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Review Article

Use of a Novel, Advanced Surgical Extracellular Matrix Promotes Tissue Regeneration, Augments Wound Healing, and Improves Patient Outcomes

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Abstract

Wound healing is a complex, dynamic process that can be negatively impacted by patient factors, despite appropriate medical management. As the population ages and becomes increasingly burdened by medical comorbidities known to complicate the body's innate healing ability, the use of advanced surgical extracellular matrix (ECM) particulates that simultaneously promote tissue regeneration and prevent infection is paramount. The purpose of this article is to discuss the complex process of wound healing, as well as to identify and address areas of concern. The product XCelliStem® is a multitissue platform (MTP) graft composed of 45% biphasic collagen and 55% unique bioactive molecules from an ECM source. To the author's knowledge, XCelliStem® is the only product that can appropriately intervene and augment the various pitfalls associated with wound healing, ultimately promoting tissue regeneration to a degree in which other products fall short. It would stand to reason that use of a surgical ECM containing a high concentration of unique bioactive proteins with a multifaceted ability to augment the healing process would reduce the healthcare burden associated with poor wound healing and improve patient outcomes overall.

Introduction

Chronic, nonhealing wounds are considered a silent epidemic in the United States [1]. Affecting 1 in 6 Medicare beneficiaries, or 10.5 million people, these ailments cost an estimated $22.5 billion each year [1]. In addition, over 90 million patients undergo a surgical operation in the United States each year, and with every incision created, a wound is simultaneously created [2,3]. For these reasons, wound care expenditure in the US is substantial, with annual costs exceeding $148 billion [4]. Wound healing is a dynamic process occurring in four set stages and involving a complex interplay of multiple cell types and mechanisms. Disruption to any part of the wound healing process increases patient risk for surgical site infection (SSI) and surgical site complications (SSC), such as seroma and nonhealing wounds. Components that commonly alter or disrupt the wound healing process can be intrinsic or extrinsic. Intrinsic factors are patient dependent and include medical comorbidities such as diabetes mellitus, peripheral artery disease, kidney disease, obesity, and advanced age. Extrinsic factors commonly include smoking, alcoholism, and the presence of foreign materials, such as hardware or mesh. While this list is not exhaustive, all variables have the potential to disrupt wound healing despite appropriate medical management, contributing to poor outcomes, increased and prolonged pain, as well as excessive and unnecessary healthcare related costs. US census data estimates that the elderly population will surpass 94.7 million by 2060, suggesting that wound healing aberrancies will become an increasingly relevant issue in the coming years [5]. In an aging population with nearly 40 million individuals suffering from type 2 diabetes mellitus, data suggests that a considerable portion of the US population is at an increased risk for the patient specific and healthcare associated consequences of dysfunctional wound healing postoperatively [5,6]. Dynamic wound care solutions that augment tissue regeneration and reduce rates of infection are a promising strategy for patients at high risk for poor wound healing and the associated complications. The purpose of this article is to discuss the complex process of wound healing, as well as to identify and address areas of concern. The product XCelliStem® is, to the author's knowledge, the only product that can appropriately intervene and augment the various pitfalls associated with wound healing, ultimately promoting tissue regeneration to a degree in which other products fall short. XCelliStem® is a multitissue platform (MTP) graft composed of 45% biphasic collagen and 55% unique bioactive molecules from an extracellular matrix (ECM) source. Another emerging organ derived matrix is liver extracellular matrix (LEM). As the body's

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only fully regenerative organ, the liver produces an ECM that is also uniquely rich in bioactive components, and the author anticipates that LEM will appear with increasing frequency in the literature. Collagen matrices dynamically interact with the wound bed and are able to stimulate ECM deposition by providing a scaffold that supports growth. In the past, ECMs were thought to operate solely as a structural framework; however, recent research shows that the bioactive proteins such as elastin, laminin, fibronectin, as well as a plethora of various growth factors, possess extensive cell signaling abilities for spatiotemporal modification of a multitude of cells. Following placement into a wound, ECMs modulate the inflammatory immune response and stimulate mononuclear cell infiltration at the site, thereby initiating, accelerating, and augmenting the complex process of tissue repair and remodeling, even in infected wound beds [7]. Most ECM matrices currently in practice are typically from single tissue sources and contain less than a 10% concentration of biomolecules; therefore, they are unable to generate the robust immune and stem cell differentiation, modulation, mobilization, and proliferation as is seen with use of XCelliStem®. By aiding the healing process, minimizing bacterial colonization, and reducing scarring, XCelliStem® has been shown to effectively manage orthopedic trauma wounds, even in the setting of contaminated wound fields, avascular structures, hardware, and exposed bone and tendon. To the author's knowledge, there is no other intervention that enhances the tissue's innate wound healing ability by providing high concentrations of the constituents integral to the healing process directly to the wound site. It would stand to reason that use of a surgical ECM matrix containing a high concentration of unique bioactive proteins with a multifaceted ability to augment the healing process would reduce the healthcare burden associated with poor wound healing and improve patient outcomes overall.

The Role of Collagen and ECM Biomolecules in Wound Healing

Wound healing is a complex, involved process that occurs in four stages: coagulation and hemostasis; inflammation; proliferation; and remodeling. The early stages of inflammation are characterized by an M1 macrophage, proinflammatory phenotype, where macrophages work to clear debris, amplify the host immune response, and recruit proinflammatory cytokines to the wound bed. During the proliferation stage, a phenotypic change to the M2 macrophage phenotype decreases inflammation, directing focus toward tissue healing and regeneration. At this time, fibroblasts produce collagen, fibronectin, and proteoglycans. These ECM components work alongside other proteins and molecules to establish new granulation tissue, effectively replacing the fibrin scaffold and reepithelializing damaged tissue for wound closure [8]. Chronic, nonhealing wounds are characterized by persistent inflammation that fail to progress into or through the proliferation stage. This imbalance can be measured in different ways, one of which is an increased M1 (proinflammatory) to M2 (antiinflammatory) ratio [9]. Failure to generate granulation tissue in the proliferation phase not only delays healing but increases the risk of infection in multiple ways: first, the wound remains exposed and is more susceptible to bacterial colonization; second, without vascularized granulation tissue, bacteria are less effectively cleared by immune cells. This failure to progress can occur secondary to poor fibroblast activity or destruction of the ECM, both of which limit collagen bioavailability to the wound site. Fibroblast migration and proliferation at the wound site is required for tissue formation, repair, and remodeling. Fibroblasts themselves depend on growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) for signal transduction. These growth factors play a complex, involved role in each of the four stages of wound healing [10]. FGF plays a critical role in angiogenesis, granulation, ECM formation, and tissue reepithelization of the wound. Multiple studies have shown that the FGF family is able to improve cell proliferation ability, promote ECM synthesis, increase blood supply to the wound, establish and accelerate growth of granulation tissue, and maintain tissue repair and regeneration.11 One study found that FGF-1 markedly increased the amount of fibroblasts and capillaries in the wound body of diabetic foot ulcers, ultimately improving healing of ulcerated tissue [12]. Proangiogenic growth factors EGF and VEGF play a similar role, and have been shown to increase supply of both oxygen and nutrients to damaged tissue. EGFs also have a unique ability to stimulate both proliferation and differentiation of specific stem cells required for tissue reconstruction. Formation of granulation tissue and tissue reepithelialization is also accomplished by EGFs, which initiate the migration of vascular endothelial cells, keratinocytes, fibroblasts [10]. Studies have shown that aging of the stromal tissues is associated with dysfunctional wound healing ability, primarily due to the significantly reduced proliferative life span and early onset senescence of fibroblasts [13]. Additionally, Cialdai and colleagues found that high glucose levels inhibit the ability of fibroblasts to migrate to the wound site, properly remodel the ECM, and adequately support neoangiogenesis for newly developing tissue [14]. In an aging population with nearly 40 million individuals suffering from type 2 diabetes mellitus, the results of these studies would suggest that over 11% of the population is at an increased risk for dysfunctional wound healing postoperatively [15]. Collagen bioavailability is also limited following damage and destruction of the ECM, which can occur when concentrations of elastase and matrix metalloproteins (MMPs) surpass those of their inhibitors. Elastase degrades elastin, an ECM protein responsible for the elastic properties of tissue, and also converts MMPs into their active, collagen degrading form. Furthermore, elastase has a high affinity for the triple helix portion of endogenous collagen and is able to bind and degrade it [16]. These activities explain why the ratio of elastase and MMPs to collagen is elevated in chronic, nonhealing wounds. Application of wound dressings containing collagen can help balance this elevated ratio, acting as a substrate for both elastase and MMPs. This maintains the ECM and allows wound healing to progress with the production of new granulation tissue. Collagen production and activity within granulation tissue is high, and literature shows that wounds failing to develop appropriate granulation tissue demonstrate delayed progression and increased susceptibility to infection [17]. When applied exogenously, collagen augments the healing process by ensuring healthy granulation tissue deposition during the proliferative phase. Following application of collagen to a wound, proteases such as collagenases and matrix metalloproteinases hydrolyze the protein into soluble amino acid peptides. The resultant activated collagen peptides support a multitude of cellular activities associated with granulation, angiogenesis, and ultimately, re-epithelialization [18,19]. Interestingly, a study from George Washington University demonstrated that collagen powder alone was equally as effective as primary closure with nonabsorbable sutures in the management of patients undergoing skin biopsy. Das and

