# HDFx: A Novel Immunomodulator for the Amelioration of Hypovolemic Shock in the OR, Cancer Patients and on the Battlefield

## Altura BM[1-5*], Gebrewold A[1], Carella A[1] and Altura BT[1,3,5]

[1]Department of Physiology and Pharmacology, The State University of New York Downstate Medical Center, Brooklyn, New York, USA

[2]Department of Medicine, The State University of New York Downstate Medical Center, Brooklyn, New York, USA

[3]Center for Cardiovascular and Muscle Research, The State University of New York Downstate Medical Center, Brooklyn, New York, USA

[4]The School of Graduate Studies in Molecular and Cellular Science, The State University of New York Downstate Medical Center, Brooklyn, New York, USA

[5]Bio-Defense Systems, Inc, Rockville Centre, New York, USA

*Corresponding author: Altura BM. Department of Physiology and Pharmacology, The State University of New York, Downstate Medical Center, Brooklyn, New York, USA; Tel: 718 -270-2194; E-mail: baltura@downstate.edu

**Citation:** Altura BM. HDFx: A Novel Immunomodulator for the Amelioration of Hypovolemic Shock in the OR, Cancer Patients and on the Battlefield. J Clin Med Ther. 2016, 1:1.

## Editorial

As one of us has stated: "shock is a significant and sustained loss of effective circulating blood volume" [1]. It eventuates in the hypoperfusion of critical peripheral tissues, thus leading to a deficit in transcapillary-exchange function [2]. Clinically, there are five major types of circulatory shock: cardiogenic; septic; distributive; anaphylactic; and hypovolemic [1,3]. Hypovolemic Shock (HS) is, primarily, due to a marked decrease in venous return, falling arterial blood pressure, and ventricular preload, and usually is caused by hemorrhage, dehydration, excessive diarrhea, excessive fluid loss from severe burns, increased positive intrathoracic pressure, excessive urinary fluid loss resulting from diuretics, side-effects of many chemotherapeutic agents, or depressed vasomotor tone in the microcirculation [1-3]. Often, the sites of vasomotor tone failure are, primarily, found in the muscular venules of the microvascular tree [2]; i.e., these microscopic venous vessels either lose their ability to maintain a normal, partial contraction of the smooth muscle cells or become loaded with pooling of plasma and blood -formed elements (e.g., red blood cells, polymorphonuclear leukocytes, macrophages, and monocytes, platelets, etc.) [2,3,4]. Close microscopic examination of the postcapillaries and the muscular venules, *in situ*, in states of HS also reveal inflammatory-like responses with adhesion of leukocytes, platelets, and mononuclear elements to the endothelial cell walls [4-6]. Ongoing HS is characterized by increased plasma levels of numerous cytokines and chemokines with breaks in the postcapillary vessel walls and diapedesis of blood-formed elements, primarily leukocytes, monocytes, and macrophages [2,4-7]. These ongoing HS episodes, thus, lead to a greater and greater inflammatory component.

Although prevention and treatment of HS, particularly during- and post-surgery, over the past decade, has resulted in better management with whole blood, plasma, intravenous fluids, hygiene, and certain vasopressor drugs, it is often difficult to prevent morbidity and mortality, in numerous patients who present with blood-fluid loss in excess of 35% of the blood volume [8,9 ]. Unless HS patients can be managed quickly, and vital signs restored, this often leads to super-imposed infections which will result in septic shock and increased morbidity and mortality [3,9]. This very precarious situation is seen very often on battlefields.

One of the major consequences of wars/conflicts is loss of the ability to regenerate normal physiologic functions of numerous organs and tissues in the body, particularly when the blood/plasma volume exceeds 30%. Under these conditions of severe, prolonged HS, it becomes difficult to treat many chronic internal and external wounds resulting from assaults by superimposed bacterial microorganisms, fungi, and vectors. These superimposed assaults often result in sepsis and antibiotic resistance to other microorganisms, vectors, gangrene, and amputation of body parts. Such wounded troops in the presence of prolonged HS are, thus, at high-risk and particularly susceptible to slow healing and external, painful wounds.

