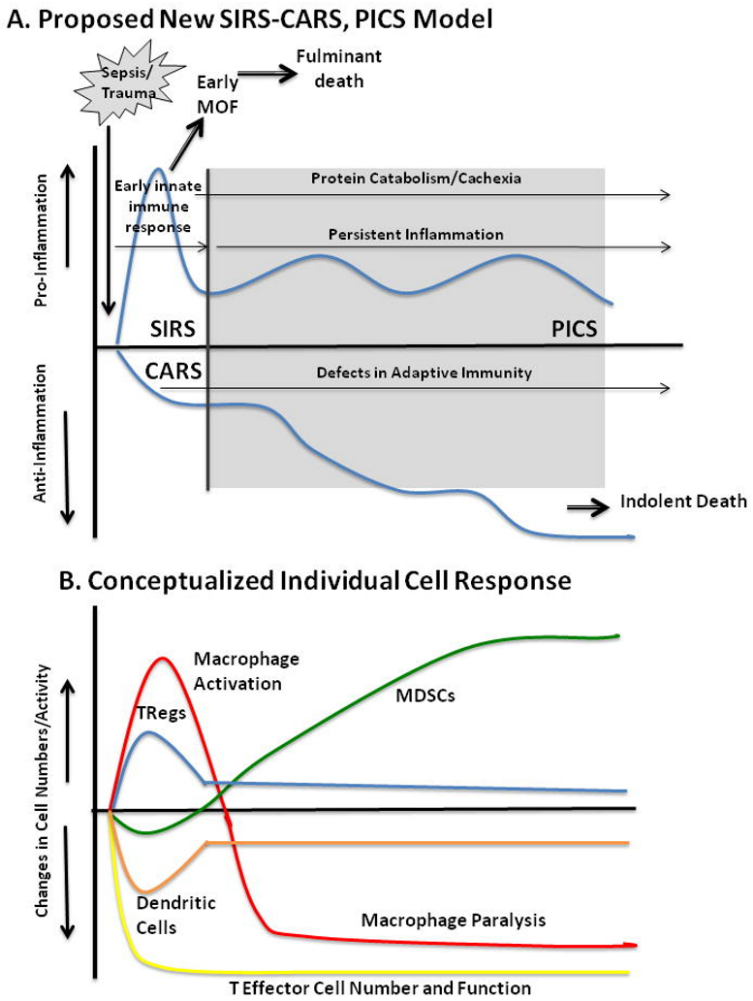
One Possible Drawback

While the logic and current data points toward potential positive outcomes in Athersys' phase 2 trauma trial, there is one drawback. It is known that one mechanism of MAPC/MSC treatment efficacy has been linked to the induction of myeloid-derived suppressor cells and other regulatory cells, of course. The potential problem is that MDSC expansion after trauma is correlated with inflammatory insult, and potentially plays a role in the development of PICS, as these cells are both immunosuppressive and inflammatory. In cancer, they are regarded as a tumor-promoting cell type along with tumor-associated macrophages (M2 phenotype).

> ***"myeloid-derived suppressor cells (MDSCs) may also play a critical role in the development of PICS by augmenting both the immunosuppressed and pro-inflammatory state*** *[17]. Following severe trauma or infection, granulocytes rapidly demarginate from the bone marrow and lymphocytes undergo massive apoptosis, creating space for hematopoietic progenitor production in an 'emergency myelopoiesis-granulopoiesis' [17]. Production in these disease states is shifted towards myelopoietic precursors, including MDSCs, with the degree of expansion and persistence of MDSCs being proportional to the severity of the inflammatory insult. MDSCs are both pro-inflammatory and immunosuppressive through their interaction with T-cells and the production of various cytokines. Though the precise incidence and evolution of PICS after combat injury has not been studied, injured combat personnel may suffer from a milder form of PICS as identified by chronic manageable organ dysfunction [71]. Stewart et al. [71] demonstrated that of the combat injured personnel admitted to an ICU, the*

> *ISS at admission was consistently associated with an increased risk of development of hypertension, coronary artery disease, diabetes mellitus, and chronic kidney disease. The development of these chronic diseases is likely, at least in part, driven by a chronic inflammatory response initiated by the initial injury and subsequent medical care, as a number of pro-inflammatory cytokines have been implicated in the development of hypertension, diabetes mellitus, coronary artery disease, and chronic kidney disease"* (Thompson, K. B., Krispinsky, L. T., & Stark, R. J. (2019). Late immune consequences of combat trauma: A review of trauma-related immune dysfunction and potential therapies. *Military Medical Research*, 6(1).)

However, it is also possible that the massive expansion of MDSCs is actually reduced with MSC/MAPC administration within an appropriate time window, if the demargination of granulocytes is somewhat prevented as well as the apoptosis of leukocytes. Thus, the space for hematopoietic progenitor production might be diminished, reducing the long term persistence of MDSCs. To play devil's advocate, certain studies show that MDSC expansion is critical in survival in sepsis/trauma and other outcomes. So, the role of MDSCs in trauma is far from clear, as opposed to in the setting of cancer. Our conjecture is that MAPC administration, if early enough, will help quell both the SIRS and CARS responses and may ultimately prevent PICS via immunomodulation and reducing immune exhaustion. The expansion and persistence of MDSCs after trauma can be seen in the graphs below:



From: Gentile, L. F. (2012). Persistent Inflammation and Immunosuppression: A Common Syndrome and New Horizon for Surgical Intensive Care. *Journal of Trauma and Acute Care Surgery*, 72(6), 1491-1501.

Other Reasons for Anticipating Encouraging Data

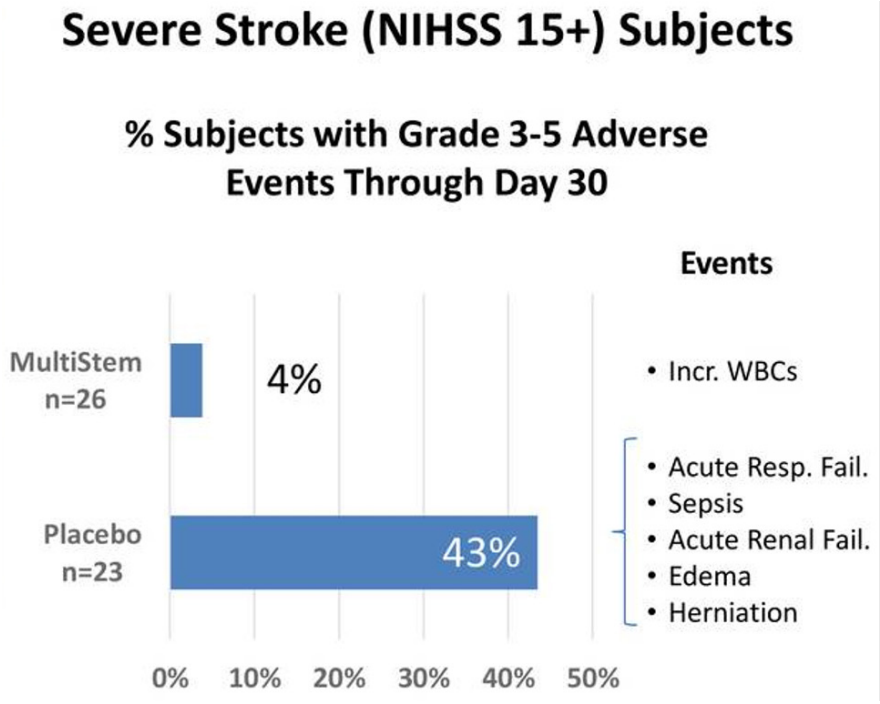
Overall, there are great reasons that MultiStem would offer broader therapeutic benefit across many different trauma patients as trauma phenotype can vary greatly, a bit similar to ARDS, which can precipitate from trauma, but also pneumonia, etc. The one common thing is the intense inflammatory response.

Indeed, according to the Athersys press release detailing the collaboration with UTHealth in trauma treatment, mortality due to trauma can be attributed to:

> *"Seventy-five percent of trauma-related deaths occur during the first three days after injury and are primarily due to uncontrolled bleeding and TBI. After three days, the remaining twenty-five percent of deaths occur at a low, but steady, rate and result from inflammation or immune complications, blood vessel damage, and poor clotting associated with the initial injury, shock and resuscitation. These inflammatory-related complications include acute kidney injury, acute respiratory distress syndrome, venous thromboembolic disease, multiple organ failure, neurological swelling and tissue death after TBI, as well as secondary infections."*

It appears that MultiStem may be able to directly affect the outcomes of most, if not all, of these complications. For instance, a key outcome in Athersys' trauma trial (if endpoints haven't changed) is incidence of acute kidney injury (AKI, also known as acute renal failure (ARF)).

There are numerous reasons to speculate that MultiStem will show success in its trauma trial. The systemic hyperinflammation cascade seen in ischemic stroke and acute respiratory distress syndrome is the common denominator. First of all, as seen in the MASTERS-1 trial, severe stroke victims that might be subject to severe complications of systemic hyperinflammation were largely free of complications in the treatment arm as seen in the picture below, taken from Athersys' investor presentation.



From: Athersys Corporate Presentation

As can be seen, only one MultiStem-treated patient developed a substantial adverse event, that is an increase in white blood cells, as opposed to almost half of the placebo patients, who developed much more severe complications such as acute respiratory failure and sepsis, which might qualify as "other inflammatory complications", edema and herniation, and notably acute renal failure, which is the tentative key endpoint in Athersys' trauma trial. If MultiStem worked in the context of stroke, we believe it will work in the context of trauma. The systemic inflammation is arguably the same problem.

With respect to mortality, MultiStem showed reduced mortality in its ARDS trial, with an even more impressive performance in the severe ARDS subgroup. Encouraging outcomes in ARDS shines a promising light on trauma:

> *"Of note, the lungs, with their numerous immune cells, not only represent the main target of the innate immune response after lung contusion and extra-pulmonary trauma but also can influence the responses of distant organs."* (Huber-Lang, M. (2018). Innate immune responses to trauma. *Nature Immunology*, 19(4), 327-341.)

