The Difficult to Heal and Chronic Wound;
(A Review of a Matrix Deficiency State)
(The potential role of a matrix replacement therapy)

Robert H. Demling, M.D.
Professor of Surgery
Harvard Medical School
Brigham and Women’s Hospital
Boston, MA
rhdemling@partners.org
1. Abstract

The normal skin dermis is composed of cells mainly fibroblasts and macrophages, and a complex extracellular matrix ECM. Both of these dermal components are responsible for the exact anatomical and physiological reproduction of both epidermis and dermis during the normal tissue turnover process. This replacement occurs every several weeks for epidermis and every several months for dermis.\(^1,2\)

These same cells and the components of extracellular matrix (ECM), are also necessary for the healing of any wound. Matrix components are signals and questions for new tissue formation.\(^3-8\)

The discussion that follows will focus on the importance of the ECM components in both acute, difficult to heal, and chronic wounds. The emphasis will be the matrix deficiency state that exists in chronic wounds which is a major factor perpetuating the poor healing process. Current technology provides the development of ECM and its components to correct a deficiency state and assist in healing.

There are a large variety of products which can be considered as Matrix Products. Synthetic ECM (or ECM components) appear to play a more passive scaffold-like role whereas the more material components provide both tissue scaffolding and bioactivity in the healing process.

In order to understand ECM use in wounds, an understanding of their normal biological properties is needed. In addition, a distinction between acute, difficult to heal and chronic wounds will be required especially as to the characteristics of the chronic matrix deficiency state seen in the poorly healing wound.
I. Role of Extracellular Dermal Matrix in Normal Healing

(Table 1)
The components of a mature ECM and their biological functions are listed below.\textsuperscript{3-22}

<table>
<thead>
<tr>
<th>Extracellular Dermal Matrix Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Collagen (protein)</td>
</tr>
<tr>
<td>- scaffold for cell migration and matrix</td>
</tr>
<tr>
<td>- deposition</td>
</tr>
<tr>
<td>- cell guidance</td>
</tr>
<tr>
<td>- Elastin (protein)</td>
</tr>
<tr>
<td>- tissue elasticity</td>
</tr>
<tr>
<td>- Fibronectin (protein)</td>
</tr>
<tr>
<td>- cell-to-cell adherence</td>
</tr>
<tr>
<td>- contact orientation for cells</td>
</tr>
<tr>
<td>- increases epithelial cell division, migration</td>
</tr>
<tr>
<td>- chemo attractant for fibroblasts, macrophages</td>
</tr>
<tr>
<td>- Growth Factors (proteins)</td>
</tr>
<tr>
<td>- stimulate all phases of wound healing</td>
</tr>
<tr>
<td>- Proteoglycan (glycosylated protein)</td>
</tr>
<tr>
<td>- cell adherence properties</td>
</tr>
<tr>
<td>- conduit for healing factors</td>
</tr>
<tr>
<td>- deactivator of proteases</td>
</tr>
<tr>
<td>- scaffold or foundation for dermal elements</td>
</tr>
<tr>
<td>- Hyaluronic Acid (complex carbohydrate)</td>
</tr>
<tr>
<td>- maintaining matrix hydration</td>
</tr>
<tr>
<td>- decreases inflammation</td>
</tr>
<tr>
<td>- stimulates healing</td>
</tr>
<tr>
<td>- proper cell alignment</td>
</tr>
</tbody>
</table>

For the most part ECM is produced by fibroblasts, which require instructions mainly from matrix components to produce more matrix components.\textsuperscript{3-7} Components include proteins, complex carbohydrates and a combination of the two (Table 1)

Collagen is the most prominent protein present.\textsuperscript{8,9} There are a variety of collagens but collagen type I makes up 96\% of the dermal collagen. Collagen type II makes up most of the remaining collagen. Collagen type IV is present in the basement membrane and plays
a significant role in epithelial cell adherence to the ECM and subsequent migration. Collagens not only provide structure or a scaffold, but also provide critical cell signaling for cell proliferation, and migration into the wound.