For more than 50 years, our laboratories have been working on approaches to the HS syndrome that attack the problem from several points, namely

1. The design of new molecules that can pharmacologically manipulate the microvascular arterioles and muscular venules by promoting ceilings on vasoconstriction and restoring close-to near-normal microvascular tone [10-19].

2. The design of molecules that stimulate various arms of the mononuclear phagocytic system [3,15,17-30].

3. Searching for molecules that stimulate the innate immune system to ameliorate HS-induced inflammatory responses [31-35].

4. Searching for molecules that would reduce the need for large transfusions of blood, plasma and fluids on the battlefield [unpublished studies].

5. Searching for molecules, in the body, that prevent and stem super-imposed infections caused by "superbugs" found in many hospital environments [36].

6. Searching for molecules that accelerate wound healing after severe HS [33].

It has been our feeling ever since the Nobel Prize-winning studies of Elie Metchnikoff in the late nineteenth century and Walter B. Canon in the early 20th century, that the body might produce its own powerful host-defence factor(s) to defend itself against HS caused by severe blood/plasma loss in order to maintain homeostasis. Metchnikoff's early studies [38] pointed to the important contributions of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. Over the past three to four decades, considerable evidence has accrued to support a strong relationship to the functional (physiological) state of macrophages-phagocytes and Natural Killer (NK) cells , as well as "pit cells" in the liver to host defence and resistance to pathogens[ 31,32, 34-36, unpublished findings]. Our studies with T-lymphocytes and macrophages, obtained from animals subjected to various forms of HS, suggested that these cells could contribute both detrimental and protective molecules to the host's survival [31,32,36,37]. These findings are particularly important as both T-cells and macrophages have been linked to the development of continuing inflammatory conditions, atherogenesis, cytokine and chemokine production, alterations in vasomotor tone, and regulation of arterial blood pressure [3-7,39]. Moreover, the interaction of the T-cells and macrophages with the endothelial cells of the arteriolar and venular walls are known to result in the generation and release of vasorelaxant and vasoconstrictor molecules such as nitric oxide and endothelin [7,39].

Our laboratories, over the past several years have discovered a unique, new host-defence protein molecule (i.e., HDFx) found, so far, in the bodies of rodents, rabbits, guinea-pigs, dogs, and subhuman primates, which we believe may have the necessary attributes for ameliorating, preventing and combating the life-threatening effects of HS both in the OR and on the battlefield [31-37]. Its attributes include: the unique ability to restore tissue perfusion, restoration of near-normal vasomotor tone, prevention/amelioration of falls in arterial blood pressure, acceleration of wound healing, stimulation of the ability of macrophages, phagocytic leukocytes, platelets, mononuclear cells, and "pit cells" to engulf foreign particulate matter at increased volumes and rates, and reduce the need for total blood replacement after HS [31-37].