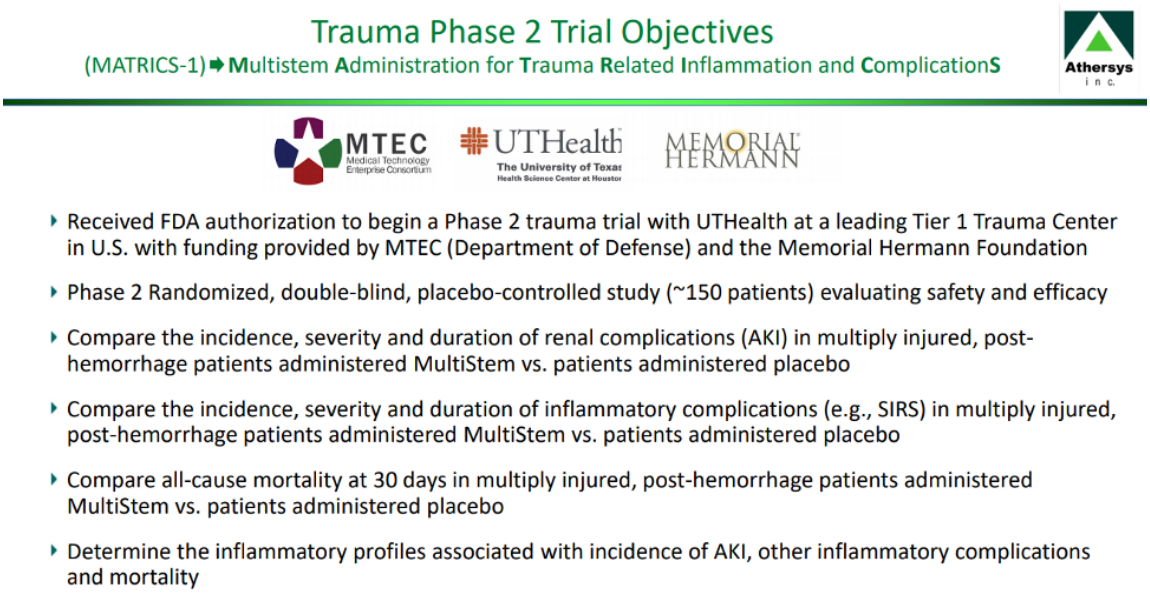
Clinical success in ARDS suggests that MuliStem will be successful in other indications such as trauma, TBI, and hemorrhagic shock, where SIRS/MODS/sepsis are complications.

Couple the reduced mortality and reduced hospital and ICU stays seen in Athersys' ARDS phase 2 trial with the responses seen in the MASTERS-1 ischemic stroke trial, and the picture of success begins to paint itself. The one big difference that might be noted is that trauma involves bleeding, whereas ischemic stroke and ARDS really aren't necessarily a function of things like blunt force trauma, lacerations, etc. However, MultiStem has shown encouraging results in preclinical models of hemorrhagic stroke. Therefore, the overall combination of these pieces of evidence point to likely success in the trauma trial.

Additional Perspective On Specific Late Complications With Respect To Stem Cells

While hemorrhagic shock is a primary reason for death within the first day of trauma, significant room for reduction in deaths and improvements in recovery lie with treating the inflammatory responses in subsequent days or weeks. Therefore, it is important to focus on how therapies such as MultiStem can affect the inflammatory response from a molecular biology perspective as opposed to the aforementioned pro-inflammatory or anti-inflammatory only therapies and the generally described SIRS/CARS and PICS dysfunctions. In fact, hemorrhagic shock essentially occurs simultaneously with ischemia-reperfusion injury, which MultiStem treats against in the setting of ischemic stroke. The difference in trauma, however, is that it is difficult to determine what damage is caused by ischemia reperfusion, injury, or hemorrhage, since they are concurrent, to some extent. As opposed to stroke, the ischemia in trauma is systemic and due to hypotension/hypovolemia due to blood loss. Reperfusion is considered a major reason for systemic inflammation in trauma.

Athersys' press release announcing the trauma program with UTHealth mentions various complications seen after trauma: "acute kidney injury, acute respiratory distress syndrome, venous thromboembolic disease, multiple organ failure, neurological swelling and tissue death after TBI, as well as secondary infections." MultiStem's potential effects on various complications such as ARDS and infections have already been covered in this review; however, there are other interesting complications to study in order to determine whether they might be prevented in Athersys' upcoming study.



From: Athersys Corporate Presentation

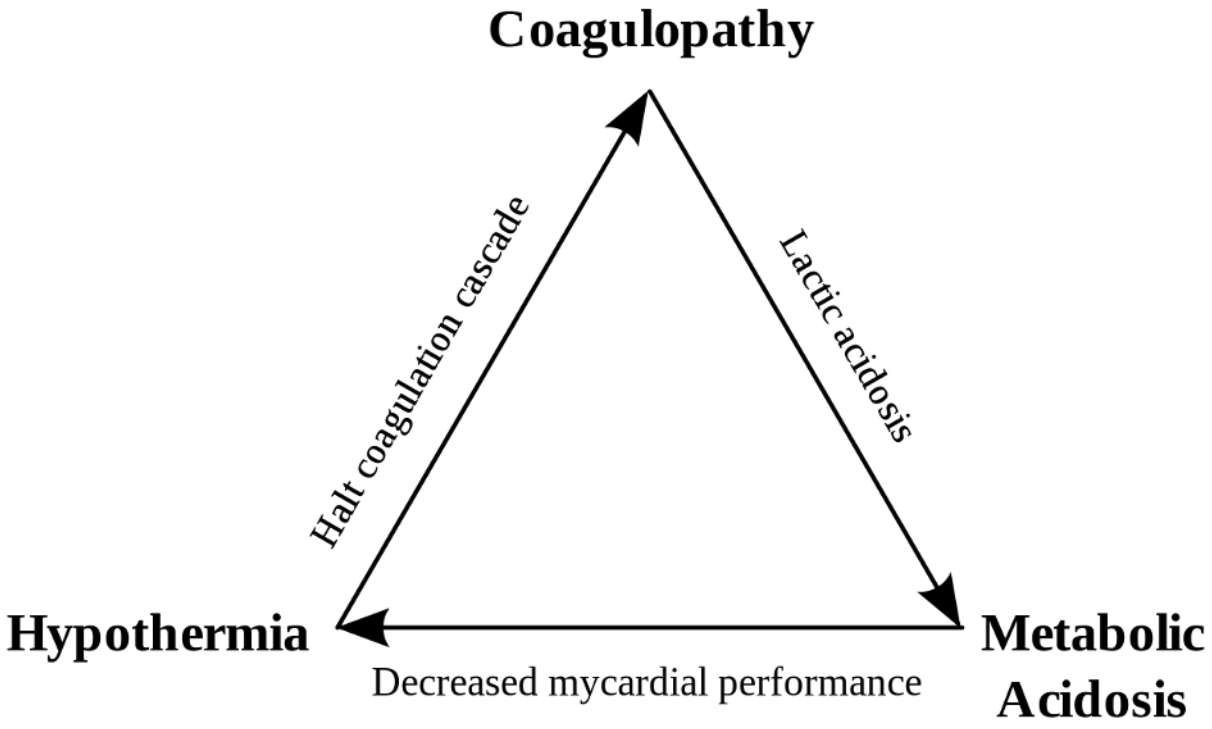
In addition to all-cause mortality at 30 days, overall benefit to the patients can be ascertained by the examination of inflammatory profiles as well as these various secondary complications discussed below.

Venous Thromboembolic Disease

Venous thromboembolic disease is observed when clots form in the bloodstream and then dislodges, traveling around in the bloodstream until it blocks a blood vessel somewhere else. This problem can be more common after a particularly pro-coagulopathic state, chronic disseminated intravascular coagulation (DIC) can develop, where complement system inflammation and coagulation systems cross-talk can result in small blood clots developing throughout the bloodstream. This results in ischemia and impaired organ perfusion (necessarily related to MODS and MOF).

There is a distinct concern of using immune stimulation therapies to fix trauma associated immune dysfunction in the injured site because the immune stimulating therapies could induce inflammation systemically. Inflammation, specifically the complement system, cross talks with the coagulation cascade and can theoretically induce late coagulopathy.

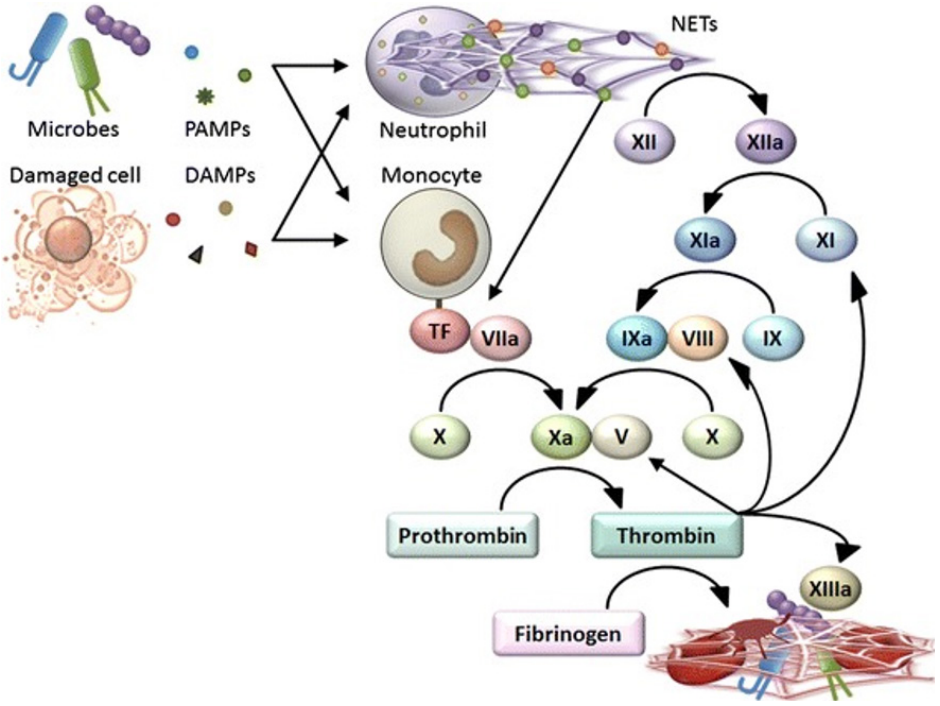
On the other hand, anti-inflammatory therapies could reduce clotting ability in the context of subsequent surgeries. This potential coagulopathy discussed is "late" or "chronic" in nature and is in contrast to trauma-induced coagulopathy or acute traumatic coagulopathy, which is generally associated with the initial responses to trauma as well as the trauma triad of death—hypothermia, acidosis, and Rav vqr:



From: Trauma triad of death, *Wikipedia.*

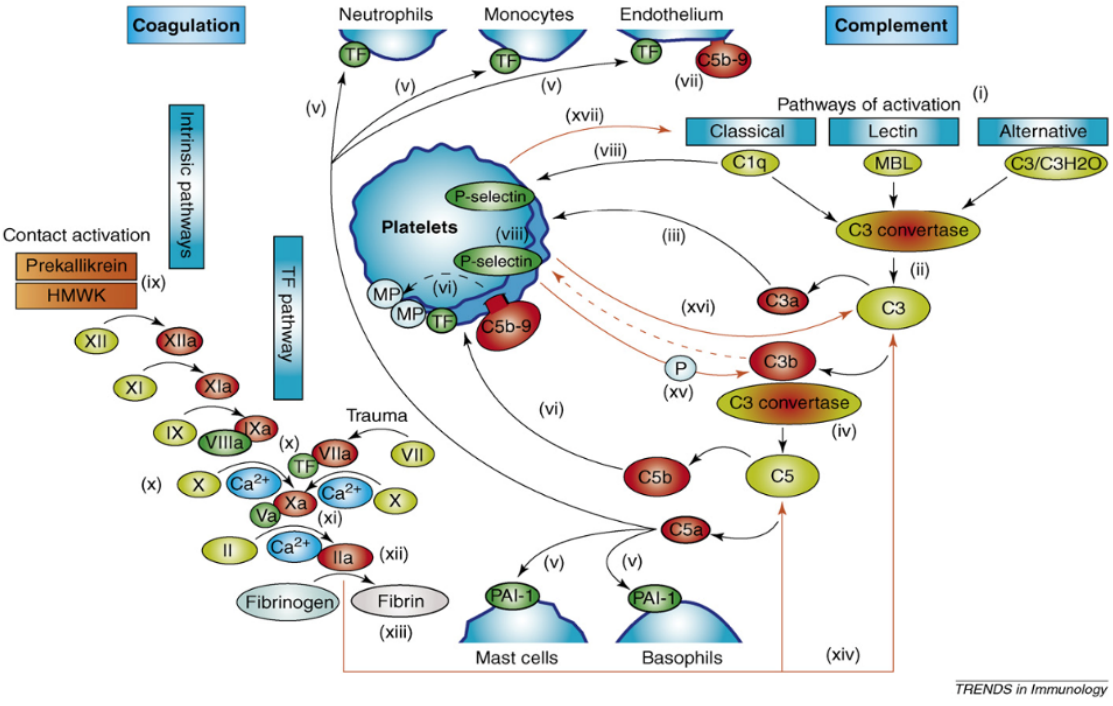
> *"Severe bleeding in trauma diminishes oxygen delivery, and may lead to hypothermia. This in turn can halt the coagulation cascade, preventing blood from clotting. In the absence of blood-bound oxygen and nutrients (hypoperfusion), the body's cells burn glucose anaerobically for energy, causing the release of lactic acid, ketone bodies, and other acidic compounds into the blood stream, which lower the blood's pH, leading to metabolic acidosis. Such an increase in acidity damages the tissues and organs of the body and can reduce myocardial performance, further reducing the oxygen delivery."*

However, in the long term, after the acute phase of trauma, where sepsis can develop or the immune system is reactivated via another hit, thrombotic disseminated intravascular coagulation (DIC) as opposed to fibrinolytic DIC is a distinct risk. This is caused by cross talk between the complement and coagulation cascades (as well as some other factors), where damage associated molecular patterns (DAMPs), pathogen associated molecular patterns (PAMPs), and complement activation cause the expression of tissue factor (TF), a key protein involved in catalyzing coagulation, and cause activation of immune cells including neutrophils and monocytes:

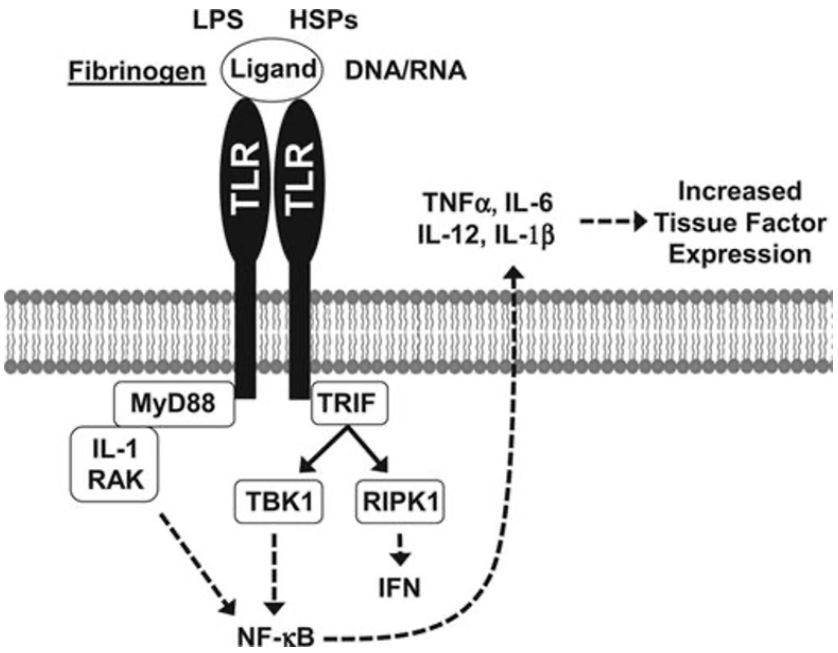


From: Ito, T. (2014). PAMPs and DAMPs as triggers for DIC. *Journal of Intensive Care*, 2(1).

In addition to tissue damage, (DAMPs) and foreign substances (PAMPs) causing the initiation of the coagulation cascade, which is essentially a feedback loop, the complement system and general inflammation can trigger the coagulation cascade. The two systems—complement and coagulation systems—simply aren't mutually exclusive. The coagulation cascade and its interaction with the complement system is shown below, as well as the interaction of DAMPs with TLRs, and the subsequent inflammatory cytokine production:



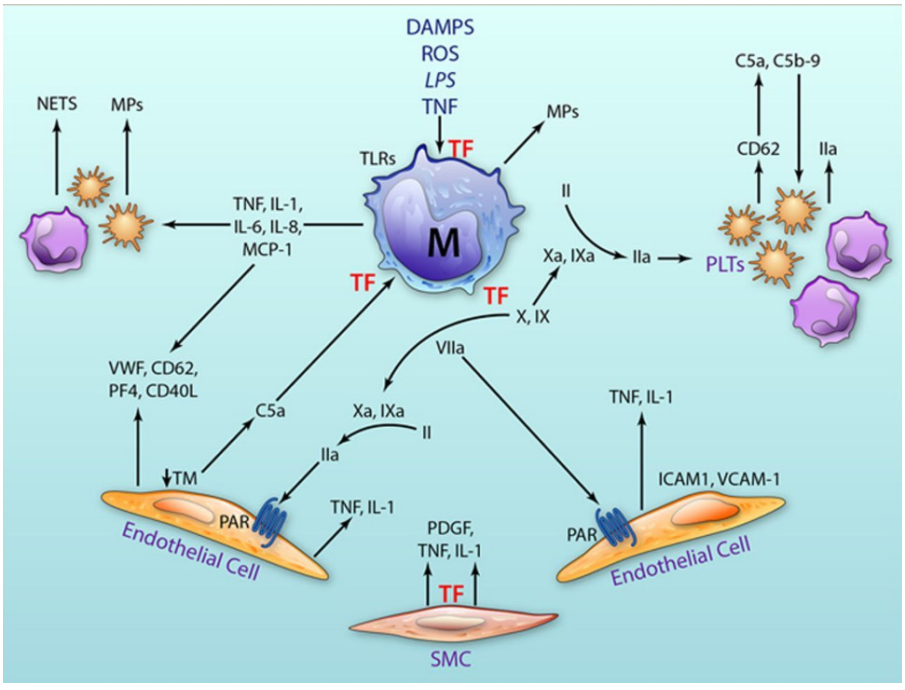
From: Markiewski, M. M et al. (2007). Complement and coagulation: Strangers or partners in crime? *Trends in Immunology*, 28(4), 184-192.



From: Foley, J. H., & Conway, E. M. (2016). Cross Talk Pathways Between Coagulation and Inflammation. *Circulation Research*, 118(9), 1392-1408.