Proteoglycans (a combination of protein and carbohydrates) are involved in both the necessary scaffolding for developing the new granulation tissue and also provide a conduit for cell and nutrient movement in the wound. In addition they help deactivate excess proteases.\textsuperscript{10}

Hyaluronic acid, besides maintaining matrix hydration, also directs the healing process.\textsuperscript{11-13} The higher molecular weight molecules help to modulate inflammation protecting the new granulation tissue while the smaller molecules often fragments of the large molecule, activate angiogenesis and granulation tissue formation.

Other proteins include fibronectin, laminin, tenascin and thrombospondin. The most prominent protein is fibronectin, which has many important functions, especially in the earliest stage of healing. Fibronectin is essential for cell adherence on the new ECM or early granulation tissue. Without adherence the cells can’t migrate into the wound.\textsuperscript{14-20}

Growth factors are cytokines (proteins), which activate and direct every stage of wound healing. Macrophages are the major producers of growth factors.\textsuperscript{21-23}

Acute wound healing is characterized by a short inflammatory phase initiated by release of pro-inflammatory cytokines, which are wound cell messengers, initially attracting granulocytes, then macrophages and fibroblasts into the wound.\textsuperscript{24-26} Granulocytes are responsible for removing bacteria and devitalized tissue through the release of proteases. The macrophages, which then migrate into the wound, play a critical role in the transition from inflammation to granulation tissue formation by causing the wound to enter the cell proliferation phase. This period is characterized by endothelial cell and fibroblast proliferation and ECM production to replace that lost in the wounding process.\textsuperscript{27-28}
subsequent phases of healing, including remodeling can be identified by characteristic patterns of the cellular infiltrate and by the compositional changes of the ECM.\textsuperscript{29, 30}

Fibroblasts migrating into the wound, especially at the wound edges, begin to produce an early form of ECM, termed \textit{provisional matrix}.\textsuperscript{30-32} This process begins around day 5. This lag time is needed for fibroblast arrival and then fibroblast activation to produce the new matrix.

This early matrix is composed mainly of fibrin, fibronectin and hyaluronic acid. These components allow the necessary adherence of cells to the ECM for subsequent cell migration into the wound. A temporary scaffold is also created by these components to direct cell movement.\textsuperscript{32, 33} The initial ECM production is also necessary to move the wound healing process beyond the inflammatory state to new tissue formation. Fibroblasts entering the wound are instructed to produce collagen and the endothelial cells to form new vessels, both components of new granulation tissue. Fibronectin appears very early, binding to fibroblasts, thereby signaling these cells to start producing collagen. The amount of available fibronectin appears to be a rate-limiting step in subsequent formation of granulation tissue.\textsuperscript{33, 34}

The provisional ECM then evolves to a more mature matrix containing collagen and the other components previously described. The collagenous matrix provides more structure to the healing wound, and with the new vessels being created, form granulation tissue.

The ECM components and growth factors work synergistically to generate the necessary cell signals to produce key molecules from fibroblasts such as integrins which cause the necessary cell adherence to matrix needed to form granulation tissue. In addition, the alterations in ECM during healing regulate the cell response to growth stimulants needed for orderly healing. Therefore there is an ongoing cell-ECM interaction as the provisional fibronectin rich matrix evolves to a collagen based vascular matrix called granulation tissue. In turn an abnormal matrix as seen in chronic granulation tissue will have a deleterious effect on the healing process.
II. ECM and Re-epithelialization

The extracellular matrix plays an important regulatory role in the biological behavior of epidermal cells. For epidermal cells to migrate from the wound edges they must be in contact with early matrix containing fibronectin, fibrin and collagen. Migrating cells move from the wound edge toward the center adhering to the ECM traveling along the fibrin, fibronectin and collagen strands. The ongoing signaling between cell and ECM direct migration of the single epithelial sheet then activate proliferation to a multilayered epidermis.