colleagues found that skin graft patients receiving collagen based dressings showed improved healing and better postoperative pain scores throughout recovery than patients receiving conventional paraffin gauze dressing. The authors stated that collagen dressings confer an observable antiinflammatory, antifibrotic, angiogenic, and analgesic effect [20]. These characteristics ultimately reduce the risk of infection, minimize pain and discomfort for the patient, promote early mobilization, and reduce analgesic dependence, saving healthcare related time and resources [21]. Collagen dressings are primarily composed of sheet collagen, which is ideal for epidermal coverage, epithelial migration, and temporary wound closure. Cellular activity and proliferation is highest with keratinocytes, early fibroblast behavior, and initial activity of endothelial cells. This functions as a protective barrier to the wound and improves mechanical integrity of the wound bed. Porous collagen is collagen that has been processed into a three dimensional (3D) wound matrix that supports granulation, neovascularization, and dermal regeneration. Cellular activity is much more dynamic and is greatest among 3D fibroblasts, which deposit new collagen and ECM and promote granulation tissue formation; endothelial cells, which generate capillary sprouts within the scaffold to facilitate angiogenesis; macrophages, which regulate inflammation and tissue remodeling; and mesenchymal stem cells. If collagen dressings composed primarily of sheet collagen confer substantial wound healing benefits in multiple parameters, it would stand to reason that biphasic ECM wound matrices composed of both sheet and porous collagen would exert an even greater regenerative response on injured tissue. The ECM is composed of over 300 different protein types, which can be isolated into fragments by enzymatic degeneration from an organ source. These fragments have substantial effects on the wound environment and exert a dynamic, synergistic effect on tissue repair. The regenerative capacity of ECM was demonstrated in a study by Williams and colleagues, which showed that in vitro administration of cardiac ECM to postnatal cardiomyocytes, which do not proliferate past the neonatal period, demonstrated cellular expansion [22]. A more common source of ECM fragments includes decellularized urinary bladder matrix (UBM), which has been shown to increase the proliferation and migration of perivascular stem cells, particularly in injury environments, to augment the healing process overall [23,24]. UBM is an ECM scaffold derived from the basement membrane or lamina propria of urinary bladder, a single tissue source. UBM primarily provides structural support and has demonstrated efficacy in wound healing through constructive remodeling; however, LEM may provide enhanced bioactivity due to retained cytokines, adhesion molecules, and basement membrane components, which can promote rapid cellular infiltration, differentiation, and neovascularization. This could be particularly advantageous in chronic or nonhealing wounds where signaling deficits impair normal repair cascades. Therefore, it would stand to reason that use of ECM scaffolds derived from multitissue platforms (MTP), such as dermis, fascia, and other connective tissue layers, would provide the wound site with a wider array of bioactive molecules and amplify the regenerative capacity of the tissue to an even greater extent.

Surgical Site Infection

Surgical site infections (SSIs) are a disastrous complication with a substantial impact on both patient and healthcare system alike. In addition to a 3% mortality rate, SSIs carry an 11-fold increase in patient morbidity [25]. The American College of Surgeons and Surgical Infection Society states that standard treatment of SSIs costs up to $10 billion each year, increases hospitalization costs by $20,000 per admission, and extends hospital length of stay by 9.7 days. In addition, SSIs are difficult to fully eradicate and require over 90,000 readmissions per year, contributing to over $700 million in ancillary treatment costs [26]. Patients with preexisting medical comorbidities, such as type 2 diabetes mellitus, are at higher risk for poor wound healing and SSI [27]. This patient demographic is anticipated to reach 1.31 billion worldwide by 2050, increased from approximately 424.9 million in 2017 [28]. High glucose levels, a common feature in poorly managed diabetics, inhibit the ability of fibroblasts to migrate to the wound site, properly remodel the ECM, and adequately support neoangiogenesis for newly developing tissue [14]. Delays in remodeling increase the tissue's susceptibility for bacterial colonization, and literature has shown that chronic wound infections are deficient in collagen due to impaired generation of granulation tissue [29]. This patient population would benefit from treatments that increase the amount and availability of the bioactive molecules required for wound healing. Collagen provides a biological matrix that promotes and supports fibroblast migration, keratinocyte attachment, and angiogenesis, ultimately accelerating granulation and epithelialization. By reducing the amount of time the wound remains open, bacterial colonization is mitigated and infection is reduced. In addition, collagen aids in maintaining sterility of a surgical site due to its innate resistance to bacteria and intrinsic ability to combat infection [30]. Nowrouzi and colleagues evaluated the effect of activated collagen (AC) applied subcutaneously prior to wound closure. The result of the study was a significant decrease in overall SSI rate with use of AC (AC SSI=0.63%, Non-AC SSI= 1.52%, p=.012), a significant decrease in SSI rate in clean cases (AC SSI=0.30%, Non-AC SSI=0.97%, p=.027), and a trend towards decreased SSI rate in clean contaminated cases (AC SSI=1.54%, Non-AC SSI=3.36%, p=.064). Overall, the use of activated collagen in patients undergoing elective surgery resulted in a significant, 59% reduction in SSI rate, particularly notable in the clean cases which demonstrated a 69% decrease. The study also found that minimum inhibitory concentration studies of activated collagen applied in vitro not only demonstrated decreased growth of gram positive bacteria, but actually arrests gram positive bacterial growth with a zone of inhibition comparable to vancomycin [18]. These results support research by Lima and colleagues, who found that hydrolyzed collagen demonstrated antibacterial activity against one gram positive bacterium, Staphylococcus aureus, and two gram negative bacteria, Escherichia coli and Bacillus subtilis, in all three tests [31]. The authors hypothesized that the observable immune benefit is due to collagen activity during the inflammation phase, where soluble fragments of activated collagen recruit macrophages and other types of immune cells that remove microbes and devitalized tissue from the wound site [18]. Similar, more pronounced results have been observed with application of biological scaffolds composed of ECM. Porcine derived ECM composed of small intestinal submucosa (SIS) has been successfully used as a resorbable biological scaffold due to tissue engineering properties and deliberate resistance to bacterial infection. In vitro studies of the ECM degradation products contained within SIS-ECM and urinary bladder submucosa-ECM possess antibacterial activity against gram positive Staphylococcus aureus and gram negative Escherichia coli [32]. Brennan and colleagues found that LEM also possessed antibacterial activity against S. aureus and E.

coli, suggesting that antibacterial activity is a common feature of all ECMs. LEM offers a meaningfully different biological profile compared to matrices derived from UBM and SIS, particularly in its biochemical diversity and retained functional proteins. While UBM and SIS are well characterized structural scaffolds composed predominantly of collagen types I and III, LEM contains a broader spectrum of collagen subtypes, including IV and VI, alongside a richer array of matricellular proteins, glycoproteins, and endogenous growth factors. This reflects the highly metabolic and regenerative role of the liver, potentially offering a more instructive microenvironment for cell signaling, angiogenesis, and tissue remodeling. The authors stated that the progressive in vivo degradation and remodeling of an ECM bioscaffold by host tissues may permit slow release of antimicrobial peptides, ultimately yielding a sustained antibacterial effect at the application site. These findings suggest that ECM biological scaffolds would be beneficial in cases at high risk for bacterial contamination, such as in preventing implant infection, as they confer immediate antibacterial protection while host inflammatory responses and humoral immune responses are still in the process of activation [33]. ECM materials, such as UBM and SIS, have demonstrated the ability to modulate macrophage phenotype toward a pro-remodeling (M2) state, and are able to support bacterial clearance indirectly through restoration of host tissue function. LEM may extend these benefits by providing a denser repertoire of bioactive cues, such as basement membrane components and retained cytokine binding domains, that help reestablish cellular communication disrupted by infection. Additionally, certain ECM degradation products, such as cryptic peptides, generated during remodeling have been reported to possess antimicrobial and chemotactic properties. These findings suggest that a more compositionally complex source, like LEM, could enhance these effects. In the case of XCelliStem® specifically, release of specific ECM bactericidal peptides allows for the simultaneous reduction of microbial load while fostering a regenerative environment for wound healing. This feature provides a positive solution to wound healing in contaminated, infected environments. Noah and colleagues observed this effect in a five patient case series, where three of the five patients presented with infected abdominal wall mesh. XCelliStem® was applied directly to each wound bed and covered with an oil emulsion sheet between the superficial dry dressing layer. Three of three patients with infected mesh resolved and healed completely, negating the need for mesh removal surgery. This is a notable finding, as the literature shows that nearly 73% of mesh infection cases require explantation in abdominal wall hernias [34]. The authors concluded that the combination of antimicrobial activity with the regenerative capacity of ECM biomolecules contained within XCelliStem® fosters infection control and drives lasting tissue repair, potentially negating the need for surgical management. Application of XCelliStem® has the potential to mitigate surgical debridements and mesh explantation rates, reduce healthcare associated expenditure, and improve the healing process in patients with high risk, infected wounds [35].