> *"The nonspecific nature of the innate immune system unfortunately means that it regularly engages in friendly fire, causing inflammation and damage to host cells and organs. TLRs and the complement system have recently gained notoriety in the pathogenesis of thrombosis because these systems are inextricably linked to the pathways/ proteins that activate or enhance coagulation"*

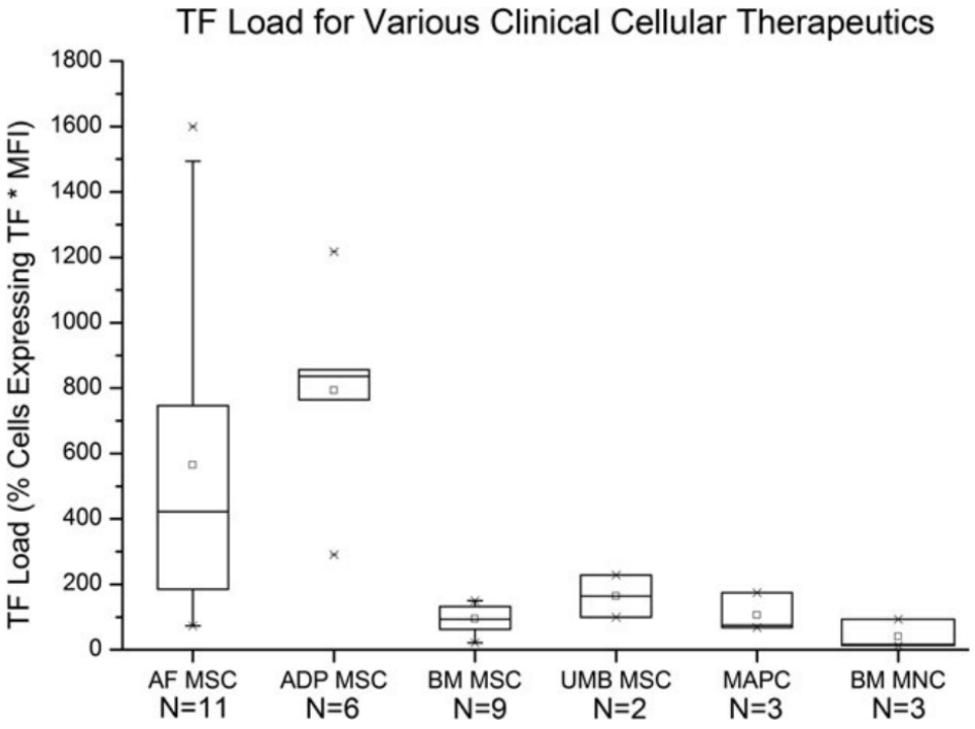
In addition to the above coagulation cascade graphics, another is provided below that nicely illustrates the coagulation cascade working in between different cell types:



From: Foley, J. H., & Conway, E. M. (2016). Cross Talk Pathways Between Coagulation and Inflammation. *Circulation Research*, 118(9), 1392-1408.

> *"It is well established that the key trigger for activation of coagulation is TF, and that initiating events that lead to its exposure to blood drives an escalating circle of events in which inflammation and coagulation positively feed back on each other. If not stopped by natural inhibitory systems or therapeutic interventions, tissue damage featuring vascular thrombosis and inflammation ensues."*

Due to the inflammation and coagulation cross talk involving TF, it could be concerning that stem cells such as MSCs and MAPCs express TF. However, this didn't seem to be an issue in either Atherys' ischemic stroke or ARDS trials, at least for the doses Athersys is using in each trial, each roughly +/-1 billion cells. Regardless, the bone marrow derived cells such as MAPCs seem to express much less TF than other MSCs such as those derived from adipose tissue, as shown in the chart below:



From: George, M. J. (2018). Clinical Cellular Therapeutics Accelerate Clot Formation. *STEM CELLS Translational Medicine*, 7(10), 731-739.

All three complement system pathways are activated in ischemia reperfusion injury, so the fact that MultiStem has shown benefit immunologically and clinically in ischemic stroke and ARDS trials bodes well for the upcoming trauma trial. It appears the overall immunomodulatory benefit of MultiStem administration prevents any risk of tissue factor-mediated coagulation due to the lack of safety issues observed in ischemic stroke clinical trials. Furthermore, MAPCs have been shown to accelerate hematoma resolution in preclinical hemorrhagic stroke models, so it is a possibility that MultiStem can be of benefit in the context of bleeding, but at the same time not increase the risk of thrombus formation, effectively governing the coagulation (and immune) responses. In this way, MAPCs could strike a solid balance between bleeding control and avoiding hypercoagulation. For instance, MAPCs have been shown to produce collagen, plasminogen and plasminogen activation inhibitor 1 (PAI-1), thus potentially regulating clotting and fibrinolysis from both sides:

> *"The data are consistent with the concept that MAPCs secrete an array of factors that maintain the ECM in a state of repose, ready to respond appropriately to exogenous stimuli that would be expected to be generated as a result of local physical injury of tissue or infiltration by various cell types."* (Burrows, G. G et al. (2013). Dissection of the Human Multipotent Adult Progenitor Cell Secretome by Proteomic Analysis. *STEM CELLS Translational Medicine*, 2(10), 745-757.)

Thus, although on the surface the expression of TF seems to contraindicate stem cell administration for IS, ARDS, and trauma, digging through the details suggests that MultiStem should reduce the complication of venous thromboembolic disease since TF is not highly expressed and MultiStem administration can be anti-inflammatory in nature, preventing massive amounts of immune cell activation and migration. It also suggests a potential competitive edge of MultiStem compared to MSCs in general, or at least MSCs sourced from certain tissues:

> *"allogeneic MSC infusion was found to be associated with development of allo-antibodies in 13% of patients in a phase II clinical trial for GvHD. In a phase I clinical trial of allogeneic MAPC in patients with GvHD, infusion was associated with increased serum anti-class I titres compared to baseline, but there was no evidence of MHC class II antibody induction [...] It has also been hypothesized that the clearance of MSC may be due to triggering of innate immunity independently of HLA-disparity, mediated by a lack of haemocompatibility [...] characterized by activation of complement/coagulation cascades, binding of activated platelets to the cells, and clot infiltration by neutrophil granulocytes and monocytes, eventually leading to cell destruction. Moll et al. demonstrated that patients infused with MSC had increased formation of blood activation markers. Tissue factor/CD142, which is expressed on MSC, was deemed to be the key determinant of cell haemocompatibility. [...] This would suggest that use of MAPC would be significantly advantageous for intravenous infusion because of the potential for reduced cell clearance/enhanced engraftment"* (Khan, R. S., & Newsome, P. N. (2019). A Comparison of Phenotypic and Functional Properties of Mesenchymal Stromal Cells and Multipotent Adult Progenitor Cells. *Frontiers in Immunology*, 10.).

Regardless of the edges MAPCs are perceived to have over MSCs, they have potential in various inflammatory processes in trauma and its complications. Below is a great summary graphic of the onset of inflammation in trauma as well as the potential complications and healing:

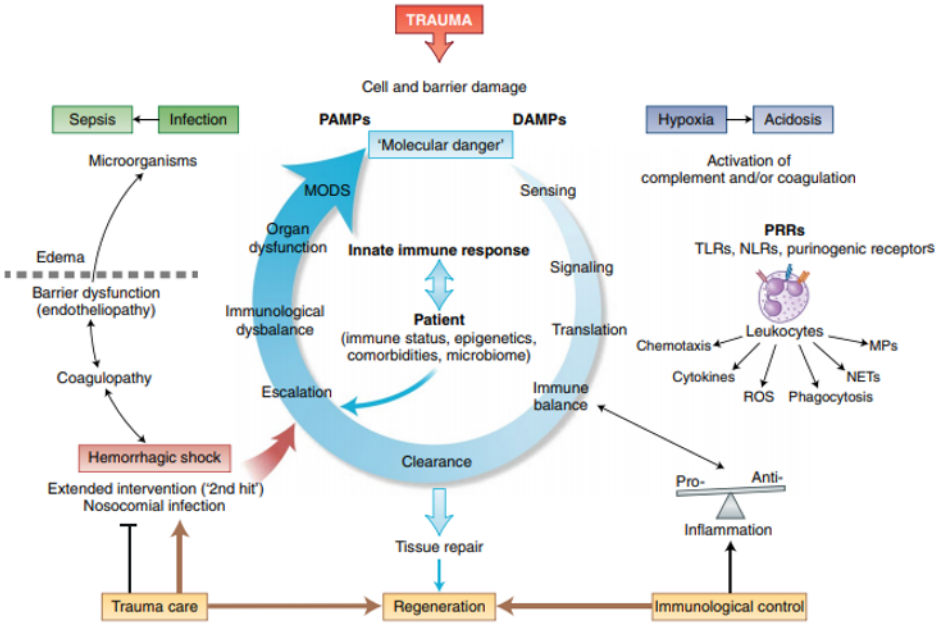


Fig. 1 | Protective and harmful innate immune responses to trauma. Trauma leads to the damage of external and internal barriers and thus exposes the immune system to DAMPs and PAMPs. Molecular danger signals and the destruction of local barriers are sensed by the complement and the coagulation systems and induce intracellular signaling in leukocytes via PRRs, which leads to translation into an instantaneous cellular immune response. Ideally, a balanced pro-inflammatory and anti-inflammatory reaction leads to rapid clearance of debris and the induction of effective tissue repair and regeneration; adverse events can be caused by individual factors of the patient or aggravated tissue damage after hemorrhage, nosocomial infection or extended surgical intervention. Escalation of the innate immune response in the form of coagulopathy and excessive inflammation leads to barrier disturbance, edema formation and compromised innate defense against invading microorganisms. Such changes can aggravate hypoxic conditions, the accumulation of metabolites and bacterial invasion, all of which can 'feed in' more DAMPs and PAMPs and thus generate a vicious cycle of the innate immune response. This eventually results in organ dysfunction and systemic infection, which emphasizes the importance of damage-adjusted trauma-care principles as well as control of the balance of the immune system, particularly in the acute phase after injury. MPs, microparticles.