The failure of re-epithelialization, which occurs in a poorly healing wound, was initially felt to be due to a deficit in the epithelial cell itself. Typically in slow to heal wounds, for example venous and diabetic ulcers, the epithelial cells proliferate and bunch up on the wound edges but fail to migrate.

Lack of a normal ECM at the wound edges is now recognized to be the problem, as fibronectin and to a lesser extent collagen are required for the cells to attach to the surface and migrate. The composition of the ECM (granulation tissue) must be accurate and precise for the epithelial cells to detach from the wound edge and migrate across the ECM scaffold. Abnormal ECM as is present in chronic wound retards re-epithelialization. Failure of re-epithelialization is therefore an excellent example of a matrix deficiency state.

III. Difficult to Heal and Chronic Wounds (Definitions and Pathophysiology)

The normal healing process, and the role of ECM, contrasts dramatically with the healing process seen in difficult to heal and chronic wounds. To understand the contrasts, definitions of these types of wound are needed.

Difficult to Heal Wounds

Difficult to Heal Wounds are often defined prospectively by wounds type (diabetic, venous stasis, or pressure) or retrospectively by a prolonged healing rate. The term
difficult to heal generally describes wounds, which are known to have an intrinsic impairment in the normal healing process but can heal in time. *A Clinical Definition of Difficult to Heal* may be considered to be wounds that began healing by the normal healing process but the rate of closure is delayed for months instead of weeks due to an attributed intrinsic impairment in healing. *A Biological Definition* would be a documented intrinsic impairment to normal healing characterized by a prolonged inflammatory phase, a slow forming extracellular matrix and a decrease in the rate of epithelialization.\(^{40-42}\)

**Difficult to Heal Wound**\(^{(40-46)}\)

- A prolonged inflammatory phase
- A slow forming ECM
- A decreased rate of epithelialization

The wound types of diabetic, venous stasis and pressure wounds are well described to all have a delayed healing rate relative to a typical acute wound. It is therefore safe to categorize them, as difficult to heal along with any other wounds which have intrinsic impediments to healing.\(^{49-55}\) Of course, any wound with a decreased healing rate can also evolve to a chronic wound.

The causes of the healing abnormalities are somewhat different in different types of wound as described in Table 2.\(^{40}\)
<table>
<thead>
<tr>
<th>Wound Type</th>
<th>Impediments to Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ulcer (full thickness)</td>
<td>• Elevated glucose</td>
</tr>
<tr>
<td></td>
<td>- Altering activity of proteins, lipids in ECM by glucose binding (glycosylation)</td>
</tr>
<tr>
<td></td>
<td>- Increasing red cell rigidity from high glucose impeding perfusion</td>
</tr>
<tr>
<td></td>
<td>• Impaired blood flow</td>
</tr>
<tr>
<td></td>
<td>• Tissue trauma from peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>• Absent ECM components from the onset</td>
</tr>
<tr>
<td>Venous Stasis Ulcer (Full Thickness)</td>
<td>• Calf venous pump failure leading to ischemia</td>
</tr>
<tr>
<td></td>
<td>• Peri capillary fibrin cuffs trapping ECM components such as growth factors</td>
</tr>
<tr>
<td></td>
<td>• Wound fluid impeding healing</td>
</tr>
<tr>
<td></td>
<td>• Absent ECM components</td>
</tr>
<tr>
<td>Pressure Ulcer (Full thickness)</td>
<td>• Ischemic necrosis decreasing blood flow</td>
</tr>
<tr>
<td></td>
<td>• Excess moisture, causing irritation</td>
</tr>
<tr>
<td></td>
<td>• Loss of sensation and tissue padding, leading to increased tissue pressure</td>
</tr>
<tr>
<td></td>
<td>• Malnutrition, increased age, etc.</td>
</tr>
</tbody>
</table>

*Any of these difficult to heal wounds can become a chronic wound

Many of the mechanisms involved in this healing impairment, which involve changes in wound molecular biology, are still not well understood. Clearly ECM abnormalities play a critical role.
**Chronic Wound**

The changes seen in chronic wounds may be a further accentuation of those abnormalities seen in the difficult to heal wound leading to an eventual halting of healing. Or there may be characteristics of the wound that leads directly to a chronic wound.