Postoperative Seroma

Seroma formation is a surgical site complication (SSC) occurring secondary to decelerated angiogenesis and epithelization during the second phase of wound healing. As a result, extensive soft tissue dissection occurs and leads to the creation of an anatomic dead space that collects serous fluid containing plasma and lymph [36,37]. The subsequent fluid collection is not only an undesirable complication in and of itself, but is also a nidus for bacterial proliferation that increases patient susceptibility to surgical site infection [38]. The incidence of seroma formation is procedure specific, occurring in up to 80% of breast surgeries, 78% of open hernia repairs, and 50% of laparoscopic hernia repairs [37,39]. Clinical presentation is also variable, as small seromas often resolve with conservative management, whereas resolution of larger, more severe seromas often require additional surgical interventions. The strongest management strategy is initial prevention of seroma formation, which can be accomplished by reducing inflammation, minimizing dead space, promoting fluid clearance, and increasing adherence of regenerating tissues. Application of collagen and ECM products provides the host's inflammatory cascade with a scaffold required for structural support and creates an environment that supports both tissue ingrowth and remodeling, effectively addressing each risk factor to provide a promising solution to postoperative seroma formation. In an animal study evaluating the application of porcine dermal collagen following mastectomy and axillary dissection, a procedure at high risk for seroma formation, seroma formation was inversely proportional to the amount of dermal collagen applied to the operative site. Furthermore, vascular proliferation and granulation tissue formation was higher in the dermal collagen group. The authors concluded that the reduction in seroma formation with application of porcine dermal collagen is achieved by increasing the adhesion, neovascularization, and granulation tissue, as well as filling in the dead space and accelerating the wound healing [40]. A retrospective review of 850 breast reconstructions reported that out of the 450 breast reconstructions using porcine acellular dermal matrices, a processed ECM scaffold derived from a skin source, only 12.2% cases were complicated by seroma formation [41]. This value is considerably lower than the average incidence of seroma formation following mastectomy or axillary lymphadenectomy, which can be as high as 80% [42]. A recent study by Creger and colleagues evaluated the effect of XCelliStem® Wound Powder when incorporated into wound closure of type III ventral hernias that necessitated an open repair with abdominal wall reconstruction [37]. This particular procedure is considered high risk, with a reported 78% seroma formation rate, a 42% hernia specific complication rate, and a 26% recurrence rate [39,43]. 97 patients were included in the study. Among the patients who did not receive XCellistem during closure, 49% developed a seroma or seroma related complication, whereas in the XCelliStem® group, only 4 patients developed a seroma or seroma related complication. The results of the study would suggest a statistically significant ($p=0.0042$) association between the use of XCelliStem® during closure and a reduction in seroma and seroma related complications [37].

Nonhealing Wound

Up to 3% of Americans over 65 years of age are suffering from an open wound at any given time, and chronic, nonhealing wounds cost an estimated $22.5 billion annually [1]. A wound is considered chronic or nonhealing when it does not progress appropriately within a predictable amount of time, or remains open after 12 weeks [44]. Nonhealing wounds remain arrested in the inflammatory phase of wound healing, failing to progress into the proliferative phase where healthy granulation tissue is generated, permitting approximation of wound margins. They are often characterized by an increased ratio of both M1:M2 macrophages, as well as elastase and MMPs to

collagen. Application of ECM and collagen to the wound site can create a shift from a proinflammatory environment to the antiinflammatory environment required for tissue regeneration. This is possible as ECM and collagen have been shown to support a multitude of cellular activities associated with granulation, angiogenesis, and ultimately, reepithelialization [18,19]. The summation of these activities explains why multiple studies have shown that application of activated collagen not only promotes wound healing, but prevents wound dehiscence, a complication that increases with delayed healing [45,46]. A meta-analysis of 961 patients showed that application of collagen dressings to nonhealing wounds was associated with a higher wound healing rate, as well as a higher healing velocity compared to the control group [47]. A recent case series evaluated the efficacy of a collagen matrix wound dressing containing partially denatured collagen, carboxymethyl cellulose, alginate, and ethylenediaminetetraacetic acid in chronic lower extremity ulcers. Carboxymethyl cellulose and alginate are implemented to enable greater absorptive capacity of collagen to wound layers, as well as to maintain moisture balance. Even with appropriate care, lower extremity ulcers are notoriously difficult to treat and highly likely to recur, subjecting patients to debilitating pain, impaired work productivity, and poor quality of life [48,49]. Diabetic foot ulcers (DFUs), specifically, are a leading risk factor for lower extremity amputation and markedly increase patient mortality rate within 5 years of presentation [50]. Furthermore, they are highly susceptible to superinfection with multiple strains of bacteria, often starting with gram positive strains, and as the wound becomes chronic, progressing to gram negative colonization with resultant tissue necrosis [50,51]. The wounds included in Alavi and colleague's case series were all characterized by complex local wound physiology and severe wound etiology, such as neuropathic ulcers and pyoderma gangrenosum. These patients also suffered from multiple medical comorbidities, further contributing to poor likelihood of resolution. Despite the presence of multiple risk factors, application of collagen was associated with an average wound size decrease of 73%, with two patients achieving full resolution at 8 weeks [49]. Literature shows that with standard therapies, only 32% of lower extremity ulcers heal after 12 weeks and 54.3% after 24 weeks, with an average treatment duration of 25 weeks [52]. Furthermore, duration increases by 28 days with each additional bacterial strain present within the ulcer [53]. The results of this study demonstrated marked improvement in healing times compared to standard therapy, suggesting that an advanced collagen matrix dressing represents a clinically effective, cost efficient, and safe treatment strategy for healing refractory chronic lower leg ulcers. Application of urinary bladder matrix (UBM), an extracellular matrix scaffold derived from the mucosa of porcine urinary bladder, showed similar results in both diabetic and nondiabetic patients with nonhealing wounds. The diabetic patients in this study were characterized by significantly elevated M1:M2 ratios prior to treatment. Paige and colleagues found that application of UBM was associated with significant ($p < 0.05$) wound size reduction in both patient groups, with the diabetic group showing a 35% ± 14% reduction and the non diabetic patients showing a 43% ± 18% reduction. Furthermore, significantly accelerated wound healing, measured by a reduction in the area of the wound, was observed in both groups. The elevated M1:M2 ratio observed in the diabetic patients was reduced to comparative levels in both patient groups following treatment with UBM [9]. This finding is supported by several animal and in vitro studies, which have shown that UBM increases concentrations of M2 macrophages, promoting tissue regeneration [54,55]. The results of this study would suggest that UBM provides a structural scaffold for cell migration, adhesion, and proliferation, while promoting and restoring an antiinflammatory state that is conducive for wound healing.

Over 150,000 patients require lower extremity amputation (LEA) in the United States each year, which include below knee amputation (BKA) and above knee amputation (AKA) [56]. As the population ages and the incidence of diabetes and peripheral vascular disease continues to rise, these procedures are expected to increase by 145% prior to 2060 [57]. The patient demographic requiring these procedures often suffer from multiple medical comorbidities and are at increased risk for surgical site complications due to poor wound healing. Both procedures, but particularly BKAs, are highly associated with a plethora of wound healing complications including superficial skin breakdown, complete stump dehiscence, recurrent osteomyelitis, and progressive ischemic insults [58]. All of the aforementioned complications typically require management with reoperation, including stump revision or further amputation; for this reason, some studies have shown that the 5 year mortality rate following LEA can be as high as 77% [59]. In a recent study, Creger and colleagues evaluated the effects of XCelliStem® Wound Powder applied during closure of LEA. In the control group, 35% of BKAs and 20% of AKAs required additional operations, resulting in an overall operative revision rate of 30.0%. In the XCelliStem® group, only 6.4% of BKAs required reoperation. The results of the study showed a 70% ($p=0.00058$) reduction in the need for reoperation in amputees receiving XCelliStem®, indicating that treatment with XCelliStem® improves healing and angiogenesis while reducing the incidence of superficial skin breakdown, stump dehiscence, and osteomyelitis [58].