Early-on, in our studies [40], we hypothesized that the loss of functional macrophages and NK cells from the circulation might be a major reason for morbidity and increased mortality when animals and humans are either subjected to systemic insults such as massive HS (>30% blood/plasma loss), trauma , peripheral ischemic events, combined injuries (HS plus trauma or superimposed infections), battlefield wounds, a variety of chemotherapeutic agents, and high-risk surgeries(e.g., lung, cardiac); all of these insults will result in losses in immuno-competence. Using various, specific inhibitors, antibodies, and chemical agents, we found that depletion of only macrophages caused about a 75-80% of the loss in resistance of animals to various forms of experimental HS; the other 20-25% to loss of NK and "pit cells" [31]. Selective depletion of only polymorphonuclear leukocytes or monocytes when challenged with lethal HS -stressors exerted very little effects on mortality [31]. After a great many experiments, over several years, and thousands of animals, we were able to isolate a heat-labile protein of about 35-40 KDa, larger than known defensive peptides and much smaller than the larger MW fibronectins and complement products [31]. When highly-purified extracts (free of any endotoxins) of HDFx was given to rats, mice, guinea-pigs, rabbits, and subhuman primates, over several months, we could not detect any obvious pathologies in various organ regions [31]. However, highly-purified HDFx protected, to a large degree, these experimental animals from a variety of insults, including HS, trauma, bacterial infections, fungal infections, and combined injuries [31,32,34-37, unpublished findings]. In addition , HDFx stimulated macrophages and platelets to engulf more foreign particulate matter than normal and resulted in stimulation of NK cells and liver "pit cells" [31,35,36,37,unpublished studies]. To our knowledge, a molecule/peptide/protein that possesses these characteristics/qualities has not, as yet, been reported. Lastly, HDFx appears to possess remarkable actions on platelets, cytokine and chemokine release from lymphocytes, as well as regenerative properties that may account for a great deal of its recuperative powers [31,33,36,37].

Blood platelets are crucial in primary hemostasis [41]. They circulate continuously in the vascular compartment and serve to help repair injured epithelial and endothelial tissues [41]. Under pathological conditions such as HS, the needs for platelets often exceed the basal levels. When the latter takes place; the need for transfusions may become excessive. As of this writing, there are no real-substitutes available to replace platelets. Platelets contain diverse granules which contain many cytokines, chemokines, ATP, $Ca^{2+,}$ serotonin, platelet-derived growth factors, etc. Platelets can also act as a source of proteins and glycoproteins [41-45] and can ingest a variety of pathogens and interact with phagocytic cells such as macrophages [40-43]. In addition, platelets express important toll-like receptors, an array of direct antimicrobial peptides, and kinocidins [41,42]. Although it is thought that most of the explosive release of cytokines and chemokines released in HS states is derived from macrophages, lymphocytes, and mononuclear cells [39-44], evidence is accumulating that platelets may play a very significant role in these responses as well [41,42]. Interestingly, we have found that HDFx seems to preserve near-normal platelet volumes and functions in HS states [36]. In addition, using high-resolution TV-image intensification microscopy of in situ splanchnic, cutaneous,

skeletal muscle and cerebral areas of rats and mice, we have found that HS-induced alterations in platelet adhesion, coagulation, and emigration in the postcapillaries are greatly attenuated [31,32,36]. Moreover, HDFx prevents/ameliorates disseminated intravascular coagulation induced by severe and prolonged HS [31-32,36-37].

In summary, our findings, so far, demonstrate that we have discovered a naturally-occurring biologic protein which possesses very unique characteristics and qualities not seen in any protein, heretofore, to our knowledge. HDFx ameliorates morbidity and mortality induced by a variety of HSs and agencies which result in circulatory shock, falls in arterial blood pressure, and hypoperfusion of critical organ regions. In addition, and not to be minimized, is HDFx's ability to accelerate wound healing and preserve platelets and their physiologic functions.

The development and judicious use of HDFx in the OR, in cancer patients treated with a variety of chemotherapeutic agents, and on the battlefield should result in better quality of life, and the saving of many lives, as well as the decreased morbidity and mortality of troops on the battlefield. An added boon, and not to be minimized, is the potential use of HDFx in veterinary clinics and hospitals as well as zoos.

## Acknowledgement

## References

1. Altura BM, Lefer AM, Schumer W (1983) Handbook of Shock and Trauma. Raven Press, New York 1: 1.

2. Suteu I, Bandila T, Cafrita A, Bucur A, Candea V (1977) Shock: Pathology, Metabolism, Shock Cell Treatment. Abacus Press, England.

3. Altura BM (1983) Endothelium, reticuloendothelial cells, and microvascular integrity: Roles in host defense. In: Handbook of Shock and Trauma, Raven Press, New York 1: 51-95.

