

Public Abstract

Armed Forces Institute of Regenerative Medicine-Warrior Restoration Consortium

With better body armor in use in contemporary warfare, the heightened prevalence of serious extremity injury on the battlefield has increased requirements to treat, reconstruct, and rehabilitate Wounded Warriors suffering massive tissue loss. Patients typically have multiple injuries, which may include damage to skin, muscle, nerve, blood vessels, bone, and connective tissues. Regenerative medicine encompasses many novel approaches to the treatment of damaged tissues and organs by using therapies that promote the self-regenerative capacity of the body. Furthermore, integrating cells with other technologies may help create engineered tissues and organs for therapeutic use. These innovations are possible because of several key advances, including the development of systems that can reliably induce progenitor and stem cell proliferation and differentiation, the discovery of growth factors that control tissue morphogenesis, and derivation of biomaterials and scaffolds that can guide tissue regeneration and reconstruction. Regenerative medicine technologies present many opportunities for the treatment of combat-related traumatic injury. Therapies developed by the AFIRM II program are intended to aid traumatically injured Wounded Warriors. To address these important needs, the Armed Forces Institute of Regenerative Medicine Warrior Restoration Consortium (AFIRM-WRC) has been formed from the two successful consortia of AFIRM I—the Wake Forest Pittsburgh Consortium and the Rutgers Cleveland Clinic Consortium—as well as new investigators and is dedicated to repairing battlefield injuries through the use of regenerative medicine technologies and associated sciences.

Program Description

One of the goals of AFIRM-WRC is to position promising technologies and therapeutic/restorative practices for entrance into human clinical trials. This will be done with basic through translational regenerative medicine research and development including basic scientific research, development of animal models, preclinical studies required for initiation of FDA-regulated human clinical trials, and Phase I – II human clinical trials. To do this, we have assembled an expert team from over 30 academic institutions and industry partners to satisfy the objectives of the AFIRM II. We have assembled an experienced, diverse team of medical and scientific professionals in an outcome-driven environment that efficiently designs, tests, compares, and evaluates discoveries leading to the selection of promising technologies for translation to investigational human studies.

The Warrior Restoration Consortium will address the five focus areas identified as areas of need to help the wounded warrior. The five focus areas to be addressed are (1) Extremity Regeneration, (2) Craniomaxillofacial Regeneration, (3) Skin Regeneration, (4) Genitourinary/Lower Abdomen Reconstruction, and (5) Composite Tissue Allotransplantation and Immunomodulation

It is envisioned that integration of basic science, translational and clinical research efforts will be necessary to advance effective regenerative medicine treatments for combat-related injuries. We also will actively seek out and establish partnerships with industry to ensure that the technical innovations emerging from the research will transition into clinical applications and result in FDA approved treatments. In addition we intend to collaborate with Government laboratories and Medical Centers/Medical Treatment Facilities including the Army, Navy, Air Force, NIH and the VA.

AFIRM-WRC is uniquely positioned to meet and exceed the military's vision of translating advances in regenerative medical science to soldiers who have sacrificed their health and fitness in service to our country.

1) Experience in translating regenerative medicine advances to patients: During AFIRM I, our team members have successfully brought AFIRM funded technologies to hundreds of patients. The AFIRM team's experience in translational regenerative medicine has provided us with valuable experience in designing and implementing animal and clinical trials as well as industrial partnering to shepherd intellectual property to the marketplace and the patient.