*A Chronic Wound* is defined as a wound, which no longer follows the normal healing process. The term non-healing is often used to describe a chronic wound. However, the exact definition is somewhat arbitrary.

A Chronic Wound is one which can no longer heal, by the normal healing process.

*A Clinical Definition* can be a wound, which fails to show any significant healing over a 3 month period (or longer) despite optimum wound care. This clinical diagnosis overlaps somewhat that of a difficult to heal wound. Diabetes, venous stasis and pressure ulcers commonly become chronic wounds.41-47

*A Biological or Academic Definition* is a wound, which cannot restore normal tissue anatomy or cannot effectively repair itself due to its abnormal biological characteristics. It is a wound stuck in a self-perpetuating inflammatory phase.

The typical biological characteristics of a chronic wound include the following:47, 56-58

- A chronic self-perpetuating state of wound inflammation
- A deficient and defective wound ECM
- Poorly responding (senescent) wound cells especially fibroblasts, limiting ECM production
- Failure of re-epithelialization due in part to lack of the necessary ECM orchestration and lack of scaffold for migration.

The evolution of a chronic wound is described in Table 3.40, 41-46
Unfortunately the physical appearance of the wound cannot distinguish whether healing will be slow (difficult to heal) or has actually stopped (chronic).\textsuperscript{41}

Table 3. Evolution of a Chronic Wound\textsuperscript{(40, 41-46)}

<table>
<thead>
<tr>
<th>Acute Inflammation Evolving to Chronic Inflammation and Cessation of Normal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Increased Neutrophils</td>
</tr>
<tr>
<td>o Excess of inflammatory cytokines</td>
</tr>
<tr>
<td>o Excess of matrix degrading proteases</td>
</tr>
<tr>
<td>o Deficiency of protease inhibitors</td>
</tr>
<tr>
<td>o Degradation of growth factors</td>
</tr>
<tr>
<td>o Impaired epithelialization</td>
</tr>
<tr>
<td>o Breakdown of new tissue synthesis</td>
</tr>
<tr>
<td>o Matrix deficiency state</td>
</tr>
<tr>
<td>o Cell senescence (unresponsiveness)</td>
</tr>
</tbody>
</table>

Non-healing wound with perpetuation of chronic inflammation.

The chronic inflammation is characterized by an excess of pro-inflammatory cytokines resulting in an excess production of matrix metalloproteinases (MMP\textsuperscript{s}) mainly by macrophages and a decreased production of the natural tissue inhibitors of MMPs called TIMPS. The prolonged inflammation leads to degradation of new ECM retarding progression of healing, as well as production of an abnormal ECM (chronic granulation tissue). This process can be documented in a wound by the identification of fragments of fibronectin, collagen and hyaluronic acid and increased MMP activity. The chronic ECM degradation process is further deleterious to the wound as these degradation fragments also act as chemotactic peptides, which attract more inflammatory neutrophils into the wound.

The prolonged inflammation also leads to decreased production of ECM or an abnormal ECM as the fibroblast signal molecules, the growth factors are also degraded by the MMPs.\textsuperscript{58-61}

Therefore, a significant component of a chronic wound can be considered to be a matrix deficiency state.\textsuperscript{58-63}
A key question, yet to be answered, is whether a chronic wound can evolve back to a healable wound. If so, what treatment approach is needed to make this transition?

