Clinical Research and Trials

Short Communication ISSN: 2059-0377

HDFx: A novel biologic immunomodulator may have the potential to prevent bacteria in space from becoming aggressively infectious and lethal

Burton M. Altura[1-6*], Asefa Gebrewold[1], Anthony Carella[1] and Bella T. Altura[1,3-6]

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

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

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

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

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

[6]Orient Biomedica, Estero, Florida, USA

Recent studies and experiments from several groups indicate that several, different types of bacteria (e.g., *E. coli, S. enteriditis, S.typhimurium, and S. aureus*) as well as the fungus *Aspergillus* fumigatus become many times more virulent in space than on Earth [1-7]. They also grow faster, mutate more readily, become more infectious, and become more resistant to antibiotics [1,7,8], thus posing potential hazards to astronauts and space-travelers. Already, from several space missions, particularly at the space station, astronauts have (and are) responding in unexplained ways [1,7-9]. Soviet-era astronauts in the 1960s- 1970s showed that *Staphylococcus microorganisms* aboard their spacecrafts demonstrated increased resistance to at least five common antibiotics [10-12]. Zea and his colleagues have found that *E.* coli grew 13-times faster on the space station than on Earth [7]. Overall, such data indicate that physiologic alterations of normally, non-lethal bacteria and viruses in space may change the health of astronauts in unpredictable manners during space voyages between planets, asteroids, and stars.

Here on Earth, a disturbing trend in antimicrobial resistance of both gram-negative and gram-positive pathogens and "superbugs" has seriously complicated the treatment of many immune-compromised, hospital patients [13- 20]. Too this problem, one must add the numerous hospitalizations and deaths from contaminated meats, poultry, vegetables, seafoods, and dairy products [21-23]. Almost one million people per year are killed by bacteria and "superbugs" due to antimicrobial resistance. If we add the untold millions per year who are dying from drug-resistant tuberculosis in Africa and India, the number of deaths becomes staggering. By about 2075, the number of people dying from drug-resistant infections could reach in excess of 35 million per year. But, if contaminated astronauts and future space travelers would return to Earth harboring the "super, super-bugs", developed in space, we could see a worldwide new series of global plagues.

For more than five decades, our laboratories have been working on a new approach to develop host-defense factors that stimulate various arms of the innate and adaptive immune systems [24-38]. To this end, we have discovered a new host-defense factor, termed "HDFx", that is a conserved protein found in mice, rats, guinea-pigs, rabbits, dogs and sub-human primates [39-44]. More than 135 years ago, Elie Metchnikoff, the great father of immunology, hypothesized that the body, under stressful conditions, might produce powerful immune-stimulants which perforce would act on different arms of the innate immune system and serve to protect against insults and diseases [45]. Metchnikoff's early studies pointed to the important contributions of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. Over the past 40 years, considerable evidence has accumulated to support a strong relationship between the functional (physiologic) state of the microcirculation, macrophages-phagocytes, natural killer (NK) cells, the reticuloendothelial system (RES), and "pit cells" in the liver to host defense and resistance to pathogens, trauma, circulatory shock, infections, and combined injuries [39-44,46-49].

A number of experimental studies, from our laboratories, have clearly shown that HDFx is protective (to different degrees) against a variety of systemic bodily insults ranging from hemorrhage, trauma, endotoxins, a variety of lethal bacteria (e.g., *E.coli, S.enteriditis, C.welchii, S.aureus, among others*), combined injuries, centripetal forces, septic shock, and several infectious fungal organisms (e.g., *A. fumigatus*) [39-44,48,49]. Interestingly, HDFx was found to be protective under normal Earth gravity conditions against the same superbugs i.e., bacteria and fungi) found to grow abnormally and become more infectious in environments seen on the space station and under zero-gravity [39,42,43,49]. A unique attribute of HDFx is that it can accelerate wound healing [41], and it has protective qualities even in diseases such as nonalcoholic steatohepatitis (NASH) which often results in liver carcinomas [48]. We have suggested that many of HDFx's attributes make it very likely to be protective in the treatment and amelioration of hemorrhagic fever viruses [42].

It appears, worldwide, that many hospitalized patients die of common and once treatable diseases, such as pneumonia and blood (septic) or urinary tract infections [13-20]. Today, it is difficult to

Correspondence to: Professor Burton M. Altura, Department of Physiology & Pharmacology, State University of New York Downstate Medical Center, Brooklyn, New York, USA, Tel: 718-270-2194; E-mail: baltura@downstate.edu