A five patient case series by Noah and colleagues further supports the regenerative and antimicrobial properties of XCelliStem®. In the study, two of the five patients presented with a vulvar wound in an area that was previously irradiated and an enterocutaneous fistula. Radiation therapy has been hypothesized to disrupt the inflammatory and proliferative phases of wound healing, severely minimizing the tissue's capacity for neovascularization, reepithelization, and granulation tissue formation. As a result of decreased angiogenesis and collagen deposition, wound healing is often delayed, at increased risk for superimposed infection, and characterized by poor tensile strength [60]. Literature shows that wound healing complications after radiation therapy occurs in approximately 60% of surgical cases, but has even been shown to reach 100% in certain cases, and typically necessitates extensive reconstructive efforts [61, 62]. Direct application of XCelliStem® to the wound bed facilitated robust granulation and reepithelization, measured by complete closure and healing of the radiated vulvar wound and the enterocutaneous fistula, without surgical management. These results would suggest that use of XCelliStem® is an effective intervention to reduce healthcare associated expenditure and improve the healing process in patients with high risk, nonhealing wounds [35].

Case Examples

DAs the patient population ages and the incidence of medical comorbidities that promote dysfunctional wound healing continues to rise, research has shifted toward the development of advanced wound particulates with the ability to simultaneously

promote tissue regeneration and prevent infection. All current ECMs are 90% to 99% collagen, whereas XCelliStem® is composed of 45% collagen and 55% unique biomolecules. This is achieved by a unique process able to retain the biomolecules within spleen and lung ECM sources. By including a greater concentration of noncollagen proteins, such as laminin, elastin, fibronectin, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and hyaluronic acid, XCelliStem® provides additional binding sites and promotes chemotaxis in a manner that cannot be achieved by other ECM tissues. The result of this increased concentration is robust, site appropriate tissue remodeling that promotes accelerated restoration of healthy tissue. Multiple sources have shown that XCelliStem® is able to improve and hasten wound healing, as well as reduce rates of infection and seroma formation.

Diaz-Valadez and colleagues evaluated the effects of intraoperative XCelliStem® application in 10 cases of complex postsurgical abdominal wall wounds. These wounds all required surgical debridement and were characterized by substantial tissue necrosis, panniculectomy dehiscence, or locations of hardware removal. At a median time of 2.5 weeks, complete healing was achieved in all patients without complication. Histological studies demonstrated adequate fibroblast activity, new collagen deposition, and neovascularization, consistent with a remodeling neutrophil and antiinflammatory macrophage response. This supports prior literature regarding ECM treated tissues, which demonstrated increased functional remodeling with decreased fibrosis and granuloma formation, as well as increased laminar collagen, with an antiinflammatory M2 macrophage predominance on histological examination [63]. Treatment with XCelliStem® alone was found to be more than adequate for wound healing, as patients in the study did not necessitate wound center visits, nurse visits, home wound care, antibiotics, or negative pressure devices. As a result, patients were spared from managing cumbersome wound care equipment, travel considerations to wound clinics, and home intrusions from members of the healthcare team. The authors concluded that use of XCelliStem® was associated with improved clinical results and an observable cost benefit compared to negative pressure treatment [64].

Two case studies have demonstrated the efficacy of XCelliStem® in promoting tissue regeneration and healing within ischemic and necrotic tissues. Wounds characterized by poor perfusion or ischemia are deprived of oxygen, nutrients, and growth factors required for healing; as a result, the healing demands of the tissue cannot be met and the risk of dehiscence and infection is markedly increased [65].

XCelliStem® was applied to a noncompliant diabetic patient with plantar gas gangrene. Gas gangrene is a life threatening infection that causes rapid muscular necrosis, microvascular thrombosis, and severe tissue destruction. Not only is the mortality rate associated with this infection as high as 40%, the recovery is long and difficult, and patients are at risk for delayed wound healing, secondary superinfections, dehiscence, and amputation [66]. Furthermore, the patient's history of poorly managed diabetes compounds the risk for tissue ischemia, necrosis, and poor wound healing to an even greater extent. The patient was managed with two debridements for complete removal of necrotic tissue, resulting in tendon exposure. The surgeon applied Lodofoam for 2 days, followed by 2000mg of XCelliStem® and a wound vac was also placed. 7 days after XCelliStem®, the exposed tendons were completely covered. (Figure 1) This is a promising finding, as the literature shows that mean time to granulation tissue in the setting of necrotizing fasciitis is over 23 days [67]. In this case, administration of XCelliStem® not only approximated wound margins at a rate faster than the average standard time, but was able to achieve this effect in an immunocompromised patient.

XCelliStem® demonstrated utility in the setting of trauma and tissue necrosis in a case where a patient was hit by a car while riding a bike. After treatment with external fixator and negative pressure wound therapy, he was instructed to follow up in 1 week for reevaluation. Due to a lack of transportation, the patient's next clinical encounter was 6 weeks after initial hospitalization. The lack of care resulted in tissue necrosis, which led to tendon exposure requiring debridement. Following debridement, 250mg of XCelliStem® was applied to the wound in the clinic and the wound vac was replaced. At follow up 1 week later, nearly all the wound was covered with healthy granulated tissue. An additional application of 250mg of XCelliStem® was applied, and at the subsequent follow up, healing had progressed to fully cover the tendon, allowing the patient to be prepped for split thickness skin grafting. (Figure 2)

Goss and colleagues compiled the effects of XCelliStem® during wound closure of 49 patients following posterior lumbar surgery. The surgeries consisted of primary and revision lumbar decompressions, single and multilevel posterior instrumented fusions, and spinal cord stimulator placement procedures. The authors maintained the same, standardized wound closure process for all patients. Among the 49 high-risk patients, primary comorbidities included obesity (21), tobacco use (14), diabetes (3), and revision surgery (20), with several patients presenting multiple risk factors. Out of the series, 49 of 49 patients displayed appropriate, timely wound healing without readmission for postoperative wound infection. This is a notable finding highlighting the utility of XCelliStem® in reducing infection and improving wound healing, as incisional complications following lumbar surgery has been shown to be as high as 18% [68].

Murphy and colleagues evaluated the effect of XCelliStem® in a 48 year old obese female with a complex tissue defect from the anterior superior iliac spine to the distal patella measuring 35cm x 20cm. In addition to extensive soft tissue damage, the patient developed a vesicocutaneous fistula and required 40 subsequent operations for debridement of necrotic tissue. Wound healing remained stagnant prior to application of XCelliStem®, after which granulation tissue began developing to allow for a split thickness skin graft [69]. (Figure 3)

Ghani and colleagues evaluated the effect of XCelliStem® on an infected scalp lesion with underlying skull exposure that had become a chronic nonhealing wound. The patient was a 41 year old female with a past medical history of diabetes mellitus, who presented on 6/30 with an infected scalp eschar. Serial debridements were performed on 7/2 and 7/30, after which it was discovered the underlying skull was also infected. There was little to no granulation tissue developing over the infected scalp lesion during this time. On 8/25, the patient underwent another debridement, during which Burr holes were drilled into the skull and 1 gram of XCelliStem® was placed into the wound. The purpose of the Burr holes was to increase XCelliStem® penetration and provide increased potential for angiogenesis and wound healing. Hypergranulation was observed 1 week following XCelliStem® administration, and complete wound

resolution was observed at 3 months. (Figure 4) Not only does this case study represent the first successful use of XCelliStem® in an infected scalp or skull wound, it demonstrates that XCelliStem® is safe and effective for use in infected wound beds. The authors also stated that it was inexpensive, easy to use, fast acting, and low maintenance for both patient and provider [70].

Fortner and colleagues evaluated the efficacy of XCelliStem® in the treatment of a severe lactational abscess with overlying skin necrosis. The patient was a 24 year old female, 3 months postpartum, who presented to the emergency department with fever and leukocytosis despite completing a course of antibiotics. Ultrasound revealed a 5 cm x 4cm abscess located at 9:00, needle guided aspiration yielded 53mL of purulent fluid. At follow up examination 5 days later, a 5.5 cm x 5.5 cm full-thickness area of dermal necrosis was observed in the region of the previous abscess. The wound was 3 cm deep and filled with breast milk. During wound management, XCelliStem® was applied, and serial applications were performed in the clinic at 5-10 day intervals. Within 48 hours of the initial XCelliStem® treatment, pain levels reduced from 10/10 to 0/10. At 5 days, the wound was significantly reduced, measuring 2.5 cm L x 3.5 cm W x 0 cm D. Complete wound healing was achieved within 6 weeks of initial XCelliStem® application. (Figure 5) Treatment with XCelliStem® allowed the patient to avoid formal surgical debridement, which is typically required to treat breast abscesses that fail to resolve with percutaneous aspiration and antibiotics, as in this case. Furthermore, the patient was able to continue breastfeeding, her pain was reduced, the cosmetic outcome was improved, and she avoided complications frequently associated with debridement, such as milk suppression, fistula, and chronic infection. This case highlights the ability of XCelliStem® to facilitate constructive remodeling and accelerate healing of contaminated wounds in challenging locations. Additionally, improved tissue regeneration seemed to confer a pain relief benefit as well. The authors concluded that XCelliStem® is an excellent choice in the treatment of severe lactational abscesses, potentially allowing patients to avoid formal surgical debridement altogether [71].