- 2) A history of working on military-centered trauma problems in regenerative medicine and established collaborations with Military Treatment Facilities:** During AFIRM I, we have conducted clinical trials with military treatment facilities at all the major services including the Army, Navy, and Air Force
- 3) Internationally recognized depth and breadth in the regenerative medicine field:** Members of AFIRM-WRC are internationally recognized as thought leaders in regenerative medicine as evidenced by their record of peer-reviewed funding and publications across the spectrum from cellular therapies to tissue engineering and biomaterials to device-assisted tissue regeneration and clinical trials. Members of AFIRM-WRC were instrumental in founding and leading the Tissue Engineering and Regenerative Medicine International Society (TERMIS), currently lead or have lead the highest impact journals and meetings in the regenerative medicine field, and have served as advisors in the launching of regenerative medicine efforts around the world.
- 4) Substantial investments in infrastructure and personnel to establish co-localized expertise in regenerative medicine:** AFIRM-WRC members have dedicated and modern facilities that co-locate collaborative teams specifically focused on regenerative medicine problems. Within these facilities are the support equipment and personnel (e.g. histological support, animal facilities) that are required for the kind of multidisciplinary efforts that characterize regenerative medicine. AFIRM-WRC members have secured funding to establish and build their regenerative medicine institutes. This investment has come from private philanthropy, university coffers, and peer-reviewed funding and has been in place for a long enough period of time to allow maturation of both efforts. Investment in this AFIRM would build upon an established base of operations unmatched in the regenerative medicine field.
- 5) Clinician-scientists make up a significant portion of the AFIRM team:** AFIRM-WRC focuses on directly meeting clinical needs. Both have leadership trained and engaged in translational approaches across the spectrum from basic science and bioengineering to clinical science. The culture of both institutions fosters interdisciplinary approaches to address the multifaceted aspects of regenerative medicine.

Mission

The Armed Forces Institute of Regenerative Medicine will deliver to the Armed Forces regenerative medicine-based technologies that will lead to functional and aesthetic recovery from injuries incurred in military service. The Institute will combine the efforts of the nation's leading experts in regenerative medicine into a team whose efforts span from research and development to clinical translation, implementation and commercialization. The focus of the Institute will be centered on alleviating the trauma profile that is currently experienced by our armed forces, with therapies aimed at addressing extremity and craniofacial trauma, skin and genitourinary injuries, and allotransplantation.

Vision

The Armed Forces Institute of Regenerative Medicine will become the international leader in developing restorative therapies for battlefield trauma. By partnering with health professionals in the Armed Forces, AFIRM will act as a catalyst to bring advances from the nation's leading regenerative medicine laboratories to the soldier. AFIRM will integrate its expertise with military clinical research efforts to form teams that develop and implement solutions for tissue deficits that restore function and, where relevant, cosmetic appearance. AFIRM will bring to bear a portfolio of research activities in its efforts. The research team has a history of clinical translation and collaboration on military-centered projects. As a result of this experience there are identifiable technologies that will be ready for clinical translation early in the life of the Institute. AFIRM is also comprised of experts whose laboratories are developing the science that will ultimately bridge the technological gaps that prevent the implementation of complex tissue generation and replacement. From these laboratories will come the advances which will allow progressively more complex tissue replacement strategies to be implemented and evaluated. AFIRM fully expects to draw in researchers and companies that are not currently part of the team as resources and needs dictate.

Operational AFIRM will serve as: 1) the military's source for regenerative medicine technologies, 2) a training facility to develop experts in the treatment of trauma with regenerative medicine, 3) a resource where military health care professionals can find expertise and collaborators to engineer solutions to identified needs in tissue replacement, and 4) a nexus through which industrial and academic partners in the field of regenerative medicine can pair with AFIRM and military professionals to develop and implement healing strategies.

Summary of Academic, Corporate and Government Team Members

Over the last five years, a team has been built that could respond, when called, to the challenge of delivering regenerative medicine technologies to soldiers. The team brings together the two consortia of AFIRM I and combines them with a broad coalition of leading academic partners and companies that have the resources and experience to deliver on the commitments being made. AFIRM-WRC has cemented a series of partnerships with 31 institutions which add substantial breadth and depth to our teams. Working together we will focus on five areas of research.

Extremity Regeneration

The high incidence of severe battlefield injuries to the extremities involving bone, muscle, nerve, vasculature, and other connective tissues is well recognized. Better body armor and improved lifesaving procedures have contributed to the increase in wounded warrior patients surviving with severely traumatized limbs. Although limb salvage efforts have also improved, composite tissue regeneration treatment strategies that provide effective restoration of limb function remain a highly significant and unmet clinical need. In current practice, wounded warriors often undergoing multiple surgeries to achieve limb salvage only to eventually elect for limb amputation to gain back a higher level of compromised function. We clearly need better options for these patients.

The overall objective of the extremity regeneration program is to restore function to severely traumatized limbs. Clinical manifestations of limb trauma take various forms, including compartment syndrome, peripheral nerve damage, volumetric muscle loss, ischemic injury, large bone defects, and post-traumatic osteoarthritis. A comprehensive set of 14 projects focused on the regeneration and functional restoration of nerve, muscle, blood vessels, cartilage, and bone have been selected through a rigorous peer review process to meet this objective. Many of the proposed projects include enabling technologies that may enhance therapeutic options for multiple tissue types within extremities.