IV. Correcting the Matrix Deficiency State in Difficult to Heal and Chronic Wounds

As stated, there is now considerable evidence that there is a matrix deficiency state whether as corrupt or absent ECM, in the difficult to heal and chronic wound, retarding healing. 49-61

ECM replacement could be an important component of wound management when added to the more basic requirements of wound care required for appropriate wound bed properties. ECM replacement therapy would be considered in the category of advanced wound care. An overview of Basic and Advanced Wound Management, incorporating ECM production, is described in Table 4.41, 46

A number of studies have demonstrated benefits of ECM or its components in the healing process especially with diabetic and venous ulcers. However, it is important to point out that a distinction is not made, in these prospective studies, as to whether wounds are difficult to heal or fall into the chronic wound category as the latter is often not evident until the wound fails to heal. Hopefully, a better assessment tool than visualization can provide an earlier diagnosis such as a wound surface biological biopsy. 66, 67
Table 4

| Overview of Difficult to Heal and Chronic Wound Management 41, 46 |
|---|---|---|
| **Basic Principles** | **Problems** | **Treatment** |
| | o Necrotic tissue | o Debridement |
| | o Edema | o Compression including VAC |
| | o Infection | o Infection Control |
| | o Inadequate blood flow | o Assure adequate blood flow |
| | o Poor healing environment | o Wound care |
| | | -Moist wound healing |
| | | -Control necrotic burden |
| | | -Control bacterial burden |

<table>
<thead>
<tr>
<th><strong>Advanced Principles</strong></th>
<th><strong>Problems</strong></th>
<th><strong>Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>o Excess inflammation (MMPs)</td>
<td>o MMP and cytokine blockers</td>
</tr>
<tr>
<td></td>
<td>o Corrupt matrix</td>
<td>o Matrix Replacement Therapy</td>
</tr>
<tr>
<td></td>
<td>o Cellular senescence</td>
<td>-Natural matrix (OASIS)</td>
</tr>
<tr>
<td></td>
<td>(bioburden)</td>
<td>-Skin substitute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Removal of bioburden</td>
</tr>
</tbody>
</table>

There are three feasible approaches to correcting the matrix deficiency state, which can be considered to be inter-related. All these approaches would require changing the biology of the wound surface.

2. Approaches to Correcting a Matrix Deficiency State

- The first would be to decrease the continuous ECM degradation from inflammation
1) **Decreasing ECM Breakdown** (56-58)

The first approach to decreasing ECM breakdown, would require correcting the chronic inflammatory state. Success would require the ability to modify the excess production of pro-inflammatory cytokines, and the resulting excess matrix metalloproteinase production, and decreased levels of MMP inhibition. 56-59 Currently there are no clinically available cytokine modifiers or MMP inhibitors available for clinical use. It is important to note that the chronic inflammation is in part caused by an ECM deficiency state and the ECM deficiency is due in large part to chronic inflammation, a self-perpetuating process. A feasible solution would be to provide a preformed ECM, which could control the wound inflammation phase and thereby slow the matrix breakdown.

**Decreasing Local ECM Breakdown**

- Correcting the chronic inflammatory state
- Modify the excess production of pro-inflammatory cytokines, and the resulting excess matrix metalloproteinase activity
- Consider use of a topical matrix to decrease further matrix breakdown

2) **Increasing Local ECM Production**

Increasing local ECM production requires the ability to turn on the somewhat dormant fibroblasts to produce the ECM components. 58-61, 69 The fibroblasts on the edges of difficult to heal wounds (e.g. venous stasis ulcers) have been shown to be less responsive to components of ECM such as growth factors, which typically stimulate healing. Current approaches are to add individual ECM components to stimulate production or to add fibroblasts themselves, which can produce their own ECM. 62, 70-75
The products currently available are listed.

