

## Could HDFx, a Recently -Discovered Biologic Immunomodulator that Accelerates Wound Healing, Ameliorate Complications after Orthopedic Surgeries?

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Various types of common orthopedic surgeries (e.g. hip replacement, knee replacement, rotator cuff surgeries, etc) are usually safe procedures when performed in modern hospitals, but are not without potential complications [1,2]. Among the latter are found blood clots, bleeding, lung congestion, infections of diverse kinds, stiffness and scarring, implant loosening, hip dislocation (for those with hip replacement), and thromboembolic complications [1,2]. To minimize blood clots in the large veins of the legs and pelvis (i.e. deep venous thrombosis, or DVT, which can take place after surgery, blood thinner medication is usually started and lasts for several weeks. If a clot develops, it could travel to the lungs causing a pulmonary embolism, which can be lethal. A high-risk after orthopedic surgeries, particularly among elderly patients, is pneumonia. After orthopedic surgery, there is also a risk for infections and hospital-borne (nosocomial) infections which can be caused by “superbugs”. Such patients are often started on various antibiotics which often fail to stem the infection(s) due to the presence of “superbugs”. After surgery, the body’s natural response is to form scar tissue, thus often making the joint replacement stiff [1,2]. Can these major risky occurrences (some life-threatening), post-surgery, be ameliorated or prevented?

### Discovery of HDFx, an Immunomodular and Wound Healing Accelerator

For approximately the past 40 years, our laboratories have been working on new approaches to develop host-defense molecules as well as molecules that would accelerate wound healing. It has been our belief that biologic molecules that could stimulate various arms of the innate and adaptive immune systems might be pivotal in host-defense and wound healing. To this end, we have discovered HDFx, a heretofore unknown host-defense factor found in all mammals so far investigated (i.e. mice, rats, guinea-pigs, rabbits, dogs, and sub-human primates) [3-7]. Since it is a conserved molecule, we assume it is present in people as well. HDFx appears to possess unique wound healing and regenerative properties, potentially making it very useful during and after major surgeries [5]. About 135 years ago, Elie Metchnikoff, the father of immunology, hypothesized that the body, under stressful conditions, would manufacture/release molecules that could stimulate different arms of the innate immune system and serve to protect the host against major insults and diseases [8,9]. Metchnikoff’s early studies pointed to the importance of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. Approximately 50 years ago, one of us found that adaptation to lethal trauma, using rodents, produced a factor (i.e. molecule) in the blood of the surviving animals that could be transferred to naïve animals, so as to prevent lethality in control

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rodents subjected to lethal body trauma [10]. A short time thereafter, we found that this factor, obtained from the traumatized surviving rodents, could confer a cross-tolerant immunity to naïve rats and mice subjected to hemorrhagic, intestinal ischemic, and endotoxic forms of lethal shock [11-19]. Further investigation in our laboratories, over a number of years, led us to discover that this heretofore unknown biologic factor, which we termed “HDFx”, could manipulate the microcirculation and the macrophage-immune system [4,5,17-19]. During these past 30 - 40 years, a considerable body of evidence, obtained on animals and human subjects, has demonstrated a strong relationship between the functional (physiological) state of the microcirculation, macrophages-leukocytes, natural killer (NK) cells, the reticulo-endothelial system, and “pit cells” in the liver to host-defense and resistance to pathogens, trauma, circulatory shock, and sepsis [10-24].

### HDFx Protects Against Blood Loss, Endotoxins, Infectious Microorganisms and “Cytokine Storms”

Numerous studies in our laboratories have clearly shown that “HDFx” is protective (to varying degrees) against a variety of systemic bodily insults ranging from hemorrhage, trauma, combined injuries (e.g. hemorrhage plus bacterial infections, and hemorrhage plus trauma), endotoxins, a variety of lethal bacteria (i.e., *E. coli*, *S. enteritidis*, *C. welchii*, among others), fungi (e.g., *Aspergillus fumigatus*), and centripetal forces to septic shock [4-8, unpublished findings]. An important attribute of HDFx is its unique ability to protect against “cytokine storms” in animals that become septic [25,26]; “cytokine storms” are clearly known to be a major cause of lethality in hospitalized patients and patients after major surgeries such as orthopedic repairs in patients who become infected with numerous microorganisms (various bacteria and fungi) and who often become resistant to antibiotic treatment [24]. To our knowledge, no host-defense factor, other than HDFx, can stem “cytokine storms”, seen in sepsis, brought about via diverse microorganisms in antibiotic-resistant subjects. Septic shock caused by severe bacterial /fungal infections account for about 10% of all human deaths in the U.S.A. each year. It should be pointed out, here, that use of HDFx in animals subjected to 30 - 35% blood loss produces survival and more rapid healing than in control subjects [4-6, unpublished findings], an attribute that would, at least theoretically, allow patients subjected to major surgeries (i.e. orthopedic procedures) to recover more quickly with reduced risk of difficult-to-treat infections.

### HDFx and Super-Superbugs

Gram-negative “superbugs” seem to be the major culprits in many hospitalized patients [24]. Gram-negative bacteria are 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 therapeutic approaches have been to design antibiotics to penetrate these membrane barriers [24]. In our opinion, another logical approach would be to engulf the bacteria and digest (neutralize) them within “supercharged” macrophages, Kupffer cells, phagocytic leukocytes, splenic macrophages, alveolar macrophages, and NK cells. HDFx appears, at least experimentally, to possess the ability to “supercharge” these phagocytic cells in all mammals we have investigated so far [4,5,19,25,26, unpublished findings]. But, for this kind of “supercharging” action to effectively, and expeditiously, take place, we believe the microcirculation in the various regional vascular beds (i.e. lungs, spleen, liver, splanchnic tract) must perforce produce optimal blood flows and capillary distribution of nutritive blood flows. Fortunately, HDFx possesses unique vasoactive properties which act to do exactly the latter in the microcirculation [4,5]. To our knowledge, no other known host-defense factor, besides HDFx, can accomplish these tasks under septic conditions.

### Conclusions

We have discovered a new host-defense biologic immunomodulator which may provide unique ways to ameliorate and prevent hospital-borne infections and accelerate wound healing processes thus reducing hospital stays, cutting hospital costs, and preventing the need for additional surgeries after various types of orthopedic procedures. Use of HDFx in elderly patients should result in fewer infections, less pain on recovery, much less uncontrolled bleeding, fewer clots and emboli. as well as less stiffening of joints, and less large scarring after orthopedic surgeries.

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