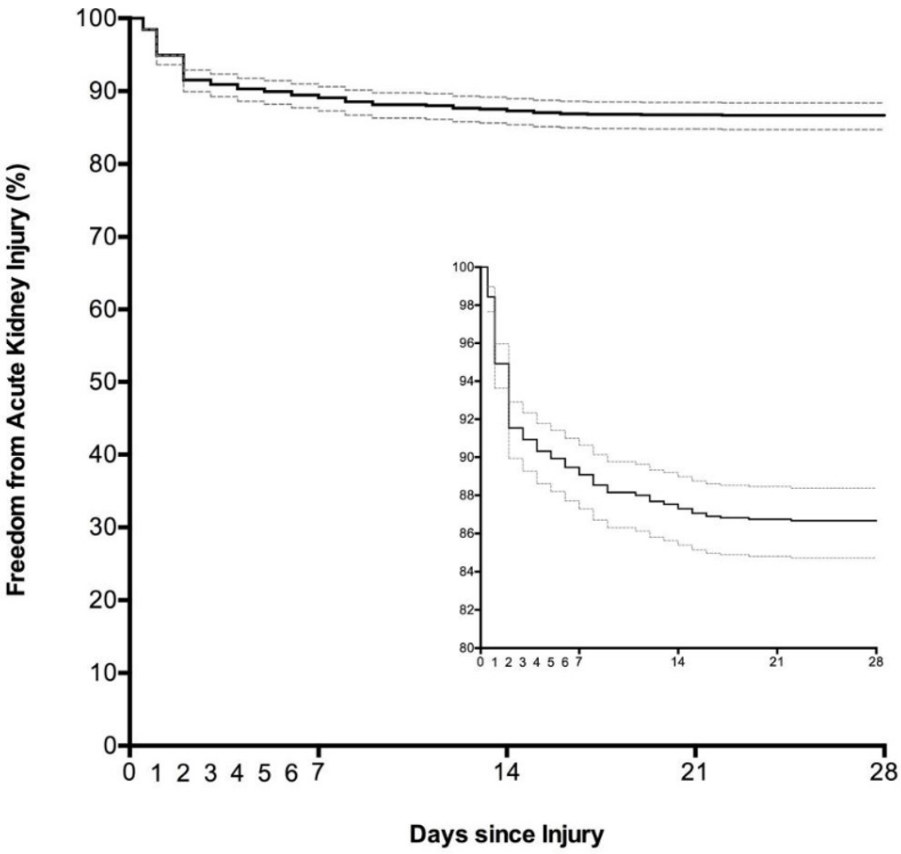
From: (Huber-Lang, M et al. (2018). Innate immune responses to trauma. *Nature Immunology*, 19(4), 327-341.)

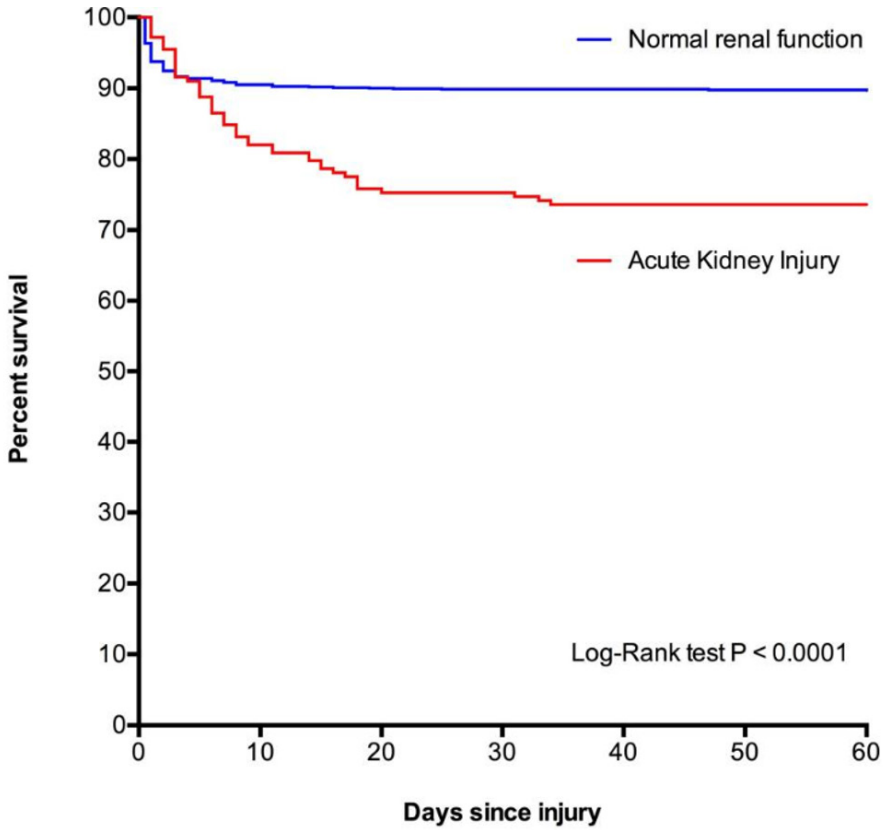
Acute Kidney Injury

Acute kidney injury (AKI), also known as acute renal failure (ARF), is a common problem in the context of trauma, as most cases of AKI are caused by impaired blood flow to the kidneys. The incidence rate of AKI in trauma patients admitted to the ICU is about 20%.

AKI is a sudden loss of kidney function, ranging from a minor loss to a total loss. Patients with AKI may require dialysis support lest they bank up salts and various waste and toxins in their blood, deregulate their blood pH, and undergo endocrine dysfunction. This of course can result in death, and studies have listed AKI mortality rates up to 60%, with one study showing a specifically trauma-induced AKI mortality rate of 17.5% versus 5.8% for non-AKI trauma patients. Needless to say, AKI is a serious issue in the context of trauma and is associated with more than 50% of patient deaths for those surviving initial injuries

Since AKI can onset fairly early after trauma and can be caused by lack of blood flow, we expect some patients who are given MultiStem to develop AKI in the study due to their predisposition towards it and a lack of time for the therapy to work. Below are Kaplan-Meier graphs for ICU trauma patients' freedom from AKI and survival.





From: Perkins, Z. B. (2019). Trauma induced acute kidney injury. *Plos One*, 14(1).

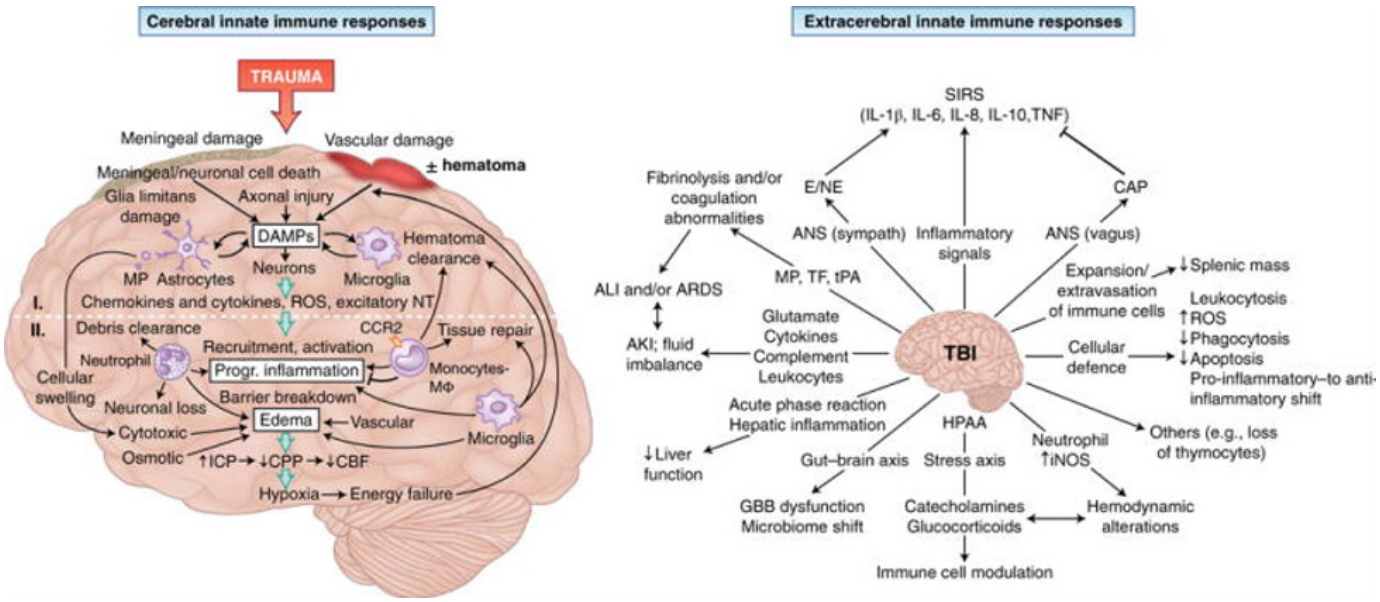
The kidneys are extremely susceptible to ischemia reperfusion injury, and the long term outcomes for trauma patients who develop AKI, yet still survive, can include chronic kidney dysfunction:

> *"Cellular damage and its associated molecular products are thought to be key triggers for inflammation after acute tissue injury.5 Within the kidney, renal tubular epithelial cells are extremely susceptible to intrinsic oxidative stress, particularly during the reperfusion phase of IR. [...] AKI often results in an abnormal repair process as a result of prolonged hypoxia and sustained secretion of profibrotic cytokine (e.g., IL-13 and TGF-β1), leading to post-AKI fibrosis and chronic renal dysfunction"* (Rabb, H. (2015). Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps. *Journal of the American Society of Nephrology*, 27(2), 371-379.).

MultiStem, in the case of a patient already presenting with AKI or developing AKI before MultiStem treatment, may improve the severity or duration of AKI through immunomodulation, repair, and improved microvascular perfusion. Preclinical research Athersys has performed in kidney transplantation, where ischemia reperfusion injury is an issue, showed that MAPC dosing with normothermic machine perfusion (NMP) can improve blood flow potentially through the production of vasodilators. The study also suggested improved tissue injury and cellular metabolism with MAPC treatment. A similar effect may be seen in trauma-induced AKI dosed with MAPCs, although administration is different and timing with respect to ischemia reperfusion would vary.

Neurological Swelling and Tissue Death after TBI

While traumatic brain injury (TBI) initial damage is quite different from damage induced by an ischemic stroke (shearing of axons, contusion, blood vessel damage versus primary ischemia), the subsequent neurological inflammation, neural necrosis, and edema is fairly similar. Both lead to an inflammatory response, breakdown of the blood-brain barrier, and ATP depletion. For a deeper understanding of the pathophysiology of TBI, see the graphic below and the discussion in the referenced publication.

