

HDFx: A Novel Immunomodulator and Potential Superbug Super - Warrior for Hospitalized Patients and Battlefield Casualties

Editorial

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Over the past decade, a disturbing trend in antimicrobial resistance of both gram-negative and gram-positive pathogens and "superbugs" has seriously complicated the treatment of many immuno-compromised, hospitalized patients [1-8]. To this major problem must be added the numerous hospitalizations and deaths from contaminated meats, poultry, vegetables, seafoods, and dairy products [9-11]. Government resources, worldwide, are being overstretched and often remain powerless to combat these assaults on our populations. 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. Each year, in the USA alone, more than 150 million prescriptions are written, 60% of which are for antibiotics. Of these, it has been estimated that 50 million of these costly prescriptions are probably unnecessary [12]. Added to this is the ever-growing and soaring worldwide use of antibiotics in agriculture. How much of this indiscriminate use of antibiotics is contributing to the ever-growing resistance of pathogens to antibiotics noted above?

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. 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, and sub-human primates [13-16]. We assume it is also present in humans since it is a conserved molecule. More than 135

years ago, Elie Metchnikoff, the great father of immunology, hypothesized that the body, under stressful circumstances, might produce powerful immuno-stimulants which would act on different arms of the innate immune system and serve to protect against major insults and diseases [17]. 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 30-40 years, considerable evidence has accumulated to support a strong relationship between the functional (physiological) state of the microcirculation, macrophages-phagocytes, natural killer (NK) cells, the reticuloendothelial system, and "pit cells" in the liver to host defense and resistance to pathogens, trauma, circulatory shock and combined injuries [18-25].

Recent 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. enteritidis*, *C. welchii*), combined injuries, centripetal forces, and septic shock [13-16]. A unique attribute of HDFx is that it can accelerate wound healing [15], and it has protective qualities even in diseases such as nonalcoholic steatohepatitis (NASH) which often results in liver carcinomas [26]. We have suggested that HDFx might be useful in the treatment and amelioration of hemorrhagic fever viruses [16].

In the past few years, many hospitalized patients have died of common and once treatable bacterial diseases, such as pneumonia, and blood (septic) or urinary tract infections [1-8]. Today, it is difficult to undertake major surgical procedures or chemotherapy

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without antibiotics, as patients die afterwards from infections [1-8]. Gram-negative superbugs seem to be the major culprits in most of these patient deaths [1-8]. 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 approaches have been to design antibiotics to penetrate these membrane barriers. In our opinion, another likely approach would be to engulf the bacteria and digest them within macrophages, Kupffer cells, phagocytic leukocytes, platelets, and NK cells. But, for the latter to occur, we believe that the microcirculation to key organs, namely the liver, spleen, and lung must perforce have optimal capillary blood flow and distribution. Therefore, an ideal drug or therapeutic molecule would be one that could stimulate multiple arms of the innate immune system coupled to modulation of 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 bacterial "superbugs" [13-16].

For millennia, diseases and non-combat injuries have resulted in the vast majority of lost combat days in the battlefield. During the Mexican (1845-1848) and Spanish-American (1898) wars disease-related deaths outnumbered battlefield deaths by seven to one [27]. During recent wars in Vietnam (1969-1975), Iraq (2001-present) and Afghanistan (2001-present), American and UN coalition forces have continued to demonstrate a mounting number of diverse diseases in battlefield troops which have taken great tolls in morbidity and mortality despite improved transportation, treatment, hygiene, and new advances in management [27, 28]. Many of the infections produced by a variety of microorganisms, parasites, and vectors such as pneumonia, Q fever, brucellosis, tuberculosis, and malaria have become antibiotic- and drug-resistant and exhibit superimposed infections with *Acinetobacter* species [27-30]. In addition, many of the warfighters exhibit gastroenteritis, prolonged diarrhea, and drug-resistant respiratory infections. Inadequate treatment often results in loss of body parts, amputations, and disfigurements. Many of these men and women on return to the USA, and other native countries, require prolonged hospitalization, and treatment often at great cost without restoration to normalcy. The uniqueness of HDFx to accelerate wound healing [15] and promote tissue regeneration [15] should greatly aid treatment and recovery of our warfighters.

We believe the approaches outlined in the above, using HDFx or its derivatives, could be the ideal drug(s) to pretreat all patients scheduled for major surgeries and given post-surgery to prevent lethal infections by a variety of "superbugs".

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 diverse pathophysiological and battlefield conditions, including infections produced by "superbugs".

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