4. Majno G, Joris I (2004) Cells, Tissues and Diseases. Oxford University Press, New York.

5. Baue AE (1990) Multiple Organ Failure. Patient Care and Prevention. Mosby Year Book, Inc St Louis.

6. Kumar V, Abbas AK, Aster JC (2015) Robbins and Cotran Pathologic Basis of Disease. (9th edn.), Elsevier Saunders, Philadelphia, pp: 131-135.

7. Feuerstein GZ, Libby P, Mann DL (2003) Progress in Inflamation Research: Inflammation and Cardiac Diseases. Birkhauser Verlag, Basel.

8. Hershey SG, Altura BM (1973) Vasopressors in low-flow states. In: Pharmacology of Adjuvant Drugs. (1st edn.), Clinical Anesthesia Series, Zauder HL, FA Davis Co, Philadelphia, pp: 31-76.

9. Shoemaker WC, Ayres S, Grenvik A, Holbrook PR, Thompson WL (1989) Textbook of Critical Care. (2nd edn.), WB Saunders Co, Philadelphia.

10. Altura BM, Hershey SG, Mazzia VDB (1966) Microcirculatory approach to vasopressor therapy in intestinal ischemic (SMA) shock. Am J Surgery 111: 186-192.

11. Hershey SG, Altura BM, Orkin LR (1968) Therapy of intestinal ischemia (SMA) shock with vasoactive drugs. Anesthesiology 29: 466-471.

12. Altura BM, Hershey SG (1968) Structure-activity relationships of neurohypophyseal polypeptides in the microcirculation: A molecular basis for shock therapy. In: Intermedes Proceedings 1968: Combined Injuries and Shock. Schildt B, Thoren L. Almqvist and Wiksell, Stockholm, pp: 247-259.

13. Altura BM, Hershey SG (1972) A structure-activity basis for vasotropic therapy in shock. In: Adv Exp Med Biol 21: 399-408.

14. Altura BM, Altura BT (1974) Peripheral vascular actions of glucocorticoids and their relationship to protection in circulatory shock. J Pharmacol Exp Ther 190: 300-315.

15. Altura BM (1976) DPAVP: A vasopressin analog with selective microvascular and RES actions for the treatment of circulatory shock in rats. Eur J Pharmacol 37: 155-168.

16. Altura BM (1976) Microcirculatory approach to the treatment of circulatory shock with a new analog of vasopressin, [2-phenylalanine, 8-ornithine]-vasopressin. J Pharmacol Exp Ther 198: 187-196.

17. Altura BM (1976) Sex and estrogens in protection against circulatory stress reactions. Am J Physiol 231: 842-847.

18. Altura BM (1980) Reticuloendothelial and neuro-endocrine stimulation in shock therapy. Adv Shock Res 3: 3-25.

19. Altura BM (1985) Microcirculatory regulation and dysfunction: Relation to RES function and resistance to shock and trauma. In: The Reticuloendothelial System, Reichard SM, Filkins JP. Plenm Press New York 7: 353-395.

20. Hershey SG, Altura BM (1966) Effects of pretreatment with aggregate albumin on reticuloendothelial system activity and after experimental shock. Proc Soc Exp Biol Med 122: 1195-1199.

21. Altura BM, Hershey SG (1967) Use of reticuloendothelial phagocytic function as an index in shock therapy. Bull NY Acad Med 43: 259-266.

22. Altura BM, Hershey SG (1968) RES phagocytic function in trauma and adaptation to experimental shock. Am J Physiol 215: 1414-1419.

23. Hershet SG, Altura BM (1969) Function of the reticuloendothelial system in experimental shock and combined injury. Anesthesiology 30: 138-143.

24. Altura BM, Hershet SG (1970) Effects of glycerol trioleate on the reticuloendothelial system and suevival after experimental shock. J Pharmacol Exp Ther 175: 555-564.