As previously discussed, severe trauma increases patient risk of SSI and SSC, with some studies showing SSI rates as high as 23% [72]. Zhu and colleagues evaluated the efficacy of porcine urinary bladder matrix (PUBM) and XCelliStem® in a large traumatic crush and avulsion injury to the anterior calf, ankle, and foot [73]. The patient was a 48 year old male who presented after a motor vehicle collision where his leg was trapped under 12,000 pounds of concrete rebar for over 30 minutes. Initially, the wound measured 19 cm x 14 cm x 1 cm with exposed muscle, fascia, tendon and bone. (Figure 6a) There were no fractures. He underwent debridement and washout, PUBM was placed on hospital day 4, and he was discharged on day 7. PUBM was kept in place and removed at a 4 week office follow-up. (Figure 6b) Within 8 weeks, all the exposed bone, tendon, muscle, and fascia were covered with robust granulation tissue that was level with the skin. At a 13 week office followup, healing had stalled. At this time, XCelliStem® was applied to the wound, which measured 8.5 cm x 4.4 cm. (Figure 6c) Within 6 weeks of XCelliStem® application, the wound completely epithelialized and was fully remodelled by 6 months. (Figure 6d) The recommended treatment for this case was free flap reconstruction; however, use of PUBM and XCelliStem® not only allowed wound healing to occur without this procedure, but negated the need for even a skin graft. As a result, length of hospital stay was drastically reduced and the patient was able to return to daily activities at an accelerated rate [73]. As previously discussed, PUBM has been shown to exert profound effects on wound healing. This is accomplished by increasing the proliferation and migration of perivascular stem cells, particularly in injury environments [24,25]. PUBM is derived from a single tissue source, typically the basement membrane or lamina propria of the porcine urinary bladder. This case study highlights the efficacy of MTPs, such as XCelliStem®, over single tissue ECM platforms. The greater diversity of bioactive molecules derived from liver, lung, and spleen tissue sources exerts a multiplicative effect on wound healing compared to a singular tissue source. This was demonstrated when XCelliStem® administration fostered the transition from 5 weeks of arrested healing in the lower extremity wound to complete closure in less than 6 weeks.

Law and colleagues applied XCelliStem® to a 58 year old male involved in a head-on collision with an automobile while riding his motorcycle. He suffered an open tibia fracture that was managed with ORIF. The patient was a smoker with multiple medical comorbidities, and was noncompliant to postoperative treatment recommendations. After being lost to follow up, he was eventually readmitted to the hospital due to infection of the operative site. The patient was noted to have a draining sinus track approximately 30mm in diameter with purulent drainage, malodorous discharge, and exposed bone on the medial portion of the midshaft tibia. Once the patient was stabilized, he was taken to surgery for debridement, removal of hardware, and repeat ORIF. Culture samples from a large purulent pocket in the subcutaneous tissues of the left leg grew MRSA. The patient was being treated with a wound vac for 54 days without success when the decision was made to apply XCelliStem®. After the first application, the odor from the wound resolved. By day 15, exposed bone was completely covered, necrotic tissue cleared, and the wound was granulating with healthy vascularized tissue. By day 40, the wound margins continued to approximate. Full resolution of the wound was achieved and maintained without recurrent infection or complication. (Figure 7) The patient continued smoking throughout treatment. This case demonstrates the efficacy of XCelliStem® in the presence of infection and arrested wound healing. It is notable that XCelliStem® is safe to apply with implanted material, which is known to carry a higher risk for infection.

XCelliStem® is not only effective in standard wound care, but has shown promise in treating high energy, complex trauma wounds from gunshots, explosive devices, and large surface degloving injuries. In a 15 patient case series, Irfan and colleagues evaluated the efficacy of XCelliStem® used as an adjunct to standard debridement and wound care in patients with complex ballistic and blast injuries during the 2023-2025 Israeli military assault on Gaza [74]. The purpose of the study was to determine the efficacy of the multitissue ECM biomaterials contained within XCelliStem® in increasing granulation tissue formation, improving wound closure, and mitigating early complications, such as infection or dehiscence. The study was conducted under conditions of extreme resource scarcity, supply shortages, unpredictable access to sterile equipment or negative pressure systems, and frequent power outages. The patient demographic included in the study also suffers from severe malnutrition, which is associated with delayed wound healing, poor wound tensile strength, and increased rates of infection [75]. As a result of these barriers, wound treatment in Gaza is difficult to standardize and post surgical infection and complication

rates are high. Moreover, World Health Organization (WHO) data demonstrates that the conflict-strained regions of the Eastern Mediterranean carry the highest rates of antimicrobial resistance, further increasing the likelihood of infection and complication [76]. In the study, devitalized tissue was surgically debrided and irrigated, and fractures were repaired with external fixation, intramedullary nailing, or K-wires, if indicated. 0.5-1g of XCelliStem®, with or without vancomycin powder, was then administered directly to the wound bed. A nonadherent primary layer, such as petroleum gauze, and a secondary absorbent dressing were applied after closure. Even when applied in poor conditions and in complicated wounds, such as exposed bone, devitalized soft tissue, and external fixation hardware, patients treated with XCelliStem® displayed progressive granulation tissue formation and closure within a short timeframe and without complications. (Figure 8a, 8b) The authors concluded that adding a dynamic MTP ECM scaffold to the wound bed promotes tissue regeneration by increasing angiogenesis and modulating the inflammatory immune response. The growth factors contained within XCelliStem® not only promote vascular ingrowth, but communicate with precursor immune cells to shift the healing environment from one favoring fibrosis and scarring (M1) to a constructive, antiinflammatory macrophage phenotype (M2) favoring tissue regeneration and remodeling. XCelliStem® is not only effective from a biochemical standpoint, but is useful in high risk, resource poor settings as it is dry and shelf stable, permitting flexible use at the bedside or in the operating room. It is also able to be combined and used in adjunct with other antimicrobials, such as vancomycin, for synergistic therapeutic benefit [74].

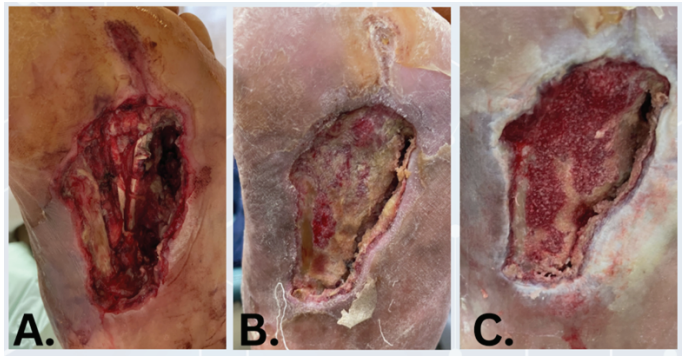

***Figure 1**: XCelliStem® in plantar gas gangrene. Initial wound (A), wound progress at 7 (B) and 21 (C.) days after XCelliStem® placement.*

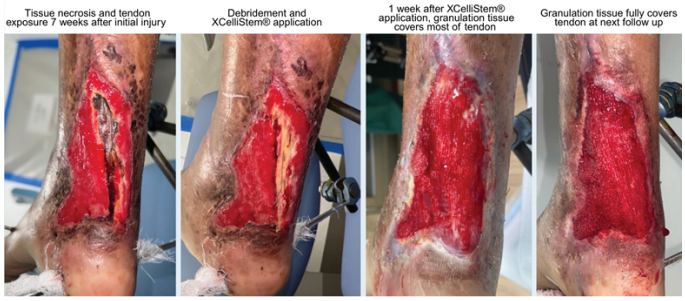

***Figure 2**: CelliStem® in exposed tendon*

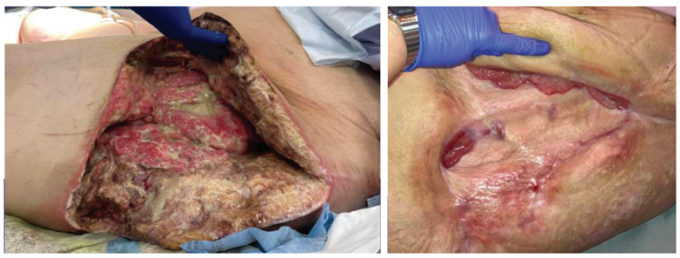

***Figure 3:** Treatment of 35cm x 20cm Soft Tissue Injury to Left Lower Extremity with XCelliStem® [69]*

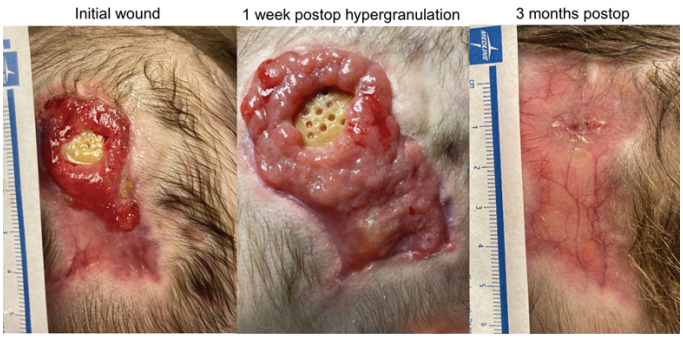

***Figure 4:** Treatment of Infected Scalp Wound with XCelliStem® [70]*

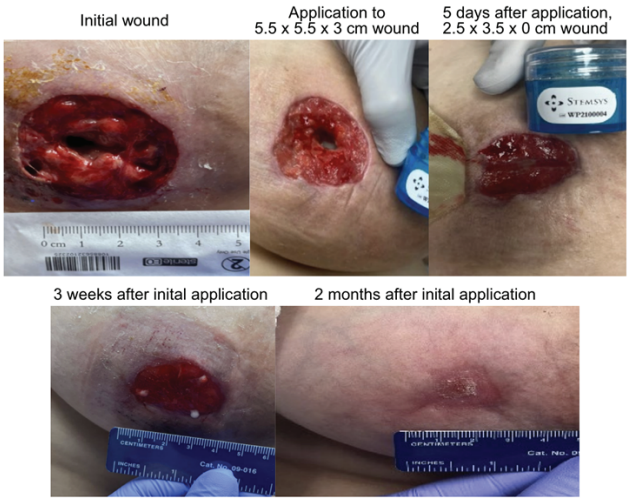

***Figure 5:** Treatment of a 5.5 cm x 5.5 cm x 3 cm lactational abscess with XCelliStem®*

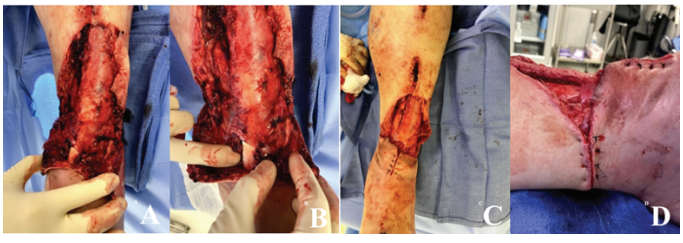

***Figure 6A:** Initial soft tissue defect (A & B) and partial closure (C & D) [76].*

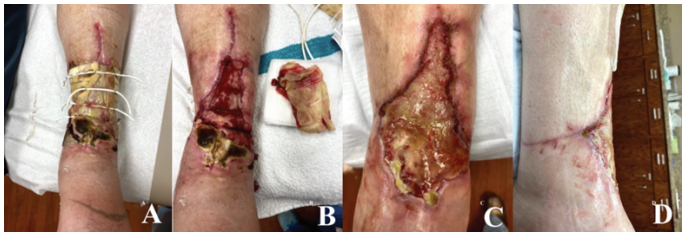

Figure 6B: *Lower extremity 4 weeks after PUBM administration, with adhesive dressings removed [76].*

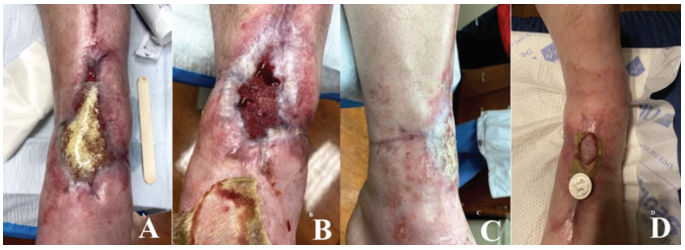

Fig 6C: Lower extremity at 13 week follow up with application of XCelliStem® (A), 17 week follow up (B & C), and 20 week follow up (D)

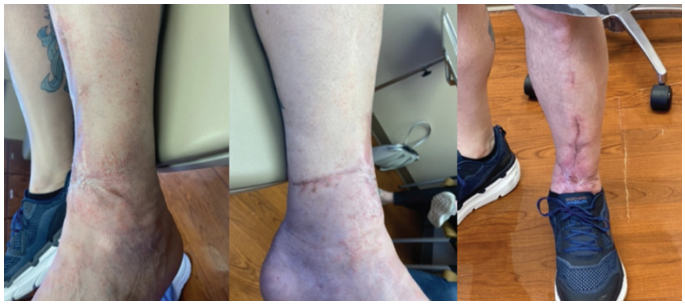

Figure 6d*: Complete lower extremity wound healing at 6 months ;76]*

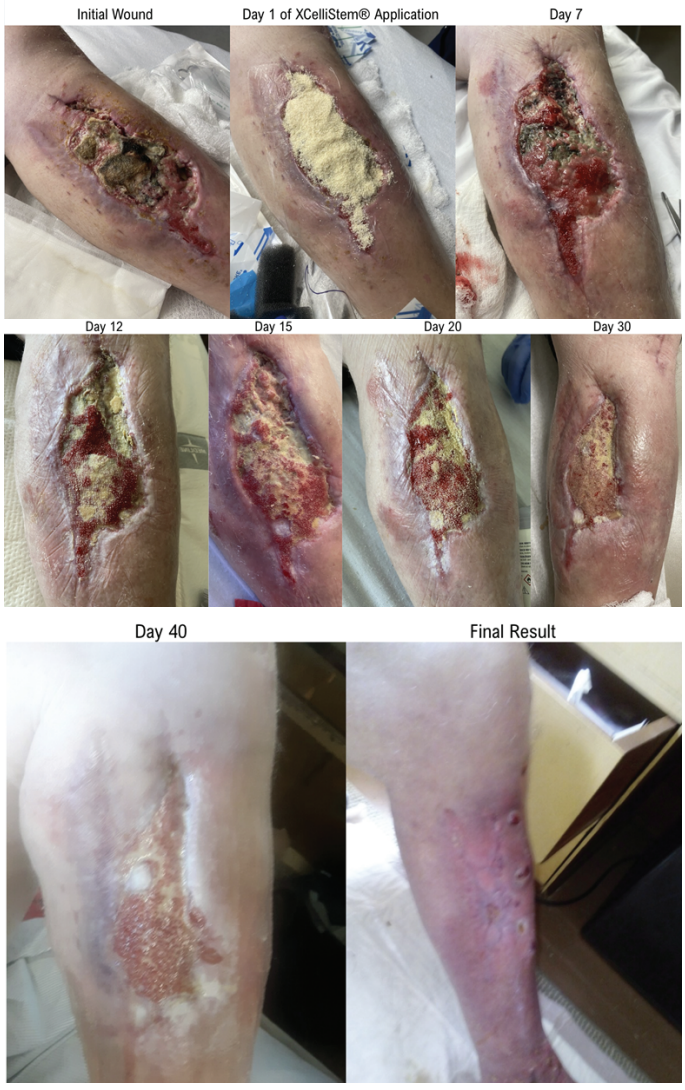

Figure 7: XCelliStem® in infected tibia ORIF

Figure 8A: Intraoperative application of XCelliStem® to 3 month post op [72]

Figure 8B: Hand injury progression [72]

Conclusion

XCelliStem® is an MTP ECM scaffold derived from porcine spleen and lung designed to augment and accelerate tissue regeneration in various wound types. Porcine ECMs have been shown to exert a multitude of beneficial effects on tissue regeneration by promoting migration of fibroblasts and penetration of epithelial cells, while enhancing neovascularization and tissue adhesion. Composed of 45% biphasic collagen and 55% unique bioactive molecules from multiple ECM sources, XCelliStem® is distinctly different from other ECMs, which typically contain less than a 10% concentration of biomolecules. As a result, XCelliStem® is able to overcome the limitations of tissue grafts currently in practice and generate novel, robust differentiation, modulation, mobilization, and proliferation of immune and stem cells. Following placement into a wound, ECMs modulate the inflammatory immune response and stimulate mononuclear cell infiltration at the site to initiate and accelerate the complex process of tissue repair and remodeling, even in infected wound beds [7]. ECM composition varies markedly between structural and parenchymal tissues. Decellularized matrices derived from SIS are composed predominantly of fibrillar collagen, exceeding 90% of dry weight, and therefore function primarily as mechanically robust scaffolds. In contrast, UBM retains a broader array of extracellular components, including basement membrane associated proteins. Parenchymal tissues, such as LEM and MTPs, exhibit a more complex and less collagen dominant ECM. This ECM consists of multiple collagen subtypes, alongside a diverse population of glycoproteins and proteoglycans, which have been identified through quantitative proteomics. Upon enzymatic or physiological degradation, these matrices release low molecular weight bioactive peptides that have been shown to modulate immune response and exhibit antimicrobial activity. Collectively, these findings support a continuum in ECM biomaterials ranging from collagen dense structural scaffolds to protein rich, signaling oriented matrices with enhanced bioactivity. It is because of these complex cellular activities that XCelliStem® is not only a useful therapeutic strategy for management of SSI and SSCs, but has even been shown to be an effective treatment that negates the need for surgical management altogether.

The most common indications for XCelliStem® include high risk surgical settings, such as infection; cases of exposed bone, or tendon; fracture, including open fracture and tibial plateau fractures; fasciotomy; achilles tendon repair; washouts; incision and drainage; incision and drainage with spacer placement; BKAs and AKAs; and implant revisions. XCelliStem® has demonstrated efficacy in notoriously difficult cases at high risk for poor healing and outcomes, such as necrotizing fasciitis in immunocompromised patients and in complex ballistic trauma wounds. Furthermore, the total cost of treatment is less than many standard wound therapy regimens currently in practice. In light of these findings, XCelliStem® has been proven clinically to improve both healing and patient outcomes. It would stand to reason that use of XCelliStem® would reduce the healthcare burden associated with poor wound healing and improve patient outcomes overall.

References

1. Sen CK. Human wound and its burden: updated 2025 compendium of estimates. Adv Wound Care (New Rochelle). 2025;14(9):429-438. doi:10.1177/21621918251359554
2. Biology Insights. How many surgeries are performed each year? BiologyInsights.com. Published December 10, 2025. Accessed May 11, 2026. Biology Insights
3. Herman J. Wound care refresher for retail health clinicians. Contemporary Clinic. 2017;3(4).
4. Queen D, Harding K. Estimating the cost of wounds both nationally and regionally within the top 10 highest spenders. Int Wound J. 2024;21(2):e14709. doi:10.1111/iwj.14709
5. Caplan Z. US older population grew from 2010 to 2020 at fastest rate since 1880 to 1890. Published 2023. Accessed May 11, 2026. US Census Bureau
6. Centers for Disease Control and Prevention. National diabetes statistics report. Published May 15, 2024. Accessed May 11, 2026. CDC National Diabetes Statistics Report
7. Creger PE, Cefalo JL, Murphy RC, Mount MG, Dillman DB, Hird RB, Currence CD. Comparative analysis of a novel multi-tissue platform (MTP) powder in lower extremity amputations. Spartanburg Regional Healthcare System. Unpublished manuscript.
8. Brumberg V, Astrelina T, Malivanova T, Samoilov A. Modern wound dressings: hydrogel dressings. Biomedicines. 2021;9(9):1235. doi:10.3390/biomedicines9091235
9. Paige JT, Kremer M, Landry J, et al. Modulation of inflammation in wounds of diabetic patients treated with porcine urinary bladder matrix. Regen Med. 2019;14(4):269-277. doi:10.2217/rme-2019-0009
10. Ostróżka-Cieślik A, Tanwar A, Michalak M. Hyaluronan-based hybrid systems as growth factor carriers in the treatment of chronic wounds. Int J Mol Sci. 2025;26(22):10871. doi:10.3390/ijms262210871
11. Liu Y, Liu Y, Deng J, Li W, Nie X. Fibroblast growth factor in diabetic foot ulcer: progress and therapeutic prospects. Front Endocrinol (Lausanne). 2021;12:744868. doi:10.3389/fendo.2021.744868
12. Xie L, Zhang M, Dong B, et al. Improved refractory wound healing with administration of acidic fibroblast growth factor in diabetic rats. Diabetes Res Clin Pract. 2011;93(3):396-403. doi:10.1016/j.diabres.2011.05.016
13. Wall IB, Moseley R, Baird DM, et al. Fibroblast dysfunction is a key factor in the non-healing of chronic venous leg ulcers. J Invest Dermatol. 2008;128(10):2526-2540. doi:10.1038/jid.2008.114
14. Cialdai F, Risaliti C, Monici M. Role of fibroblasts in wound healing and tissue remodeling on Earth and in space. Front Bioeng Biotechnol. 2022;10:958381. doi:10.3389/fbioe.2022.958381
15. Centers for Disease Control and Prevention. National diabetes statistics report. Published May 15, 2024. Accessed May 11, 2026. CDC National Diabetes Statistics Report
16. Fleck CA, Simman R. Modern collagen wound dressings: function and purpose. J Am Coll Certif Wound Spec. 2011;2(3):50-54. doi:10.1016/j.jcws.2010.12.003
17. Alhajj M, Goyal A. Physiology, granulation tissue. In: StatPearls. StatPearls Publishing; 2025. Accessed May 11, 2026. NCBI Bookshelf
18. Nowrouzi R, Awad SS. Activated collagen powder significantly reduces surgical site infections in patients undergoing elective surgery. J Surg. 2023;8:1918. doi:10.29011/2575-9760.001918
19. Li F, Li W, Johnson S. Low-molecular-weight peptides derived from extracellular matrix as chemoattractants for primary endothelial cells. J Endothel Cell Res. 2004;11:199-206.
20. Qureshi A, Murphy E, Milando R, Rengifo-Pardo M, Clayton C, Friedman A. A head-to-head comparison of topical collagen powder to primary closure for acute full-thickness punch biopsy-induced human wounds: an internally controlled pilot study. J Drugs Dermatol. 2019;18(7):667-673.
21. Das S, Singh AI, Singh LO, Sinam N, Singh SN. A comparative clinical study of collagen and paraffin gauze dressing on skin

donor site. J Med Soc. 2020;34(3):162-166. doi:10.4103/jms.jms_25_21

22. Williams C, Quinn KP, Georgakoudi I, Black LD III. Young developmental age cardiac extracellular matrix promotes the expansion of neonatal cardiomyocytes in vitro. Acta Biomater. 2014;10(1):194-204. doi:10.1016/j.actbio.2013.08.037
23. Reing JE, Zhang L, Myers-Irvin J, et al. Degradation products of extracellular matrix affect cell migration and proliferation. Tissue Eng Part A. 2009;15:605-614.
24. Tottey S, Corselli M, Jeffries EM, Londono R, Peault B, Badylak SF. Extracellular matrix degradation products and low-oxygen conditions enhance the regenerative potential of perivascular stem cells. Tissue Eng Part A. 2011;17:37-44.
25. Fields AC, Pradarelli JC, Itani KMF. Preventing surgical site infections: looking beyond the current guidelines. JAMA. 2020;323(11):1087-1088. doi:10.1001/jama.2019.20830
26. Ban KA, Minei JP, Laronga C, et al. American College of Surgeons and Surgical Infection Society: surgical site infection guidelines, 2016 update. J Am Coll Surg. 2017;224(1):59-74.
27. Dasari N, Jiang A, Skochdopole A, et al. Updates in diabetic wound healing, inflammation, and scarring. Semin Plast Surg. 2021;35(3):153-158. doi:10.1055/s-0041-1731460
28. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-234. doi:10.1016/S0140-6736(23)01301-6
29. Roy S, Santra S, Das A, et al. Staphylococcus aureus biofilm infection compromises wound healing by causing deficiencies in granulation tissue collagen. Ann Surg. 2020;271(6):1174-1185. doi:10.1097/SLA.0000000000003053
30. Ersanli C, Tzora A, Skoufos I, Voidarou CC, Zeugolis DI. Recent advances in collagen antimicrobial biomaterials for tissue engineering applications: a review. Int J Mol Sci. 2023;24(9):7808. doi:10.3390/ijms24097808
31. Lima CA, Campos JF, Filho JLL. Antimicrobial and radical scavenging properties of bovine collagen hydrolysates produced by Penicillium aurantiogriseum URM 4622 collagenase. J Food Sci Technol. 2015;52:4459-4466.
32. Sarikaya A, Record R, Wu C, Tullius B, Badylak S, Ladisch M. Antimicrobial activity associated with extracellular matrices. Tissue Eng. 2002;8:63.
33. Brennan EP, Reing J, Chew D, et al. Antibacterial activity within degradation products of biological scaffolds composed of extracellular matrix. Tissue Eng. 2006;12(10):2949-2955. doi:10.1089/ten.2006.12.2949
34. Bueno-Lledó J, Torregrosa-Gallud A, Sala-Hernandez A, et al. Predictors of mesh infection and explantation after abdominal wall hernia repair. Am J Surg. 2017;213(1):50-57. doi:10.1016/j.amjsurg.2016.03.007
35. Noah C, Makhlouf F, McAdoo A. Soft tissue remodeling in infected fields using a novel extracellular matrix: a clinical evaluation. Unpublished manuscript.
36. Kazzam ME, Ng P. Postoperative seroma management. In: StatPearls. StatPearls Publishing; 2025. Accessed May 11, 2026. NCBI Bookshelf
37. Creger P, Westby RB, Hird RB, Trujillo M. Mitigation of the consequences of seroma formation in open ventral hernia repair using ECM powder. J Pharm Res Innov. 2025;5(1).
38. Bettiol P, Cox C, Gerzina C, Simpson J, MacKay B. Novel use of a porcine bladder extracellular matrix scaffold to treat postoperative seroma in a total knee arthroplasty patient. Arthroplast Today. 2021;7:143-147. doi:10.1016/j.artd.2020.12.007
39. Sajid MS, Betal D, Akhter N, Rapisarda IF, Bonomi R. Prevention of postoperative seroma-related morbidity by quilting of latissimus dorsi flap donor site: a systematic review. Clin Breast Cancer. 2011;11(6):357-363. doi:10.1016/j.clbc.2011.04.006
40. Ağalar C, Sevinç Aİ, Aysal A, et al. Porcine dermal collagen prevents seroma formation after mastectomy and axillary dissection in rats. Eur J Breast Health. 2017;13(4):200-205. doi:10.5152/ejbh.2017.3616
41. Petrie K, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: a review. Scars Burn Heal. 2022;8:20595131211038313. doi:10.1177/20595131211038313
42. Peng JM, Ansingkar KK, Landavazo BN, Shaikh AF, Rahimi M. A comprehensive review of seroma formation, prevention, and treatment approaches. J Vasc Surg Cases Innov Tech. 2025;11(5):101879. doi:10.1016/j.jvscit.2025.101879
43. Petro CC, O'Rourke CP, Posielski NM, Criss CN, Raigani S, Prabhu AS, Rosen MJ. Designing a ventral hernia staging system. Hernia. 2016;20(1):111-117.
44. Iqbal A, Jan A, Wajid MA, Tariq S. Management of chronic non-healing wounds by hirudotherapy. World J Plast Surg. 2017;6(1):9-17.
45. Mathew-Steiner SS, Roy S, Sen CK. Collagen in wound healing. Bioengineering (Basel). 2021;8:63.
46. Kumar M, Banerjee P, Das A. Hydrolyzed collagen powder dressing improves wound inflammation, perfusion and breaking strength of repaired tissue. Adv Wound Care. 2023.
47. Shu H, Xia Z, Qin X, et al. The clinical efficacy of collagen dressing on chronic wounds: a meta-analysis of 11 randomized controlled trials. Front Surg. 2022;9:978407. doi:10.3389/fsurg.2022.978407
48. Simon DA, Dix FP, McCollum CN. Management of venous leg ulcers. BMJ. 2004;328:1358.
49. Alavi A, Archer J, Coutts P. Use of an advanced collagen matrix dressing on patients with complex chronic lower extremity ulcers: a case series. SAGE Open Med Case Rep. 2021;9:2050313X211013684. doi:10.1177/2050313X211013684
50. Durr HA, Abri S, Salinas SD, et al. Extracellular matrix repair and organization of chronic infected diabetic wounds treated with methacrylated chitosan-based hydrogels. Acta Biomater. 2025;199:166-177. doi:10.1016/j.actbio.2025.04.062
51. Andrew DGA, Boulton JM, Hardman MJ, et al. Diagnosis and management of diabetic foot infections. American Diabetes Association. Published 2020. Accessed May 11, 2026. NCBI Bookshelf
52. Läuchli S, Bayard I, Hafner J, Hunziker T, Mayer D, French L. Unterschiedliche Abheilungsdauer und Häufigkeit der Hospitalisation bei Ulcus cruris verschiedener Ursachen [Healing times and the need for hospitalization for leg ulcers of different etiologies]. Hautarzt. 2013;64(12):917-922. doi:10.1007/s00105-013-2671-5
53. Kruszewska K, Wesolowska-Gorniak K, Czarkowska-Paczek B. Venous leg ulcer healing time is increased with each subsequent bacterial strain identified in the ulcer: a retrospective study. Phlebology. 2021;36(4):275-282. doi:10.1177/0268355520961945
54. Sadtler K, Sommerfeld SD, Wolf MT, et al. Proteomic composition and immunomodulatory properties of urinary bladder matrix scaffolds in homeostasis and injury. Semin Immunol. 2017. doi:10.1016/j.smim.2017.05.002
55. Dziki JL, Wang DS, Pineda C, Sicari BM, Rausch T, Badylak SF. Solubilized extracellular matrix bioscaffolds derived from diverse source tissues differentially influence macrophage phenotype. J Biomed Mater Res A. 2017;105(1):138-147.
56. Molina CS, Faulk JB. Lower extremity amputation. In: StatPearls. StatPearls Publishing; 2025. Accessed May 11, 2026. NCBI Bookshelf

57. Rivera JA, Churovich K, Anderson AB, Potter BK. Estimating recent US limb loss prevalence and updating future projections. Arch Rehabil Res Clin Transl. 2024;6(4):100376. doi:10.1016/j.arrct.2024.100376
58. Creger PE, Cefalo JL, Murphy RC, Mount MG, Dillman DB, Hird RB, Currence CD. Comparative analysis of a novel multi-tissue platform (MTP) powder in lower extremity amputations. Unpublished manuscript.
59. Ploeg A, Lardenoye J, Vrancken Peeters M, Breslau P. Contemporary series of morbidity and mortality after lower limb amputation. Eur J Vasc Endovasc Surg. 2005;29(6):633-637.
60. Dormand EL, Banwell PE, Goodacre TE. Radiotherapy and wound healing. Int Wound J. 2005;2(2):112-127. doi:10.1111/j.1742-4801.2005.00079.x
61. Haubner F, Ohmann E, Pohl F, Strutz J, Gassner HG. Wound healing after radiation therapy: review of the literature. Radiat Oncol. 2012;7:162. doi:10.1186/1748-717X-7-162
62. Rudolph R. Complications of surgery for radiotherapy skin damage. Plast Reconstr Surg. 1982;70(2):179-185. doi:10.1097/00006534-198208000-00009
63. Sasse KC, Brandt J, Lim DC, Ackerman E. Accelerated healing of complex open pilonidal wounds using MatriStem extracellular matrix xenograft: nine cases. J Surg Case Rep. 2013;2013(4):rjt025.
64. Diaz-Valadez FD, Griffin K, Sasse KC. Case reports of clinical and histologic wound healing response with multi-tissue extracellular matrix with cost analysis compared to negative pressure wound therapy. Clin Case Rep J. 2023;4(2):1-7.
65. Rosen RD, Manna B. Wound dehiscence. In: StatPearls. StatPearls Publishing; 2026. Accessed May 11, 2026. NCBI Bookshelf
66. Centers for Disease Control and Prevention. Gas gangrene (clostridial myonecrosis). Published 2023. Accessed May 11, 2026. CDC
67. Basani M, Nemi CJ, Parveen H, Manivasagam SS, Belsariya V, et al. Revolutionizing patient care: unveiling the potential of enhanced recovery after surgery (ERAS) pathway in enhancing recovery and quality of life for lower limb necrotizing fasciitis patients. J Clin Surg Surg Res. 2024;3(1):1-11. doi:10.59657/2992-9989.brs.24.019
68. Cao L, Sun K, Yang H, Zeng R, Wang H. Risk factors for incisional complications after lumbar internal fixation via posterior midline approach: a case-control study of 455 consecutive cases. Int Wound J. 2023;20(8):2989-2997. doi:10.1111/iwj.14167
69. Murphy RC, Creger PE, Currence C. Use of multi-tissue platform and negative pressure therapy to achieve healing in a complex wound. Unpublished manuscript.
70. Ghani O, Magendran D, Davis D. Infected scalp wound treated with XcelliStem powder. Western Kentucky Heart and Lung Research Foundation and Educational Trust. Unpublished manuscript.
71. Fortner R, Zhu C, Collins RA, Ronaghan CA, Scheerer M. Treatment of a severe lactational abscess with multi-tissue platform porcine xenograft. Poster presentation. Texas Tech University Health Sciences Center School of Medicine.
72. Savio L, Simeone P, Baron S, et al. Surgical site infection in severe trauma patients in intensive care: epidemiology and risk factors. Ann Intensive Care. 2024;14(1):136. doi:10.1186/s13613-024-01370-7
73. Zhu C, Collins R, Daniel H, Puckett Y, McReynolds S, Ronaghan CA. Complex traumatic crush injury managed utilizing biologics and a dynamic tissue system. Poster presentation. Texas Tech University Health Sciences Center School of Medicine; West Virginia School of Medicine, Department of Surgery.
74. Irfan B, Hamawy A, Musallam R, et al. Utilization of a multi-tissue extracellular matrix in complex wound care in Gaza: a case series. Antibiotics (Basel). 2025;14(9):885. doi:10.3390/antibiotics14090885
75. Stechmiller JK. Understanding the role of nutrition and wound healing. Nutr Clin Pract. 2010;25(1):61-68. doi:10.1177/0884533609358997
76. Moghnieh R, Bizri N, Abdallah D, Sayegh MH. Antimicrobial resistance surveillance and trends in armed conflict, fragile, and non-conflict countries of the Eastern Mediterranean Region. Infect Dis Poverty. 2025;14:14