Craniofacial Program

Craniofacial trauma is among the most debilitating forms of injury facing civilian and military populations due to the important aesthetic and functional role of the craniomaxillofacial complex. Blast injuries and injuries from high velocity projectiles, such as those encountered on the battlefield, present a range of therapeutic challenges and often require a staged repair. A significant need exists for the development of novel regenerative medicine approaches for the generation of both soft and hard tissues to overcome the current clinical barriers to craniomaxillofacial reconstruction. The Craniofacial Reconstruction Program comprises a multidisciplinary, multi-institutional collaborative research team to address the core issues associated with traumatic injuries to the craniomaxillofacial complex. Drawing on the strengths of each investigator on the team, an optimal set of complementary technologies have been identified to achieve hard and soft tissue regeneration.

The primary focus of the projects within the Craniofacial Reconstruction Program is the development and timely clinical translation of the respective technologies to meet the needs of the Wounded Warrior. Towards this end, the projects proposed represent an interdisciplinary and complementary portfolio of technologies to effect regeneration of injured soft and hard tissues of the craniomaxillofacial complex. These projects collectively seek to regenerate both hard and soft tissues to repair the injured craniomaxillofacial structures and, more importantly, to restore function, thereby facilitating a return to duty and restoration of quality of life. The

soft tissue focus areas of the program involve the regeneration of nerve, muscle, fat and vascular tissues and, more critically, on the combination of these various tissues in functional, vascularized and viable units for treatment of the Wounded Warrior. Additional projects within the program focus on the regeneration of the hard tissues of the craniomaxillofacial complex. These projects focus on bone regeneration within the context of the known complexities of battlefield injuries to enable the development and translation of technologies specifically designed to overcome the challenges associated with these injuries, including compromised vascularity, complex geometries and infected or scarred wound beds. Collectively, these projects provide complimentary translatable technologies for the regeneration of the various soft and hard tissues of the craniomaxillofacial complex, with the vision that various technologies may be ultimately integrated, as needed, to address the complexities of composite tissue injuries.

Skin Regeneration Program

Battlefield polytrauma secondary to blasts and explosions is increasingly common in combat zones with 45,000 US soldiers having been wounded in the Iraq and Afghanistan wars, affects multiple body sites, and is especially complex when involving the face, hands, and feet. Many of these injuries, but particularly burns, induce progressive tissue damage over subsequent days. Although respiratory distress is often the critical issue immediately after burn injury, skin loss becomes the major problem within the first 24 hours. Disruption of the skin barrier results in fluid and heat loss, and a predisposition to infection. Progressive extension of burns during the first few days after injury compounds these problems. During this time, mid- to deep-partial thickness burns often extend to become full-thickness burns with resultant increased tissue loss, longer healing times, and excess morbidity and mortality. Over the long-term, burn progression results in increased scarring, wound contractures, and poor quality of life, because the magnitude and the severity of the injury literally increases. Anti-inflammatory therapies, such as nonsteroidals (NSAIDs), anti-prostaglandin agents, and antioxidants, have shown no substantial benefit in preventing these adverse events. Burn and battle injury progression, wound infection and inflammation, delays in grafting, and grafting with inadequate material such as widely meshed autograft, all can lead to increased scarring with the possibility of severe wound contractures.

First and foremost, our Program Philosophy is to clinically deliver, in an accelerated manner, new technologies aimed at improving the outcomes for Wounded Warriors, which is centered on responding to and addressing areas of military need. Secondly, our Program Philosophy assumed that maximum gain in research comes from synergy created among diverse research groups. Therefore, for the Skin Regeneration Program we selected a diverse group of investigators with both basic science and clinical backgrounds (Burn Surgery, Plastic Surgery, Craniofacial Surgery, Dermatology, Allergy/Immunology, and Dermatology) from a diverse group of institutions, including the US Army. In every instance, the collaborative effort improves the research plan, and the interaction of investigators with diverse backgrounds accentuates research implementation through the synergy of expertise.