Received: May 08, 2017; **Accepted:** May 19, 2017; **Published:** May 22, 2017

undertake major surgical procedures or chemotherapy without the use of antibiotics, as patients die afterwards from infections [13-20]. Gram-negative and fungal superbugs seem to be the major culprits in most of these patients (e.g., mutated *E.coli, S.enteriditis, S.aureus, A.fumagatus)* in these patient deaths [13-20]. Gram-negative bacteria appear to be more difficult to kill than gram-positive bacteria because they are protected by "double membranes". So, in order to kill the gram-negative bacteria, most of the pharmacological approaches have been to design antibiotics to penetrate these membrane barriers. In our opinion, another more likely approach would be to engulf the bacteria (and fungi) and digest them within macrophages, Kupffer cell macrophages, phagocytic leukocytes, platelets, NK cells, and "pit cells". But, in order for these cells to access the bacteria and fungi, we believe the microcirculation to key organs (*i.e.,* liver, spleen, lungs) must perforce have optimal capillary blood flow and distribution. Therefore, an ideal drug or therapeutic modality would be one that could stimulate multiple arms of the innate immune system coupled to modulation of optimal (and enhanced) microcirculatory blood flows in the aforementioned key organ systems. So far, HDFx appears to be the *only* molecule that combines these qualities and demonstrates therapeutic attributes against several classes of "superbugs" and fungal microorganisms [39-43,48,49].

We believe the approaches outlined in the above, using HDFx or its derivatives, could be the ideal drug (s) to pretreat all astronauts and space travelers scheduled for travel to the moon, planets, asteroids, and stars in order to prevent susceptibility to enhanced virulence of bacteria, fungi, and other micro-organisms created by zero-gravity and deep-space conditions.

A major objective of our group is to secure adequate funding to elucidate the complete, complex molecular structure of HDFx and then via genetic engineering to produce large quantities of HDFx for further testing in human subjects and animals under zero-gravity and deep-space conditions to confirm our hypothesis.

Acknowledgements

Some of the original studies and thoughts needed for the discovery of HDFx and reviewed above, were initiated while some of the authors were at New York University School of Medicine and The Albert Einstein College of Medicine of Yehiva University. Some of the original studies and experiments reviewed, above, were supported, in part, by unrestricted grants from several pharmaceutical companies (CIBA-GEGY Pharmaceuticals, Sandoz Pharmaceuticals, The UpJohn Company, and Bayer Pharmaceuticals), Research Grants from The N.I.H, as well as anonymous donors. The authors are indebted to numerous colleagues, over many years, who helped to make our studies and background experiments possible: Professor S.G. Hershey, Professor L.R. Orkin, Professor V.E. Amassian, E.W. Burton, J.Hanley, and C.Parillo, among others too numerous to name here.