25. Altura BM, Hershey SG (1972) Sequential changes in reticuloendothelial system function after acute hemorrhage. Proc Soc Exp Biol Med 139: 935-939.

26. Altura BM (1974) Hemorrhagic shock and reticuloendothelial system phagocytic function in pathogen-free animals. Circulatory Shock 1: 295-300.

27. Altura BM (1975) Glucocorticoid -induced protection in circulatory shock: Role of reticuloendothelial system function. Proc Soc Exp Biol Med 150: 202-206.

28. Altura BM, Gebrewold A (1980) Prophylactic administration of antibiotics compromises reticuloendothelial system function and exacerbates shock mortality in rats. Eur J Pharmacol 68: 19-21.

29. Altura BM (1980) Recent progress in patho-physiology of shock: reticuloendothelial and neuro-endocrine stimulation. Jap J Clin Anesth 4: 745-758.

30. Altura BM (1982) Reticuloendothelial system function and histamine release in shock and trauma: relationship to microcirculation. Klin Wochenschr 60: 1021-1030.

31. Altura BM, Gebrewold A, Carella A (2009) A novel biologic immunomodulator, HDFx, protects against lethal hemorrhage, endotoxins and traumatic injury: potential relevance to emerging diseases. Int J Clin Exp Med 2: 266-279.

32. Altura BM, Gebrewold A, Carella A (2011) HDFX: a novel biologic immunomodulator is therapeutically-effective in hemorrhagic and intestinal ischemic shock: importance of microcirculatory-immunological interactions and their implications for the warfighter and disaster victims. Int J Clin Exp Med 4: 331-340.

33. Altura BM, Carella A, Gebrewold A (2012) HDFx: a novel biologic immunomodulator accelerates wound healing and is suggestive of unique regenerative powers: potential implications for the warfighter and disaster victims. Int J Clin Exp Med 5: 289-295.

34. Altura BM, Gebrewold A, Carella A, Altura BT (2016) HDFx: A potential new treatment and prophylactic against nonalcoholic steatohepatitis (NASH) and subsequent hepatocellular carcinomas: Is hypomagnesemia a complication of the disease? J Alcoholism Drug Depend 4: 1000e133.

35. Altura BM (2016) HDFx: A novel immunomodulator for the potential amelioration of drug-resistant tuberculosis.

36. Altura BM (2016) HDFx: A novel immunomodulator and potential superbug super-warrior for hospitalized patients and battlefield casualties. Int J Vaccines and Research 3: 1-3.

37. Altura BM, Gebrewold A, Carella A (2016) HDFX: A recently discovered biologic and its potential use in prevention and treatment of hemorrhagic fever viruses and antibiotic-resistant superbugs. J Hematol Thromboembolic Dis 4: 1000252.

38. Metchnikoff E (1884) Untersuchung ueber die intracellular Verdauung beiwirbellosen Thieren . Arbeiten aus dem Zoologischen Institut zu Wien 5: 141-168.

39. Murphy K, Weaver C (2017) Janeway's Immunology. (9th edn.). Garland Science.

40. Altura BM (1980) Reticuloendothelial cells and host defense. Adv in Microcirculation 9: 252-294.

41. Michelson AD (2013) Platelets. (3rdedn), Academic Press, New York.

42. Zapata JC, Cox D, Salvato MS (2014) The role of platelets in the pathogenesis of viral hemorrhagic fevers. PLoS Negl Trop Dis 8: e2858.

43. Garraud O, Hamzeh-Cognasse H, Cognasse F (2012) Platelets and cytokines: How and why? Transfusion Clin Biol 19: 104-108.

44. Mekaj YH (2016) The roles of platelets in inflammation, immunity, wound healing and malignancy. Int J Clin Exp Med 9: 5347-5358.

45. Gavins FNE, Stokes KY (2016) Vascular responses to Pathogens. Academic Press, London.