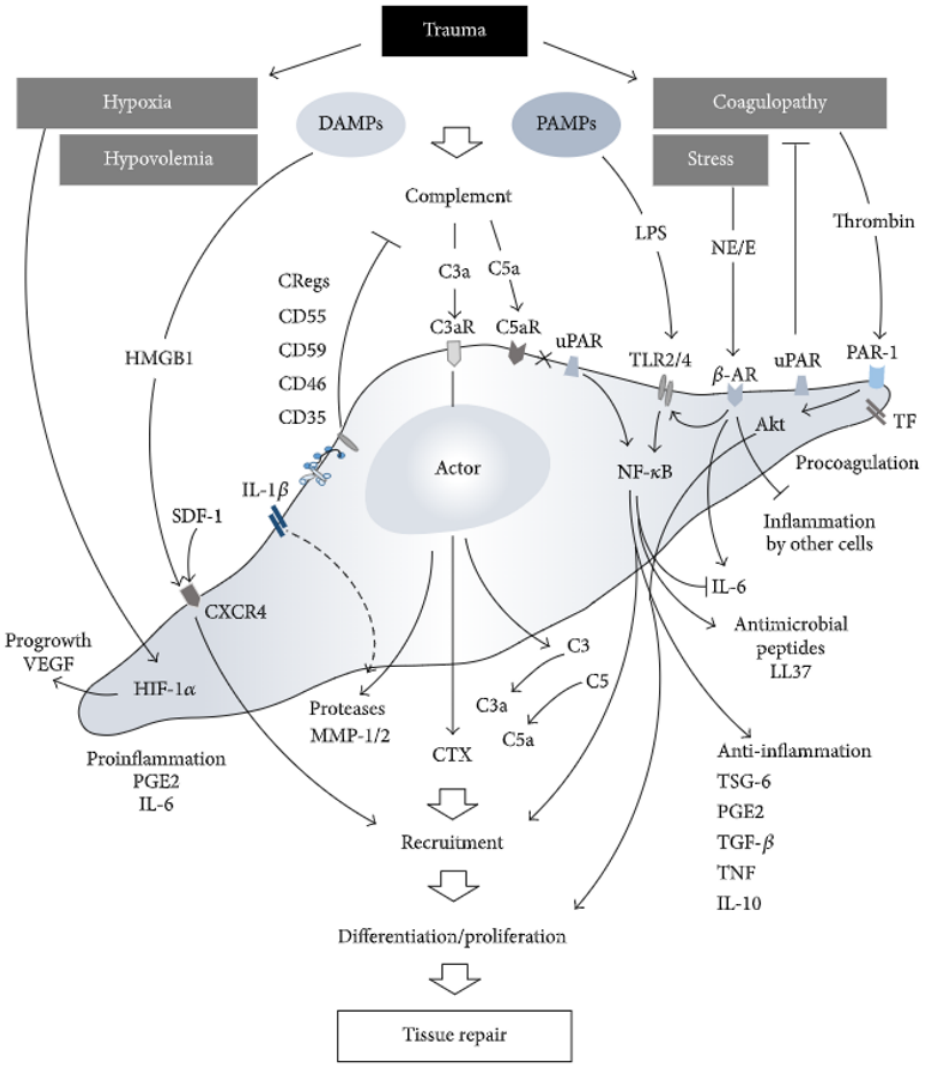


From: (Huber-Lang, M et al. (2018). Innate immune responses to trauma. *Nature Immunology*, 19(4), 327-341.)

In addition, a prior article, Athersys Is Poised to Snatch the Holy Grail of Acute Injury, discusses some aspects of stroke pathophysiology. These immunological and metabolic aspects overlap considerably. Therefore, it will not be a surprise if neurological outcomes or incidence of edema, whatever Athersys is measuring, is improved in the upcoming trauma trial.

Biological Summary

One can see from the prior discussion the wide variety of regulatory effects MSC (and similarly, MAPCs) exert in the context of a complex trauma. Unlike single drug targets, these stem cells may be able to encourage the inflammatory complement system, innate immune system, and coagulation cascade where necessary, but at the same time inhibit inflammation and massive endogenous inflammation, specifically the patients' nonspecific immune system, *and* promote inflammation resolution. In this way, MultiStem can promote healing and repair while preventing hyperinflammation and generally acting as a systemic anti-inflammatory treatment without increasing risks for infections. This, we believe, may not be possible with a typical or single-target drug such as a small molecule, peptide, RNA therapy, or mAB. Below is a diagram showing some of the therapeutic effects a mesenchymal stem cell may exert in trauma.



From: (Huber-Lang, M et al. (2016). Mesenchymal Stem Cells after Polytrauma: Actor and Target. *Stem Cells International*, 2016, 1-10.)

Furthermore, MAPCs (MultiStem) respond to different stimuli, effectively reacting to different sets of pathologies. It is like smart medicine.

Total Addressable Market

The risks of coagulopathy, infection, impaired wound healing, and other complications that require proper inflammatory and anti-inflammatory immune responses highlight the need for therapies that can correct the immune response without putting the patient at risk. Thus, cells that modulate and manage the immune system, preventing hyperinflammation while also possibly aiding in clearance and repair, and even possibly aiding in the immune response against pathogens, should in theory perform better than other agents that may be simple anti-inflammatory or pro-inflammatory drugs, such as corticosteroids or interferon.
To evaluate the size of the potential addressable market, one could look at the incidence of severe hemorrhagic trauma patients requiring massive transfusion, defined according to the critical administration threshold (CAT), surviving initial resuscitation and damage control surgery to admit to the ICU. Those that have survived the first 24 hours after a trauma is a good surrogate.

Assumptions:

- 2.8 million trauma hospital admissions per year in the USA
- 1.7% of admitted patients need massive blood transfusion (MBT—defined by 10U/24hrs)
- Only 56% of CAT+ patients were defined as MBT+
- Therefore, 3% of patients need MBT, aligning with other data
- About 40% survival after MBT

= 84,000 patients/year USA

If we speculate that MultiStem could be studied and eventually approved in severe-to-very severe injury (24 > ISS > 15 and ISS > 24, constituting 12% to 32% of patients), not just patients requiring massive transfusion, the market size could be multiple times the size of this most severe population Athersys is currently testing. Depending on how liberally MultiStem is used in stroke and trauma, the severe trauma indication could potentially be a more valuable treatment indication than ischemic stroke for Athersys. In our valuation section, we include a scenario where MultiStem is applicable to many more injuries such as motor vehicles and falls, and therefore may be used in hundreds of thousands of patients in the U.S., rather than tens of thousands.

Pricing

As alluded to in the introduction, the short term and long term health care costs in the United States is reported in the $100 billion range:

> *"Medical costs for those with unintentional injuries treated in emergency departments and released resulted in $32,691,860,000 in medical costs and $65,383,720,000 in lost work costs for total costs to the United States economy of $98,075,580,000. Those with intentional injuries treated in emergency departments and released resulted in an additional $2,393,863,000 in medical costs and $4,787,725,000 in lost work costs totaling $7,181,588,000.* ***When all of these costs are added together, injuries requiring medical treatment or resulting in death cost the United States economy $355,346,212,000 in 2005.*** *That translates to*

> *approximately 48 cents for every dollar spent on food in the United States in 2007. Seventy eight percent of this cost was due to lost wages and productivity.*
>
> *However, the true economic burden of injuries is greater than these estimates. Costs associated with lost patient and caregiver time, the nonmedical expenditures incurred by those having to deal with injury and disability, insurance costs, property damage costs, and litigation costs, for example, are not included in these estimates.* ***Additionally, while it is difficult to quantify, the value of life lost to premature mortality, decreased quality of life, and diminished functional capacity might also be included in estimates of the economic impact of injury."*** *(Cost of Injury. The American Association for the Surgery of Trauma. (n.d.).)*

As for pricing, in the prior article discussing ischemic stroke, a hospital cost savings estimate was used to estimate pricing power, based on reduced ICU and hospital stays, as well as long term care costs. A much higher price could be justified (well into the six figures USD) assuming increases in QALY, which has been extensively used to justify reimbursement or pricing for other therapies. These savings and increases in quality of life were derived from the MASTERS-1 phase 2 results. However, our discounted cash flow valuation model assumed a very conservative price of $30,200, so that will be conservatively used to value the trauma indication for Athersys. This pricing is speculative, but could be a tremendous underestimation. After all, this is cutting edge science and a single dose therapy. To put this into perspective, another single dose life-saving drug, Zolgensma, costs $2.1 million.

In addition, a systemic immune response and significant morbidity and mortality are reported in elderly patients' hip fractures as well as other considerable injuries that might not be considered "multiple trauma". Exploring MultiStem for immunomodulation and repair in other injury related indications as well as major surgery could be a future possibility. In fact, recent research has been conducted using MAPC conditioned media (MAPC secretome) for wound healing.

Financials and Valuation

Athersys had ~$80.7 million in cash as of June 30th, 2020, which should be enough to carry them through the end of 2021, though it is possible they may receive payments from Healios in the meantime. While ARDS, COVID-19 ARDS, or ischemic stroke progress may be a quicker path to revenue, we believe that in the long run, trauma could be a very significant market for Athersys, with the possibility of pricing power being considerably increased compared to ischemic stroke treatment due to the mortality and long-time morbidity (many young trauma victims) associated with multiple trauma. Nonetheless, the risk adjusted, conservative value to Athersys shares is still estimated to be about $1.00 today with relatively conservatively estimated peak sales of about ~$1 billion in the US. We believe with clinical success, demonstration of reduced incidence of secondary complications, amelioration of complications, reduced mortality, and improved quality of life potentially shown in the MATRICS-1 trauma phase 2 trial will shine a light on rationale for increased pricing.