References

1. Wilson JW, Ott CM, zuBentrup KH, Ramamurthy R, Quick L, et al. (2007) Space flight alters bacterial gene expression and virulence and reveals a role for global regulationHfq. *Proc Natl Acad*USA 104: 16299-16304.
2. Vukanti R, Model MA, Leff LG (2012) Effect of modeled reduced gravity conditions on bacterial morphology and physiology. *BMC Microbiol*12: 4.[Crossref]
3. Nickerson CA, Ott CM, Wilson JW, Ramamurthy R, Pierson DL (2004) Microbial responses to microgravity and other low-shear environments. *Microbiol Mol Biol Rev* 68: 345-361.[Crossref]
4. Crabbe A, Pycke B, van Houdt R, Monsieurs P, Nickerson CA, et al. (2010) Response of Pseudomonas aeruginosa PAO1 to low shear modeled microgravity involves AlgU regulation. *Environm Microbiol* 12: 1545-1564.
5. Sarker SF,Ott CM, Barilla J, Nickerson CA (2010) Discovery of spaceflight-related virulence mechanisms in Salmonella and other microbial pathogens: Novel approaches to commercial vaccine development. *Gravitational and Space Biol* 23: 75-78.
6. Yamaguchi NY, Roberts M, Castro S, Oubre C, Makimura K, et al. (2014) Microbial monitoring of crewed habitats in space-Current status and future perspectives. *Microbes Environm* 29: 250-260.
7. Zea L, Prasad N, Levy SE, Stodieck L, Jones A, et al. (2016) A molecular genetic basis explaining altered bacterial behavior in space. *PLoS ONE* 11: e0164359.
8. Juergensmeyer MA,Juergensmeyer EA, Guikema JA (1999) Long-term exposure to spaceflight conditions affects bacterial response to antibiotics. *Microgravity Sci Technol* 12: 41-47.[Crossref]
9. Borchers AT, Keen CL, Gershwin ME (2002) Microgravity and immune responsiveness: implications for space travel. *Nutrition* 18: 889-898.[Crossref]
10. Zhukov-Verezhnikov NN, Mayskiy IN, Yazdovskiy VI (1963) Problems of space microbiology and cytology. *Probl Space Biol* 1: 133-155.
11. Klemparskaya NN (1964) Effect of the conditions of cosmic flight on the dissociation of Escherichia coli. *J Bacteriol* 186: 8207-8212.
12. Novikova ND (2004) Review of the knowledge of microbial contamination of the Russian manned spacecraft. *Microb Ecol* 47: 127-132.
13. Gaynes R, Edwards JR; National Nosocomial Infections Surveillance System (2005) Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 41: 848-854.[Crossref]
14. Blossom DB, McDonald LC (2007) The challenges posed by reemerging Clostridium difficile infection. *Clin Infect Dis* 45: 222-227.[Crossref]
15. Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK (2009) Methicillin-resistant Staphylococcus aureus central line-associated bloodstream infections in US intensive care units. *JAMA* 301: 727-736.
16. Lee JH, Jeong SH, Cha SS, Lee SH (2009) New disturbing trend in antimicrobial resistance of gram-negative pathogens. *PLoS Pathol* 5: e1000221.
17. Kuehn BM (2007) Antibiotic-resistant "superbugs" may be transmitted from animals to humans. *JAMA* 298: 2125-2126.[Crossref]
18. Holden MT, Hauser H, Sanders M, Ngo TH, Cherevach I, et al. (2009) Rapid evolution of virulence and drug resistance in the emerging zoonotic pathogen Streptococcus suis. *PLoS One* 4: e6072.[Crossref]
19. Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS (2016) Antimicrobial Resistance. *JAMA* 316: 1193-1204.[Crossref]
20. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, et al. (2016) Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *N Engl J Med* 375: 1081-1089.[Crossref]
21. Anonymous (2009) Preliminary foodnet data on the incidence of infections with pathogens transmitted commonly through food-10 states, 2008. *MMWR* 158: 333-337.
22. Maki DG (2009) Coming to grips with foodborne infection-Peanut, butter, pepper, and Nationwide Salmonella outbreaks. *N Engl J Med* 360: 949-953.
23. Schiller LR (2009) Infectious disease: A germy world-food-borne infections in 2009. *Nat Rev Gastroenterol Hepatol* 6: 197-198.[Crossref]
24. Altura BM (1983) Endothelium, reticuloendothelial cells, and microvascular integrity: Roles in host defense. In: Handbook of Shock and Trauma Altura BM, Lefer AM, Schumer W (Eds)Raven Press, New York 1: 51-95.
25. Altura BM (1976) DVAVP: A vasopressin analog with selective microvascular and RES actions for the treatment of circulatory shock in rats. *Eur J Pharmacol* 37: 155-168.
26. 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.
27. Altura BM (1976) Sex and estrogens in protection against circulatory stress reactions. *Am J Physiol* 231: 842-847.[Crossref]
28. Altura BM (1980) Reticuloendothelial system and neuro-endocrine stimulation in shock therapy. *Adv Shock Res*3: 3-25.[Crossref]
29. 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 (Eds) Plenum Press, New York 7: 353-395.

30. 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.

31. Altura BM, Hershey SG (1967) Use of reticuloendothelial phagocytic function as an index in shock therapy. *Bull N Y Acad Med* 43: 259-266.[Crossref]

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

33. Hershey SG, Altura BM (1969) Function of the reticuloendothelial system in experimental shock and combined injury. *Anesthesiology* 30: 138-143.[Crossref]

34. Altura BM, Hershey SG (1970) Effects of glyceryl trioleate on the reticuloendothelial system and survival after experimental shock. *J Pharmacol Exp Ther* 175: 555-564. [Crossref]

35. Altura BM, Hershey SG (1972) Sequential changes in reticuloendothelial system function after acute hemorrhage. *Proc SocExpBiol Med* 139: 935-939.

36. Altura BM (1975) Glucocorticoid-induced protection in circulatory shock: role of reticuloendotheilial system function. *Proc Soc Exp Biol Med* 150: 202-206.[Crossref]

37. 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.

38. Altura BM (1982) Reticuloendothelial system function and histamine release in shock and trauma: relationship to microcirculation. *Klin Wochenschr* 60: 882-890.[Crossref]

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

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

41. 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.

42. 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: 100252.

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

44. Altura BM, Gebrewold A, Carella A, Altura BT (2016) HDFx: A novel immunomodulator for the amelioration of hypovolemic shock in the OR, cancer patients and on the battlefield. *J Clin Med Ther*1: e002.

45. Metchnikoff E (1884) Untersuchungueber die intracellulare Verdauungbe wirbellosen Thieren. Arbeitenausdem Zoologischen. *Istitutzu Wien*. 5: 141-168.

46. Baue AE (1990) Multiple Organ Failure. Patient Care and Prevention. Mosby Yearbook, Inc, St Louis.

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

48. Altura BM, Gebrewold A, Carella A, Altura BT (2016) 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: 10000e133.

49. Altura BM (2017) HDFx: A novel immunomodulator for the potential treatment of drug-resistant tuberculosis. Submitted.

Copyright: ©2017 Altura BM. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.