**Products for increasing ECM Production**

- **Topical ECM components**
  - Collagen Products usually denatured
  - Fibronectin (not currently available)
  - Hyaluronic Acid

- **Topical Growth Factors**
  - PDGF (Regranex®)

- **Neonatal Fibroblasts topically applied to make ECM components**
  - Dermagraft®

- **Natural acellular Matrix**
  - OASIS®

Collagen in the form of synthetic matrices is a commonly used topical product. With the exception of Oasis®, which has a natural collagen matrix architecture and is composed of native collagen, these products are synthetic collagen-like sponges using denatured collagen. The purpose is to provide a matrix scaffold for cell proliferation and migration. It would be expected that the dual effect of a natural scaffold for cell movement and the potent biological effect of the collagen molecule would be diminished when presented in this form. Expediting cell entrance into the wound would eventually lead to more ECM production. A natural, biologically active matrix would be a more effective stimulant.

Fibronectin is another ECM element, which could be utilized as a topical agent. Fibroblasts exposed to fibronectin proliferate and produce a much greater amount of ECM than fibroblasts exposed to collagen. There is currently no clinical use of topical fibronectin for stimulating the healing process.
Hyaluronic acid, a known wound stimulant, is available in several topical products but its pro-healing activity properties, in these types of poor healing wounds, has not been well established. 73

Another currently used approach is the topical application of growth factors, an ECM component known to be deficient in the slowly healing wound.74 A number of growth factors applied topically have been shown experimentally to increase ECM production from fibroblasts as well as directly stimulate a number of phases of healing. The topical growth factor PDGF, platelet derived growth factor (Regranex®) is the agent most commonly used.76, 77 This product has been shown to experimentally increase the healing rate by increasing fibroblast proliferation and ECM deposition. It has also been shown clinically to increase the rate of granulation tissue formation and subsequent re-epithelialization in diabetic ulcers. This product has not been specifically studied in chronic wounds, using the biological definition of a chronic wound. The problem in the chronic wound is that senescent (unresponsive) fibroblasts are not very responsive to growth factors and this unresponsiveness would not necessarily be corrected by adding a growth factor. It would seem that the more chronic the wound and the more unresponsive the fibroblast, the less likely the respond to a growth factor, especially a single growth factor.78-80 Also growth factors applied topically have not been shown to decrease the chronic inflammation which is impeding healing.

The addition of new fibroblasts to the wound is also a current more high tech approach to increasing wound ECM production. The fibroblasts are extracted from human neonatal foreskins and grown on tissue cultures. When applied to a clean wound, these cells would become matrix factories if activated to do so. (Dermagraft®)79 In theory, these juvenile fibroblasts would make provisional ECM and increase healing rate. However, at present there is no evidence that these new fibroblasts directly turn on the resident senescent fibroblasts.86 Their action is short term, corresponding to the life span of these cells. This approach, a logical solution to slow healing or dormant wounds, requires that the new fibroblasts be immediately applied after delivery, as success is dependent on the robustness of the cells applied. Repeated applications are necessary to
generate enough ECM to perpetuate the healing. There should be a lag time for improvement in wound healing to occur as the cells need to gear up to produce the ECM components by local wound stimuli.

3) Adding a Preformed ECM to the Wound

There is considerable evidence that adding an preformed ECM to a wound, especially a full thickness wound, can increase healing rate in a difficult to heal wound.\textsuperscript{63-65, 84-87} For example, use of Oasis Wound Matrix\textsuperscript{®} along with compression therapy has been compared to Compression therapy alone in a randomized prospective multi-center clinical trial of patients with difficult to heal venous stasis ulcers.\textsuperscript{64, 65} Basic wound care principles were implemented prior to the study to provide a proper wound bed. The addition of the natural matrix to the wound surface significantly increased the healing to closure rate. This study indicates the value of the application of a matrix for a typical difficult to heal wound.