Trauma (Severe Only), USA:

USA																		
Year	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043
Revenues																		
Estimated Trauma Population (K)	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800
Treatment-Eligible Trauma	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
Addressable Trauma Patients (K)	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0	84.0
Market Penetration	25%	50%	90%	100%	43%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Trauma Patients Treated (K)	21.0	42.0	75.6	84.0	36.1	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0	42.0
Price per Treatment	$30,000	$30,600	$31,212	$31,836	$32,473	$33,122	$33,785	$34,461	$35,150	$35,853	$36,570	$37,301	$38,047	$38,808	$39,584	$40,376	$41,184	$42,007
Revenue (M)	**$630.0**	**$1,285.2**	**$2,359.6**	**$2,674.2**	**$1,172.9**	**$1,391.1**	**$1,419.0**	**$1,447.3**	**$1,476.3**	**$1,505.8**	**$1,535.9**	**$1,566.7**	**$1,598.0**	**$1,629.9**	**$1,662.5**	**$1,695.8**	**$1,729.7**	**$1,764.3**
Costs (M)																		
COGS (25% of Revenue)	$157.5	$321.3	$589.9	$668.6	$293.2	$347.8	$354.7	$361.8	$369.1	$376.5	$384.0	$391.7	$399.5	$407.5	$415.6	$423.9	$432.4	$441.1
SG&A (25% of Revenue)	$157.5	$321.3	$589.9	$668.6	$293.2	$347.8	$354.7	$361.8	$369.1	$376.5	$384.0	$391.7	$399.5	$407.5	$415.6	$423.9	$432.4	$441.1
Total Spend (M)	**$315.0**	**$642.6**	**$1,179.8**	**$1,337.1**	**$586.5**	**$695.6**	**$709.5**	**$723.7**	**$738.1**	**$752.9**	**$768.0**	**$783.3**	**$799.0**	**$815.0**	**$831.3**	**$847.9**	**$864.9**	**$882.2**
EBIT (M)	$315.0	$642.6	$1,179.8	$1,337.1	$586.5	$695.6	$709.5	$723.7	$738.1	$752.9	$768.0	$783.3	$799.0	$815.0	$831.3	$847.9	$864.9	$882.2
Discount Rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Discounted EBIT (M)	$207.1	$367.4	$586.6	$578.1	$220.5	$227.4	$201.7	$178.9	$158.7	$140.7	$124.8	$110.7	$98.2	$87.1	$77.2	$68.5	$60.8	$53.9
NPV (M)	$1,534																	
NPV Terminal Value (M)	$0																	
Risk Discount	16%																	
Risk Adjusted Value (M)	$249																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, Trauma, USA)	**$0.71**																	

Other Indications Valuation: Pipeline Sum-Of-The-Parts

Expanded Trauma, USA:

USA																		
Year	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043
Revenues																		
Estimated Trauma Population (K)	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800	2800
Treatment-Eligible Trauma	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Addressable Trauma Patients (K)	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0	1400.0
Market Penetration	7.0%	16.0%	25.0%	34.0%	43.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
Trauma Patients Treated (K)	98.0	224.0	350.0	476.0	602.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0	700.0
Price per Treatment	$30,000	$30,600	$31,212	$31,836	$32,473	$33,122	$33,785	$34,461	$35,150	$35,853	$36,570	$37,301	$38,047	$38,808	$39,584	$40,376	$41,184	$42,007
Revenue (M)	**$2,940.0**	**$6,854.4**	**$10,924.2**	**$15,154.1**	**$19,548.7**	**$23,185.7**	**$23,649.4**	**$24,122.4**	**$24,604.8**	**$25,096.9**	**$25,598.9**	**$26,110.9**	**$26,633.1**	**$27,165.7**	**$27,709.1**	**$28,263.2**	**$28,828.5**	**$29,405.1**
Costs (M)																		
COGS (25% of Revenue)	$735.0	$1,713.6	$2,731.1	$3,788.5	$4,887.2	$5,796.4	$5,912.4	$6,030.6	$6,151.2	$6,274.2	$6,399.7	$6,527.7	$6,658.3	$6,791.4	$6,927.3	$7,065.8	$7,207.1	$7,351.3
SG&A (25% of Revenue)	$735.0	$1,713.6	$2,731.1	$3,788.5	$4,887.2	$5,796.4	$5,912.4	$6,030.6	$6,151.2	$6,274.2	$6,399.7	$6,527.7	$6,658.3	$6,791.4	$6,927.3	$7,065.8	$7,207.1	$7,351.3
Total Spend (M)	**$1,470.0**	**$3,427.2**	**$5,462.1**	**$7,577.0**	**$9,774.4**	**$11,592.8**	**$11,824.7**	**$12,061.2**	**$12,302.4**	**$12,548.5**	**$12,799.4**	**$13,055.4**	**$13,316.5**	**$13,582.9**	**$13,854.5**	**$14,131.6**	**$14,414.2**	**$14,702.5**
EBIT (M)	$1,470.0	$3,427.2	$5,462.1	$7,577.0	$9,774.4	$11,592.8	$11,824.7	$12,061.2	$12,302.4	$12,548.5	$12,799.4	$13,055.4	$13,316.5	$13,582.9	$13,854.5	$14,131.6	$14,414.2	$14,702.5
Discount Rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Discounted EBIT (M)	$966.5	$1,959.5	$2,715.6	$3,275.8	$3,674.5	$3,789.7	$3,361.3	$2,981.3	$2,644.3	$2,345.4	$2,080.3	$1,845.1	$1,636.5	$1,451.5	$1,287.4	$1,141.9	$1,012.8	$898.3
NPV (M)	$16,890																	
NPV Terminal Value (M)	$0																	
Risk Discount	16%																	
Risk Adjusted Value (M)	$2,736																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, Trauma, USA)	**$7.82**																	

Ischemic Stroke, USA:

USA																		
Year	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
Revenues																		
IS Population (K)	696.0	709.9	724.1	738.6	753.4	768.4	783.8	799.5	815.5	831.8	848.4	865.4	882.7	900.4	918.4	936.7	955.5	974.6
Treatment-Eligable Moderate-Severe AIS	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%
Number of Addressable AIS Patients (K)	330.6	337.2	344.0	350.8	357.9	365.0	372.3	379.8	387.4	395.1	403.0	411.1	419.3	427.7	436.2	444.9	453.8	462.9
Market Penetration	8.0%	19.0%	30.0%	41.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%
AIS Patients Treated (K)	26.4	64.1	103.2	143.8	196.8	200.8	204.8	208.9	213.0	217.3	221.6	226.1	230.6	235.2	239.9	244.7	249.6	254.6
Price per Treatment	$30,000	$30,600	$31,212	$31,836	$32,473	$33,122	$33,785	$34,461	$35,150	$35,853	$36,570	$37,301	$38,047	$38,808	$39,584	$40,376	$41,184	$42,007
Revenue (M)	**$793.4**	**$1,960.6**	**$3,220.7**	**$4,579.4**	**$6,391.3**	**$6,649.5**	**$6,918.1**	**$7,197.6**	**$7,488.4**	**$7,790.9**	**$8,105.7**	**$8,433.2**	**$8,773.9**	**$9,128.3**	**$9,497.1**	**$9,880.8**	**$10,280.0**	**$10,695.3**
Costs (M)																		
COGS (25% of Revenue)	$198.4	$490.1	$805.2	$1,144.9	$1,597.8	$1,662.4	$1,729.5	$1,799.4	$1,872.1	$1,947.7	$2,026.4	$2,108.3	$2,193.5	$2,282.1	$2,374.3	$2,470.2	$2,570.0	$2,673.8
SG&A (25% of Revenue)	$198.4	$490.1	$805.2	$1,144.9	$1,597.8	$1,662.4	$1,729.5	$1,799.4	$1,872.1	$1,947.7	$2,026.4	$2,108.3	$2,193.5	$2,282.1	$2,374.3	$2,470.2	$2,570.0	$2,673.8
Total Spend (M)	**$396.7**	**$980.3**	**$1,610.3**	**$2,289.7**	**$3,195.6**	**$3,324.7**	**$3,459.1**	**$3,598.8**	**$3,744.2**	**$3,895.5**	**$4,052.8**	**$4,216.6**	**$4,386.9**	**$4,564.2**	**$4,748.6**	**$4,940.4**	**$5,140.0**	**$5,347.6**
EBIT (M)	$396.7	$980.3	$1,610.3	$2,289.7	$3,195.6	$3,324.7	$3,459.1	$3,598.8	$3,744.2	$3,895.5	$4,052.8	$4,216.6	$4,386.9	$4,564.2	$4,748.6	$4,940.4	$5,140.0	$5,347.6
Discount Rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Discounted EBIT (M)	$396.7	$852.4	$1,217.6	$1,505.5	$1,827.1	$1,653.0	$1,495.4	$1,352.9	$1,224.0	$1,107.3	$1,001.8	$906.3	$819.9	$741.8	$671.1	$607.1	$549.3	$496.9
NPV (M)	$12,116																	
NPV Terminal Value (M)	$0																	
Risk Discount	70%																	
Risk Adjusted Value (M)	$8,481																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, Stroke, USA)	**$24.23**																	

Ischemic Stroke, Japan:

Japan																		
Year	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039
Revenues																		
AIS Population (K)	280.0	285.6	291.3	297.1	303.1	309.1	315.3	321.6	328.1	334.6	341.3	348.1	355.1	362.2	369.5	376.8	384.4	392.1
Treatment-Eligable Moderate-Severe AIS	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%
Number of Addressable AIS Patients (K)	61.1	62.3	63.6	64.8	66.1	67.5	68.8	70.2	71.6	73.0	74.5	76.0	77.5	79.0	80.6	82.2	83.9	85.6
Market Penetration	8.0%	19.0%	30.0%	41.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%	55.0%
AIS Patients Treated (K)	4.9	11.8	19.1	26.6	36.4	37.1	37.8	38.6	39.4	40.2	41.0	41.8	42.6	43.5	44.3	45.2	46.1	47.1
Price per Treatment	$100,000	$102,000	$104,040	$106,121	$108,243	$110,408	$112,616	$114,869	$117,166	$119,509	$121,899	$124,337	$126,824	$129,361	$131,948	$134,587	$137,279	$140,024
Revenue (M)	**$488.8**	**$1,207.8**	**$1,984.1**	**$2,821.1**	**$3,937.4**	**$4,096.4**	**$4,261.9**	**$4,434.1**	**$4,613.2**	**$4,799.6**	**$4,993.5**	**$5,195.3**	**$5,405.2**	**$5,623.5**	**$5,850.7**	**$6,087.1**	**$6,333.0**	**$6,588.9**
EBIT (Royalties) (M)	$39.1	$120.8	$238.1	$395.0	$590.6	$614.5	$639.3	$665.1	$692.0	$719.9	$749.0	$779.3	$810.8	$843.5	$877.6	$913.1	$949.9	$988.3
Discount Rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Discounted EBIT (M)	$39.1	$109.8	$196.8	$296.7	$403.4	$381.5	$360.9	$341.3	$322.8	$305.3	$288.8	$273.1	$258.3	$244.3	$231.1	$218.6	$206.7	$195.5
NPV (M)	$3,863																	
NPV Terminal Value (M)	$0																	
Risk Discount	80%																	
Risk Adjusted Value (M)	$3,090																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, Stroke, Japan)	**$8.83**																	

ARDS, USA:

USA																		
Year	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041
Revenues																		
ARDS Population (K)	231.0	235.6	240.3	245.1	250.0	255.0	260.1	265.3	270.7	276.1	281.6	287.2	293.0	298.8	304.8	310.9	317.1	323.5
Treatment-Eligable ARDS	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Number of Addressable ARDS Patients (K)	231.0	235.6	240.3	245.1	250.0	255.0	260.1	265.3	270.7	276.1	281.6	287.2	293.0	298.8	304.8	310.9	317.1	323.5
Market Penetration	10.0%	25.0%	45.0%	60.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%
ARDS Patients Treated (K)	23.1	58.9	108.1	147.1	162.5	165.8	169.1	172.5	175.9	179.4	183.0	186.7	190.4	194.2	198.1	202.1	206.1	210.2
Price per Treatment	$30,000	$30,600	$31,212	$31,836	$32,473	$33,122	$33,785	$34,461	$35,150	$35,853	$36,570	$37,301	$38,047	$38,808	$39,584	$40,376	$41,184	$42,007
Revenue (M)	**$693.0**	**$1,802.5**	**$3,375.6**	**$4,682.6**	**$5,277.7**	**$5,491.0**	**$5,712.8**	**$5,943.6**	**$6,183.7**	**$6,433.5**	**$6,693.5**	**$6,963.9**	**$7,245.2**	**$7,537.9**	**$7,842.4**	**$8,159.3**	**$8,488.9**	**$8,831.9**
Costs (M)																		
COGS (25% of Revenue)	$173.3	$450.6	$843.9	$1,170.6	$1,319.4	$1,372.7	$1,428.2	$1,485.9	$1,545.9	$1,608.4	$1,673.4	$1,741.0	$1,811.3	$1,884.5	$1,960.6	$2,039.8	$2,122.2	$2,208.0
SG&A (25% of Revenue)	$173.3	$450.6	$843.9	$1,170.6	$1,319.4	$1,372.7	$1,428.2	$1,485.9	$1,545.9	$1,608.4	$1,673.4	$1,741.0	$1,811.3	$1,884.5	$1,960.6	$2,039.8	$2,122.2	$2,208.0
Total Spend (M)	**$346.5**	**$901.2**	**$1,687.8**	**$2,341.3**	**$2,638.9**	**$2,745.5**	**$2,856.4**	**$2,971.8**	**$3,091.9**	**$3,216.8**	**$3,346.7**	**$3,481.9**	**$3,622.6**	**$3,769.0**	**$3,921.2**	**$4,079.6**	**$4,244.5**	**$4,415.9**
EBIT (M)	$346.5	$901.2	$1,687.8	$2,341.3	$2,638.9	$2,745.5	$2,856.4	$2,971.8	$3,091.9	$3,216.8	$3,346.7	$3,481.9	$3,622.6	$3,769.0	$3,921.2	$4,079.6	$4,244.5	$4,415.9
Discount Rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Discounted EBIT (M)	$346.5	$783.7	$1,276.2	$1,539.4	$1,508.8	$1,365.0	$1,234.9	$1,117.2	$1,010.7	$914.4	$827.3	$748.4	$677.1	$612.6	$554.2	$501.4	$453.6	$410.4
NPV (M)	$9,080																	
NPV Terminal Value (M)	$0																	
Risk Discount	54%																	
Risk Adjusted Value (M)	$4,903																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, ARDS, USA)	**$14.01**																	

ARDS, Japan:

Japan																		
Year	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039
Revenues																		
ARDS Population (K)	10.0	10.3	10.6	10.9	11.3	11.6	11.9	12.3	12.7	13.0	13.4	13.8	14.3	14.7	15.1	15.6	16.0	16.5
Pneumonia-Induced ARDS	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Number of Addressable ARDS Patients (K)	5.0	5.2	5.3	5.5	5.6	5.8	6.0	6.1	6.3	6.5	6.7	6.9	7.1	7.3	7.6	7.8	8.0	8.3
Market Penetration	20.0%	40.0%	60.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%	80.0%
ARDS Patients Treated (K)	1.0	2.1	3.2	4.4	4.5	4.6	4.8	4.9	5.1	5.2	5.4	5.5	5.7	5.9	6.1	6.2	6.4	6.6
Price per Treatment	$100,000	$102,000	$104,040	$106,121	$108,243	$110,408	$112,616	$114,869	$117,166	$119,509	$121,899	$124,337	$126,824	$129,361	$131,948	$134,587	$137,279	$140,024
Revenue (M)	**$100.0**	**$210.1**	**$331.1**	**$463.8**	**$487.3**	**$512.0**	**$537.9**	**$565.1**	**$593.7**	**$623.7**	**$655.3**	**$688.4**	**$723.3**	**$759.9**	**$798.3**	**$838.7**	**$881.2**	**$925.8**
EBIT (Royalties) (M)	$8.0	$21.0	$39.7	$64.9	$73.1	$76.8	$80.7	$84.8	$89.1	$93.6	$98.3	$103.3	$108.5	$114.0	$119.7	$125.8	$132.2	$138.9
Discount Rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Discounted EBIT (M)	$8.0	$19.1	$32.8	$48.8	$49.9	$47.7	$45.5	$43.5	$41.5	$39.7	$37.9	$36.2	$34.6	$33.0	$31.5	$30.1	$28.8	$27.5
NPV (M)	$526																	
NPV Terminal Value (M)	$0																	
Risk Discount	80%																	
Risk Adjusted Value (M)	$421																	
Shares Oustanding, Fully Diluted (M)	350.0																	
Price per Share (MultiStem, ARDS, Japan)	**$1.20**																	

There is additional upside opportunity for penetrating markets in other areas of the world, specifically through additional development or commercial partnership opportunities, such as in the European Union. One other important aspect to note is that Athersys may need fewer than 100 sales reps in the United States for ischemic stroke as there are only so many top tier stroke centers in the States. Thus, our SG&A estimate, for at least that

indication, is likely a gross overestimation. The total calculated current value of Athersys shares is ~$50/share. There is enormous potential in trauma treatment, and depending on how the program progresses, trauma could become Athersys' largest commercial indication.

Risks

There exists a number of risks for Athersys. First, Athersys is a clinical-stage biotechnology company currently operating with negative margins as it spends on development and has no substantial revenue. Second, the company's valuation is almost entirely associated with its clinical therapeutic, MultiStem. As such, clinical risk with MultiStem represents a major risk for the company. Thus, if MultiStem fails to become an FDA (or other regulatory agency) approved commercial product, Athersys may not bring in substantial revenues for the foreseeable future. There is also the possibility that Athersys' revenues and commercial market shares fall short of those projected in this report.

Athersys also has risk associated with its management and scientists, whose experience and knowledge is critical to the success of the company. The company also carries risks with intellectual property and potentially needing to raise equity in the future, as do all pre-revenue biotechs.

Conclusion

For all scientific reasons, as well as the fact that Athersys' share price tripled following the COVID-19 hysteria, we believe investors, in general, are placing little-to-no value on MultiStem's prospects in major or multiple trauma. Furthermore, we believe that the trauma indication has great potential to significantly benefit patients and to provide profits for Athersys. As a brief summary: MultiStem should ameliorate the complications as shown in other studies, and MultiStem is probably the optimal therapy for systemic anti-inflammation and healing while not disrupting the inflammatory response against infection. We do not believe that other single-target drugs can have as robust an effect in trauma as stem cells.

MultiStem could be the optimal way to address such a delicate situation such as severe or multiple trauma. As evidenced by the lack of immunomodulatory therapies for severe trauma patients, Athersys could truly make a huge difference in patients' lives in this area. As CEO Gil Van Bokkelen stated:

> *"One of the things that really drives us here at the company is that, that knowledge that we might be on the cusp of doing something that is truly special, that could change the world for the better, change medicine for the better, and could help a lot of people out there."*

Since its inception, Athersys has been on a quest to radically change medicine as we know it. We believe that Athersys in particular represents the future of medicine, and that Athersys will ubiquitously bring groundbreaking medicine to patients suffering from critical care indications. This kind of founder-operated business with incredibile vision brings us to our final point, which may be more important for investors than the entirety of this article's body.

Athersys Is Building Momentum with Recent Events

Athersys is increasing momentum in its strategy to commercialize. In 2018, Athersys appointed Greg Liposky, MBA as SVP of commercial manufacturing, assigning him a great task in paving the way to mass produced cell therapies.

Recently, the company brought on Ivor Macleod, previously the CFO/CCO at Eisai (ESALY). While Macleod was at Merck, he provided financial support and collaborated on the successful development and launch of Keytruda, which is expected to be the world's top selling drug in a few years.

Last but not least, Maia Hansen joined the company as SVP of operations and supply chain. She previously was a lieutenant for the US Navy after graduating from MIT (engineering and business). After that, she worked as a senior partner at McKinsey & Company, developing and optimizing clients' global supply chains.

Athersys partner Healios increased its investment in Athersys by exercising $7 million of its warrants.

Years ago, Athersys founders embarked on a journey to change the way medicine is done, and it appears that that dream may finally become a reality.

Important Research Disclosures

Karl Egeland (the "analyst") certifies that (1) the views expressed in this report accurately reflect my personal views about all of the subject companies and securities and (2) no part of my compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed in this report.

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