Genitourinary and Pelvis Reconstruction Program

Pelvic and urogenital injuries account for the majority (86%) of urologic injuries incurred during recent US armed conflicts. It is likely that in spite of improved protective gear, the incidence of injuries to the pelvis, its organs, anal canal and external genitalia due to fragmentation devices such as improvised explosive devices (IEDs) will increase. Most of the injuries are extensive and cause major damage to the tissues and organs in the pelvis often resulting in dysfunction of the entire anal and urogenital system. These wounds require immediate care and management. Damage to the external genitalia results in loss of tissue and ultimately dysfunction of the penis, urethra and testes leaving the wounded soldiers with anatomical and psychological dysfunction. In young men this can be debilitating.

Injuries to the bladder can lead to permanent disability as a result of obstructive uropathy, vesicoureteral reflux or scar formation. Damage to the anal sphincter and pelvic floor can leave the soldier with permanent incontinence or colostomy which results in a reduced quality of life. Extensive damage to penile tissue can lead

to loss of sexual function and affect the passage of urine. Damage to the testis can result in infertility and the need for testosterone administration. Although most of the injuries occur in male soldiers; the technology used in some of the projects can be applied to both genders as well as the civilian population.

The AFIRM II philosophy is dedicated to repairing battlefield injuries through the use of regenerative medicine technologies and associated sciences. The projects in this section deal in genitourinary, pelvic and anal reconstruction of injuries that occur due to blast injuries. Specifically the projects deal with reconstruction of the anal canal/sphincter, perineal tissue, bladder, testes, urethra, and genitals. On a broader note the data and therapies generated in these studies can be applied to civilians for various other injuries sustained to the pelvic region and for various other age-related dysfunctions and diseases.

Composite Tissue Allotransplantation Program

Extremity and craniofacial injuries account for the majority of combat wounds sustained by service members in military conflicts throughout the twentieth century. Close to 40% of all combat injuries sustained in OEF and OIF involved severe extremity and craniofacial trauma. Currently, despite the best reconstructive efforts by using native tissues, these injuries frequently result in permanent disfigurement and morbidity. In addition, morbidity from extensive surgery, prolonged rehabilitation, and escalating costs of multiple procedures further compromise outcomes. For most devastating combat injuries for which conventional reconstruction is not feasible or optimal, composite tissue allotransplantation (CTA) has become a viable and immediately available alternative to reconstruct such challenging defects. Over the past decade, close to 85 upper extremity and 24 facial transplants have been performed with highly encouraging outcomes. However, the required life-long use of multiple immunosuppressants and their associated toxicities remains one of the primary obstacles that curtail the wider use of CTA for reconstruction. These risks and side effects greatly compromise recipient quality of life and jeopardize the potential benefits of CTA.

Thus, *the central challenge for the field of CTA is to develop novel immunomodulatory treatment or tolerance strategies to regulate rather than to globally suppress the host's immune system, thus achieving minimization or complete avoidance of immunosuppression.* Such strategies will not only abrogate the negative outcomes of long-term immunosuppression but also extend the benefits of these life-enhancing procedures to a wider patient population including our wounded warriors. The proposed research in this CTA program capitalizes on a comprehensive portfolio of immunomodulatory concepts, some of which have already been shown to be clinically successful in solid organ and bone marrow transplantation. Successful completion of this program will provide the most promising avenues to achieve tolerance in CTA, and deliver distinct therapies to aid wounded warriors as well as traumatic injuries in the civilian sector. In addition, the lessons learned with regard to the fundamental mechanisms of immunomodulation and tolerance in this program could have broad implications beyond transplantation and for other immune mediated diseases such as infection, inflammation, autoimmune disorders or cancer.

Turning Today into Tomorrow

Regenerative medicine offers profound hope to countless trauma victims but the treatments of today are still targeted toward sacrificing future function to save lives. Delivering on the hope and avoiding the hype will be the focus of the AFIRM. Just as important as the research AFIRM is composed of senior investigators and surgeons who have treated military patients in close collaboration with their colleagues in the military and VA healthcare systems. The group understands that their military patients desire to continue service, to be as physically active as possible, and to live long and productive lives free of pain or disability. In addition, the newly developed technologies and treatment concepts during AFIRM will significantly benefit the many civilian patients requiring reconstruction subsequent to devastating injuries.