It also appears that a complete ECM is more effective than single ECM components. An example is the clinical comparison of an intact natural matrix product (Oasis\textsuperscript{®}) with the single growth factor PDGF (Regranex\textsuperscript{®}) in the treatment of difficult to heal diabetic foot ulcers again in a randomized prospective multicenter clinical trial. The use of the intact natural ECM (Oasis\textsuperscript{®}) resulted in a significant increase in healing rate compared to the single ECM component (Regranex\textsuperscript{®}).\textsuperscript{65}

There are a large variety of Preformed ECM type products, most of which are synthetic. The properties of the ECM product used will substantially impact the effect on healing. (Table 4)

Table 4: Preformed ECM Products added to the Wound \textsuperscript{64, 65, 86-95}

| o Synthetic Collagen Based ECM |
| - denatured collagen in a synthetic matrix structure |
| o Non-human ECM with a natural structure and biological activity (Oasis\textsuperscript{®}) |
| o Dermal products from human skin with natural structure and activity |
| o Permanent skin substitutes |
The addition of a complete ECM to a poorly healing wound has the advantages of adding both a mechanical scaffold as well as the bioactive components of matrix to direct healing. 64,65,88-95

A number of other studies, showing success of dermal like-matrix in acute wounds, has led to the increased development and increasing use of these products in difficult to heal and chronic wounds. The obvious advantages are the fact that an ECM, containing all the active components and a normal scaffold, can provide the necessary cell signaling and direction for new ECM production by resident fibroblasts. There would also be no lag time to stimulate healing if an active preformed ECM is provided.

However, all matrixes are not the same. Of importance is that there is considerable variability in the wound cell response depending on the composition of the matrix dressing used. For example, fibroblasts placed in a fibronectin or fibrin rich surface matrix produces a much greater matrix expression than those placed in a pure collagen matrix. 88-98

Several synthesized collagen based matrix are clinically available. These products produce scaffolding properties but do not have a natural collagen structure in place, necessary for the normal collagen signaling, and do not contain the other bioactive components of matrix such as fibronectin and glycosaminoglycans. 88-98

Products produced from human skin such as processed cadaver dermis, an example being Alloderm®, are incorporated into the wound and direct epithelial cell migration. 88, 90, 95 These products typically are frozen prior to use to maintain tissue viability on placement. Availability will always be limited.

Oasis® wound matrix is a natural ECM derived from the small intestinal submucosa of the pig intestine. The submucosal components, which direct the continuous gut mucosal turnover, are basically identical in composition to human extracellular matrix. 64, 65, 99, 100
The other category of matrix products, living skin equivalence, are used as a permanent skin replacement. Their role is therefore not to heal a wound but rather permanently close a wound. 98, 101-103

**VI. Rationale for the use of ECM in Difficult to Heal vs. Chronic Wounds**

As described, scientific studies both experimental and clinical, have demonstrated that ECM components do improve healing of an acute wound and more complicated wounds such as diabetic, venous and pressure ulcers. All the studies in the latter category of wound are combinations of difficult to heal and chronic wounds. As stated earlier, diabetic, venous and pressure wounds start out as difficult to heal wounds.

It is fair to say that wounds in the difficult to heal category have a matrix deficiency and also can respond to the addition of ECM components, especially topical use of an already formed ECM. At present, the same cannot be said, at least scientifically, for the use of ECM in matrix deficient chronic wounds. Although it is very possible that matrix application can control the self-perpetuating chronic inflammation, the studies have not yet been done on this specific wound population. Is it possible to reverse cell senescence with ECM? It is more likely that this cell burden would have to be removed or replaced with cells still responsive to ECM application for the wound healing benefits to be demonstrated. These studies also need to be done.

Therefore at present it would seem most logical to use ECM components earlier on wounds known by their nature to be difficult to heal rather than wait until there is evidence of non-healing. This delay may well eliminate the potential beneficial wound healing effects of the use of the potent healing properties of ECM in matrix deficiency states.
REFERENCES:


