2014

A pilot study: pirfenidone, 8% (KitosCell) as a treatment for striae distensae

Koontz, Jeremy Parco

https://hdl.handle.net/2144/15087

Boston University
A PILOT STUDY: PIRFENIDONE, 8% (KITOSCELL) AS A TREATMENT FOR STRIAE DISTENSAE

by

JEREMY PARCO KOONTZ

B.S., Brigham Young University, 2009

Submitted in partial fulfillment of the requirements for the degree of Master of Science

2014
Approved by

First Reader

Byungwoo Ryu, Ph.D.
Assistant Professor of Dermatology

Second Reader

Estuardo Aguilar-Cordova, M.D. (inf), Ph.D.
C.E.O. of Advantagene, Inc.
I would like to begin by thanking my readers, Estuardo Aguilar-Cordova and Byungwoo Ryu, for your thorough feedback and guidance. I also thank the members of the Advantagene, Inc. team who have helped me in countless ways during the course of this thesis, and have been wonderful supporters and coworkers: Laura Aguilar, Jill Brace O’Neill, Kandarp Prajapati, Evrim Erdem, Andrea Manzanera, Brian Guzik, Katherine Manzanera, Daniel Sanchez, Stephanie Hawkinson, Priya Subramanian, Lachezar Ranchev, Maya Gotova, Patricia Dower, and Hector Lemus. Above all, I would like to give my deepest appreciation to my loving and beautiful wife, Rachel Koontz, and my adorable little girls, Brinley and Brooke. Your support and patience has left me speechless and meant the world to me. Again, thank you.
A PILOT STUDY: PIRFENDIONE, 8% (KITOSCELL) 

AS A TREATMENT FOR STRIAE DISTENSÆ 

JEREMY PARCO KOONTZ 

ABSTRACT 

Striae distensae (SD; stretch marks) are well-recognized skin lesions that occur in a large percentage of the population. Although they rarely cause significant medical concern, they can be a source of extreme physiological stress to affected patients. They occur commonly in pregnancy, puberty and obesity, but also become manifest following various medical conditions and therapeutic interventions. The precise etiological mechanism of SD has yet to be determined, however numerous theories have been proposed and risk factors have been identified. To date, there are many different treatment modalities to improve size and color of striae including diet and exercise, topical and laser therapies and surgery but none have demonstrated a consistent effectiveness. This unmet medical need may be addressed by the use of Pirfenidone. 

Pirfenidone is a small synthetic non-peptide molecule of low molecular weight (185.2 Daltons) that has been identified to have immuno-modulatory and anti-inflammatory properties. Clinical evidence indicates that Pirfenidone can modulate collagenase and fibroblastic activity by the modulation of cytokines in the wound healing process, such as TFG-β and TNF-α, which lead to effective collagen remodeling. Pirfenidone has exhibited low-toxicity in pre-clinical and clinical studies. These in vitro and in vivo findings suggest that Pirfenidone may be a safe and effective treatment of patients with SD.
# TABLE OF CONTENTS

**TITLE** ........................................................................................................................................... i

**COPYRIGHT PAGE** ......................................................................................................................... ii

**READER APPROVAL PAGE** ........................................................................................................... iii

**ACKNOWLEDGMENTS** ..................................................................................................................... iv

**ABSTRACT** ....................................................................................................................................... v

**TABLE OF CONTENTS** ..................................................................................................................... vi

**LIST OF TABLES** ............................................................................................................................... ix

**LIST OF FIGURES** ............................................................................................................................. x

**LIST OF ABBREVIATIONS** ................................................................................................................. xi

**INTRODUCTION** ............................................................................................................................... 1

Striae Distensae: Overview ................................................................................................................. 1

Risk Factors and Etiology ..................................................................................................................... 2

Histology and Pathophysiology of SD ................................................................................................. 4

Abnormal Histology and Pathophysiology of SD ............................................................................... 7

**CURRENT TREATMENTS FOR STRIAE** .......................................................................................... 10

Diet and Exercise ................................................................................................................................. 10

Topical Treatments ............................................................................................................................... 11

Laser Treatments ................................................................................................................................. 14

Other Treatments ................................................................................................................................. 19
VITA.............................................................................................................................................. 61
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Study Time and Events Table</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Vancouver Scar Scale</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>Adverse Event Reporting Schedule</td>
<td>50</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Structural formula and information on Pirfenidone</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Protocol Schema</td>
<td>38</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

6MET ..................................................................................6-minute steady-state exercise test
AE .........................................................................................Adverse event
AHA .......................................................................................Alphahydroxy acid
COL1A1 ..............................................................................Collagen, type I, alpha 1
CTCAEv3.0 ............................................................Common Terminology Criteria for Adverse Events Version 3.0
CTGF .....................................................................................Connective tissue growth factor
DEJ .........................................................................................Dermal-epidermal junction
ECM .........................................................................................Extra-cellular matrix
EI ....................................................................................... Erythema index
FDA .......................................................................................Food and Drug Administration
FVC .....................................................................................Forced vital capacity
HRCT .................................................................................High-resolution computerized tomography
IL-1β ...................................................................................Interleukin 1-beta
iNOS ......................................................................................Inducible nitric oxide synthase
IPF .......................................................................................Idiopathic pulmonary fibrosis
IRB .....................................................................................Institutional review board
MI .......................................................................................Melanin index
MMP ..................................................................................Matrix metalloproteinase
MS .....................................................................................Multiple sclerosis
Nd:YAG ...............................................................................Neodymium:yttrium-aluminum-garnet
NF-κB ..............................................................Nuclear factor kappa-light-chain-enhancer of activated B cells
NIH ........................................................................ National Institutes of Health
OBA ......................................................................... Office of Biotechnical Activities
OH-PFD .................................................................. Hydroxypirfenidone
PDGF ....................................................................... Platelet-derived growth factors
PDL .......................................................................... Pulse dye laser
PFD .......................................................................... Pirfenidone
PFT ........................................................................... Pulmonary function test
POSAS ................................................................. Patient and Observer Scar Assessment Scale
QOL .......................................................................... Quality of life
RGD .......................................................................... Arginine-Glycine-Asparagine
ROI .............................................................................. Region of interest
SD ........................................................................ Striae distensae
SpO₂ ....................................................................... Oxygen saturation
TB ........................................................................... Transforming growth factor-beta-binding protein-like
TCA .......................................................................... Trichloroacetic Acid
TGF-β ..................................................................... Transforming growth factor-beta
TID ........................................................................... Three times a day
TNF-α ..................................................................... Tissue necrosis factor-alpha
TIMP ....................................................................... Tissue inhibitor of metalloproteinase
UVB .......................................................................... Ultraviolet B
VAS .......................................................................... Visual Analog Scale
VC ........................................................................... Vital capacity
VEGF ................................................................. Vascular endothelial growth factor
VSS ................................................................. Vancouver Scar Scale
XeCl ................................................................. Xenon diode
INTRODUCTION

Striae Distensae: Overview

*Striae distensae* (SD) are defined as atrophic linear dermal scarring with overlying epidermal atrophy (Bak et al., 2009; Yang & Lee, 2011). Striae most commonly occur on the abdomen, buttocks, thighs, upper arms, and breasts. They can have differing etiologies and characteristics and are found in both genders across all ethnic backgrounds. They occur frequently during adolescence or pregnancy when there is rapid tissue growth, influencing an estimated 90% of pregnant women, 70% of adolescent females, and 40% of adolescent male (Al-Himdani, Ud-Din, Gilmore, & Bayat, 2014). They occur in numerous other physiological and pathological conditions such as obesity, connective tissue disorders, Cushing’s syndrome, Marfan syndrome, hypercortisolism, diabetes, and long-term systemic or topical steroid use or exposure (Yang & Lee, 2011).

Although striae are not usually a life-threatening medical problem, they have the potential to cause great emotional distress and serious health complications to patients. The highly pigmented, broadly distributed red/purple striae (striae rubra and striae caerulea) can persist for decades without change. Often seen in young cancer survivors and adolescents, these prominent scars can have a significant impact on quality of life (QOL). Children afflicted with striae were more susceptible to depression, loss of self-esteem, emotional distress, eating disorders (Strumia, 2005), and in some cases, body dysmorphic disorder (Tedeschi, Dall’Oglio, Micali, Schwartz, & Janniger, 2007).
Patients may also face serious medical risks due to the ulceration of SD due to excessive stretching forces or the increased use of concurrent corticosteroid and bevacizumab therapy. In malignant glioma patients, there has been an increase in the incidence of ulcerated striae. Bevacizumab, used to treat glioma, is an anti-vascular endothelial growth factor (VEGF) antibody, which plays an important role in wound healing and collagen production (Peters et al., 2011). Patients with ulcerated striae are at a higher risk of infection. Thus, SD can have a significant negative impact on quality of life and can lead to an increased risk of secondary adverse events.

**Risk Factors and Etiology**

Although the exact cause of SD is unknown, many hypotheses have been proposed in the literature. As one of the earliest explanations for the cause of SD, in 1925 Kogoj et al. suggested that the formation of SD was a direct result of toxic damage to tissue architecture from striatoxins (Gauglitz, Reinholtz, Kaudewitz, Schaubler, & Ruzicka, 2013). Some researchers argue that striae are a result of excessive mechanical stress applied to the dermis, resulting in damage to the connective tissue framework (Elsaie, Baumann, & Elsaaiiee, 2009). The common name “stretch marks” comes from this belief. For example, marks caused by tensional stress in pregnancy, adolescent growth spurts, and weight gain due to bodybuilding or obesity. However, others dispute this theory citing research that finds no correlation between abdominal girth in pregnant women and resulting striae (Elsaie et al., 2009). It has also been suggested that striae develop more easily in skin that has a high proportion of rigid cross-linked collagen, as
occurs in early adult life (Shuster, 1979). Increased adrenal cortical activity has also been implicated in the formation of striae, as in the case of Cushing’s syndrome (Stevanović, 1972). Corticosteroids can have catabolic effects on the activity of fibroblasts, resulting in inhibited collagen deposition and a decreased activity of extracellular matrix components (Tsuji & Sawabe, 1988). Striae are a common side effect of glucocorticoids (Schoepe et al. 2006), such as when they are used in the treatment of cancer. Though many similarities exist between the maturation of SD and that of normal wound healing, research to elucidate the definite pathogenesis of SD is ongoing.

Clinically, the maturation of SD may occur in stages. First, the acute stage is characterized by flattened areas of pink-to-violaceous skin that form along Langer’s lines and may be slightly raised and itchy (Shuster, 1979). These lesions, or striae rubra, tend to be oriented perpendicularly to the direction of greatest tension and typically in areas of high adipose tissue deposition (Elsaie et al., 2009). Most of the time, the striae rubra change gradually to a blue-to-purpuric color during the sub-acute stage and are predisposed to increase in length, flatten and take on a smooth or finely wrinkled appearance. Over time, some highly-pigmented striae may evolve into a final stage, known as the chronic stage. In the chronic stage, the dark scars may fade in color and evolve into white atrophied depressions, or striae alba, generally several centimeters long and 1-10 mm wide.

Although some striae may eventually fade to striae alba, there is no defined timeframe for this transformation. The darker color of earlier SD is likely due to the inflammatory response associated with the vasodilatation. Other forms of striae rubra are
striae caerulea (blue) and striae nigra (black). These denominations of deeply colored SD may appear darker than surrounding skin due to increased melanization (Hermanns & Piérard, 2006). For some patients, the maturation of striae rubra to striae alba can take months, while other patients experience scars that persist for decades without maturation. For the population of adolescents and young adult patients that are affected by the latter, striae can be the source of significant psychological stress and greatly influence quality of life.

**Histology and Pathophysiology of SD**

The histology and natural evolution of SD is similar to the process of wound healing and scar formation (Atwal et al. 2006). The normal wound healing process is both complex and highly orchestrated. This process is mediated in large by interacting molecular signals, primarily cytokines, which participate in the various stages of tissue reconstruction after injury: initiation (clotting), inflammation, migration/proliferation and remodeling.

Initiation begins with vasoconstriction and platelet activation soon after injury. In areas where the damage to cellular architecture has resulted in vascular damage and hypoxia of adjacent tissue, platelets initiate the clotting cascade and release growth factors and cytokines to influence tissue edema and initiate inflammation. Some of these prominent growth factors include platelet-derived growth factor (PDGF), VEGF and the transforming growth factors-beta (TGF-β). VEGF is in part responsible for the extravasation of plasma proteins to create a temporary structure for cell migration to the
wound site and, along with PDGF, the process of angiogenesis, new blood vessel growth. The TGF-β family of cytokines is involved in the coordinating the wound-healing process from the initial insult and clot formation, to the final phase of matrix deposition and remodeling. TGF-βs are released in large quantities and have the most potent stimulatory effect on extracellular matrix deposition of any cytokine so far examined (Jacobsen, Ruscetti, Roberts, & Keller, 1993). Autocrine expression of TGF-β by leukocytes and fibroblasts leads to a cascade of additional cytokine release including tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1β) and other chemokines (Wan et al., 2012).

During the inflammation stage of healing, neutrophils, macrophages and lymphocytes infiltrate the wound site. These cells are attracted to the wound site by the cytokines released in the initiation stage. Neutrophils release cytoplasmic granules containing proteases that eliminate necrotic residues. Macrophages further aid the removal of bacteria and necrosis by engulfing offending debris. They also secrete growth factors for fibroplasia and angiogenesis. Finally, lymphocytes participate in the regulation of wound healing, although their role is less understood.

The inflammation stage is followed by migration and proliferation. Cellular transformations such as wound closure, neovascularization, and re-epithelialization highlight this stage of wound healing. Endothelial cells participate in angiogenesis and the generation of a de novo network. Re-epithelialization is the hallmark process of proliferation. As early as 12 hours after injury, epidermal cells, responsible for maintenance of structural integrity of the dermis, develop pseudopods and lose their
intercellular adhesion leading to cell migration to the wound site. The epidermal cells proliferate quickly to ameliorate the epithelial deficit. Fibroblasts are guided by fibroblast-derived chemotactic factors to migrate to the wound margins. In addition to physical structure, fibroblasts have many other important functions. Their main role is the production of fundamental extracellular matrix components such as collagen, elastin, and proteoglycans. The process by which the fibroblastic recruitment and matrix synthesis are accomplished is coordinated in large part by signaling from TGF-β (Wahl, 1994).

Remodeling is a dynamic process in response to the biomechanical stress that the wound site experiences and may last for months following the injury. Over time, cell density increases and vascularization diminishes towards pre-injury levels. Also, tensile strength increases through the replacement of type III collagen, which is quickly deposited after the injury during the migration/proliferation stage, with type I collagen that is placed down in an orderly natural state during the remodeling stage. In normal collagen deposition, a balance is established between collagen synthesis and degradation. This process is accomplished through the actions of the fibroblasts and macrophages. The fibroblasts are involved in the synthesis of collagen, which is regulated at the transcriptional and translational level. Collagen degradation, performed by macrophages, is regulated by matrix metalloproteinases (MMPs) (Macías-Barragán et al., 2010). The MMP family of enzymes is predominately produced by macrophages and is capable of breaking down many components of the ECM for migration and tissue remodeling in wound healing. Tissue inhibitors of metalloproteinases (TIMPs) regulate MMPs. Shortly after injury, the amount of collagen deposition produced by the fibroblasts exceeds that
which is degraded. Yet, as the wound matures the level of collagen and extracellular matrix production and degradation become equal reaching a homeostatic equilibrium.

**Abnormal Histology and Pathophysiology of SD**

In comparison to the timely and tightly orchestrated reparative process of normal wound healing, the process of abnormal wound healing, like keloid scars and SD, is significantly altered. The resulting tissue architecture lacks anatomical and functional integrity. The disorganized structure may be a result of an attenuation or disruption of cellular and molecular signals from growth factor and cytokines released during the wound repair process. In the case of keloid scars the rate of deposition of collagen at the wound site exceeds the rate collagen degradation. Conversely, in SD, the rate of collagen degradation exceeds that of collagen deposition. This change from equilibrium leads to the different pathologic outcomes.

In early stages of striae development, skin elastolysis is followed by excessive mast cell degranulation leading to activated macrophages that envelop fragmented elastic and collagen fibers (Arem & Kischer, 1980). Inflammatory changes may predominate with edema around the dermal venules. In later stages, SD is characterized by the thinning of the overlying epidermis, diminished rete ridges and shallower dermal papillae. In common with fibrosis and scars, scanning electron microscopy of striae show dysfunction of the skin connective tissue yielding a formation of collagen fibers preferentially aligned in a single direction (De Pasquale et al., 1987). In SD, the collagen in the upper third of the dermis is layered in thin eosinophilic bundles oriented in straight
lines, parallel to the surface of the skin (Piérard et al., 1999). Contrarily, collagen in normal skin is interwoven in a meshwork distribution.

Also, Watson et al. (1998) observed that the dermal elastic system shows breakage and retraction of the elastic fibers in the reticular dermis. This system allows the skin to spring back to its resting conformation after being distended. The elastic fibers in normal skin form a complex and intertwining system that forms a continuum of thick elastic fibers from the dermal-epidermal junction (DEJ) through the papillary dermis and to the reticular dermis. However in SD, the broken elastic fibers curl at the sides of the striae forming a characteristic pattern on scanning electron microscopy. SD have a statistically significant reduction in the number of vertically oriented elastin and fibrillin fibers proximal to the DEJ (Watson et al., 1998).

Damage to the fibrous framework of SD has fueled research of the cellular interactions that mediate the balance between fibrous deposition and degradation and their influence on wound repair. In SD, damage to the fibrillin framework may induce additional TGF-β release and activation (Watson et al., 1998). Fibrillin—a component of elastic fibers—shares a signature eight cysteine TGF-β-binding protein-like (TB) domain with latent TGF-β-binding proteins and contains Arg-Gly-Asp (RGD) integrin binding domains (Robertson, Jensen, & Handford, 2011). The effects of TGF-βs are considered a link between the processes by which cells and tissues respond to infection or injury and initiate repair (Wahl, 1994). As stated previously, TGF-βs has complex and far-reaching effects in the process of wound repair. For example, TGF-βs acts as a conversion factor regulating repair by orchestrating the inflammatory response, inhibiting the response and
then converting to a response of matrix deposition. TGF-βs can recruit and activate leukocytes, namely the macrophages, in inflammation and tissue remodeling, but can also down-regulate these catabolic processes of this same populations of cells by inhibiting activated inflammatory cells and stimulating activity in fibroblasts for matrix synthesis. Thus, TGF-βs acts in a bi-directional manner (Jacobsen et al., 1993; Wahl, 1994). Chronic stimulation of TGF-βs, as is the case in SD, may lead to variations in wound healing control and lead to pathological diseases.

It is no surprise that understanding the nature and effects of TGF-βs have drawn the interest of researchers aiming to modulate the wound healing process and alter SD pathology.
CURRENT TREATMENTS FOR STRIAE

Despite the increasing knowledge of wound healing and collagen metabolism, treatment for SD remains disappointing and frustrating for patients. Several treatment modalities have been proposed for the treatment of striae but many are considered ineffective or do not offer complete resolution of the SD.

Diet and Exercise

Many people develop striae where weight gain is common; such areas include the abdomen, thighs, upper arms, hips and buttocks. Schwingel et al. examined the effect of exercise and weight loss on stretch marks. In this study, women between 24 and 53 years of age participated in a 3-month weight loss program. Participants were assigned into one of three groups; diet (n = 29), diet plus aerobic exercise program (n = 31), or diet plus resistance exercise program (n = 20). SD was prevalent in 79% of the participants. Study results demonstrated that the severity of striae did not change with weight loss, regardless of which study arm they were associated with. Although diet and exercise may slow down the progression of stretch marks and the likelihood of developing more striae, medical experts do not acknowledge them as an effective means of treating existing SD (Elsaie et al., 2009).
**Topical Treatments**

A wide variety of topical treatments have been assessed as potential treatment options for SD ranging from easily attainable household products, such as cocoa butter, olive oil and castor oil, to synthetically produced agents. Yet to date, no treatment has shown consistent results at treating SD. A Cochrane review evaluated the use of prophylactic topical creams for the prevention and treatment of SD from six trials involving a total of 800 pregnant women (Brennan, Young, & Devane, 2012). No statistically significant difference was seen in the development of SD in women who received topical preparations with active ingredients compared to women who received a placebo or no treatment. Creams evaluated included alphastria, trofolastin, cocoa butter, olive oil and verum. Alphastria and trofolastin creams are thought to stimulate fibroblasts activity and have an antagonistic effect against glucocorticoids. The hyaluronic acid content in alphastria is thought to be its active ingredient. Verum is also composed of hyaluronic acid, with vitamin E, panthenol, elastin and menthol (Elsaie et al., 2009). All were considered not effective. In a double-blind randomized controlled trial, Buchanan et al. (2010) showed no significant difference between patients developing SD in groups treated with cocoa butter or placebo.

Other approaches include massage with or without comfrey, hypericum, maritime pine, equisetum, slippery elm, sweet almond oil, wheat germ oil, olive oil, avocado oil, castor oil, wheat grass or eucalyptus tree oil. These agents’ putative mode of action is hydration, meant to increase cellular volume and oppose mechanical atrophy. Moisturizers or emollients serve to make the external layers of the skin softer and more
pliable, by increasing the skins’ hydration or water content, and reducing evaporation. Unfortunately little in the literature is available to support the success of these creams or oils in striae prevention.

Massage is frequently recommended to improve the aesthetic outcome of scars postoperatively. Regimens for how to implement massage vary greatly. Shin and Bordeaux (2012) reviewed studies including 144 patients who received scar massage, of variable frequencies and durations, and found that 90% had improved appearance or Patient Observer Scar Assessment Scale scores. Yet they also concluded that the evidence for the use of scar massage is weak with variable outcomes, which are not measured with objectivity or in any standardized manner. Specifically related to striae, there is no data to support massage as a treatment for SD.

Another set of agents proposed to treat striae are chemical peels (Elsaie et al., 2009). The mode of action of these agents is thought to involve fibroblastic stimulation, inhibition of glucocorticoids, or stimulation of collagen production/synthesis. Three different strengths of chemical peels exist: light, medium, and deep. Light chemical peels, including alphahydroxy acid (AHA) and glycolic acid, are usually applied in medical offices, with minimal discomfort, and no anesthetic necessary. Medium peels, such as trichloroacetic acid (TCA), are also applied in a medical office or ambulatory surgical center. Frequently these require a combination of tranquilizer and an oral analgesic (Halaas, 2004). Phenol is an example of a deep chemical peel. Administration of deep chemical peels typically require general anesthesia.
Topical tretinoin, a vitamin A derivative, is one of the first light chemical peels used to treat SD and has yielded variable results (Elson, 1990). In a small 22 patient study evaluating 0.1% tretinoin (n = 10) versus placebo (n = 12), the investigators reported a reduced length and width of 14% and 8% in treated lesions, compared to the increase of 10% and 24% in placebo group. There was no significant difference in dermal collagen and elastic fibers in treatment compared to placebo (Kang et al., 1996). The creams were applied once a day for six months. Eight of the tretinoin treated patients had subjective improvement compared to one in the placebo group. No significant differences between the groups were found with histologic assessments. The same study showed improvement in the clinical appearance of striae in their ‘active’ phase, striae rubra, without much effect on striae alba.

Glycolic acid (alpha hydroxyl acid) and TCA are thought to function by stimulating collagen synthesis. Various reports have claimed some efficacy from these agents with the peeling followed by hydration of skin (Crowther et al., 2008). There are various reports of the potential clinical effects of glycolic acid on rejuvenation, peeling and photoaging, but no data regarding prevention of or treatment for SD. Ash, et al (1998) compared topical treatment of striae alba with 20% glycolic acid/0.05% tretinoin and 20% glycolic acid/10% L-ascorbic acid utilizing daily applications of each for 12 weeks. Both regimens showed improved appearance of striae and were safe in study patients with minimal irritation, although it was not determined which of the ingredients provided the observed effect. No significant differences between the groups were found with histologic assessments.
Laser Treatments

The introduction of laser energy as a treatment modality for dermatologic diseases was first proposed by Anderson and Parrish (1981). This technique is characterized by the bombardment of a particular chromophore using short bursts of photoenergy (photons). Specific wavelengths of light are used to preferentially target the desired chromophore, while leaving the neighboring tissue undisturbed to achieve localized photothermal injury. Lasers and light source treatments may produce energy that selectively targets oxyhemoglobin in the dilated vessels of immature SD or may induce changes in collagen and elastin formation (Savas, 2013). Despite the characterization and popularity of selective photolysis treatments, the exact mechanism by which lasers treat SD is largely unknown.

Laser ablation is the process of removing and resurfacing skin by irradiating it with a targeted beam of light, either superficially or involving the deeper layers. Carbon dioxide laser resurfacing is thought to illicit fibroblast activity and epidermal vaporization and coagulation of the underlying dermis (Lee et al., 2010). Initially, the predictable depth of tissue ablation and thermal denaturation and preliminary results of argon and carbon dioxide laser ablation seemed promising. Yang and Lee (2011) evaluated carbon dioxide laser resurfacing in 24 South Korean patients with varying degrees of striae alba. Patients were randomly stratified into a treatment protocol of nonablative Er:glass laser or ablative fractional carbon dioxide laser. Patients were treated three times over four-week treatment intervals. Although two patients were
ultimately excluded during treatment due to pruritus and hyperpigmentation, the study authors stated that carbon dioxide laser resurfacing treatment may help to improve the appearance of striae alba in Asian skin. This treatment modality was not evaluated as an effective treatment of the more prominent striae rubra.

Ablative laser treatments have many disadvantages. Treatments require pain management, carry the risk of adverse reactions, and ultimately have shown inconclusive results. Ablative laser treatment procedures require physician administered anesthesia, conscious sedation and other types of treatment for pain. Therefore, after ablative laser treatment the patient requires an intense post-operative care and recovery time, during which the skin granulates (i.e. scabs) and is shed. This process carries with it the potential of adverse events such as infection, poor wound healing and the risk of dyspigmentation, hyperpigmentation and scarring, particularly in the darker skin types. In the previous study, authors Yang and Lee cautioned patients with Fitzpatrick skin types IV to VI to avoid the use of carbon dioxide laser due to the probability of developing postinflammatory dyschromia. After treatment, patients have a period of transient mild erythema and hyperpigmentation and are required to avoid prolonged sun-exposure (Goel et al. 2011). Carbon dioxide and argon, both ablative laser modalities, were not shown to yield permanent results. The use of both laser treatments resulted in uniform scar reoccurrence (Alster, 1997).

Nonablative lasers modalities, such as 585-nm flashlamp-pumped pulse dye laser (PDL), 308-nm xenon chloride (XeCl) excimer laser, 577-nm copper-bromide laser, 1,450-nm diode laser and 1,064-nm neodymium-doped:yttrium-aluminum-garnet
(Nd:YAG), penetrate the skin, but without visible wounding. Theoretically, these laser treatments target the hemoglobin or melanin in SD.

The 585-nm PDL is the most commonly used laser treatment for SD (Elsaie et al., 2009). Researchers have attempted to target the dilated blood vessels in striae rubra with the 585-nm flashlamp PDL. Treatment is administered through a series of laser treatments done at lower energy levels, which minimizes the chances of burning, pigmentation, scarring and other unwanted side effects. McDaniel et al. (1996) evaluated the clinical improvement of SD in a controlled study of 39 patients with striae rubra. Patients were stratified into four treatment groups and treated with several courses of 585-nm PDL using dynamic cooling on affected sites, including the abdomen, thighs and breasts. McDaniel determined the optimal energy density (3 J/cm²) and measured outcomes based on subjective analysis, shadow profilometry and histopathological analysis. When compared to untreated SD, outcomes demonstrated an increased amount of collagen and dermal elastin improving the surface topography. A limitation of this study was that the principle investigator was not blinded to the different treatment protocols when evaluating subjective analysis data throughout the study. Jiménez et al. (2003) also documented collagen changes in SD lesions in a controlled study of 20 patients treated with 585-nm PDL. But, they found no statistically significant change in the SD area compared to controls. Changes were only moderately beneficial in reducing the degree of erythema in striae rubra of patients with skin types II to IV, noting also that there was no change in striae alba. They strongly cautioned against the use of PDL in patients with darker skin types, V to VI, citing the similarities between melanin and
hemoglobin as a chromophore for the light energy from the 585-nm PDL. Post-inflammatory hyperpigmentation was experienced by this melanin-rich population even with low treatment fluences. It was determined that this treatment modality should be avoided or used with extreme caution.

Technological advances have allowed the implementation of the 308-nm XeCl laser, an ultraviolet laser with characteristics close to that of ultraviolet B (UVB) light. The 308-nm XeCl laser has a good safety profile, greater precision and the ability to deliver a higher fluence in a shorter amount of time compared to previous laser treatments. Study results have shown pigment correction in some late-stage hypopigmented striae alba due to a proliferation and hypertrophy of melanocytes. Unfortunately, the repigmented changes declined back to baseline after 6-months and failed to show any improvement in skin atrophy. These results highlight the need for regular maintenance through repeated treatments, deeming the use of 308-nm XeCl laser as a temporary solution to a chronic problem.

The 577-nm copper-bromide laser emits light energy coinciding with the maximum absorption peak of hemoglobin; however only one small 15-patient study has been published supporting that this is a safe, efficacious and potentially a long-term solution for SD treatment. Furthermore, study results show that it was only evaluated on a narrow sample of skin types, II and III, without histological information collected, making further research necessary (Longo, Postiglione, Marangoni, & Melato, 2003).

Similarly, there has been only one clinical study to substantiate any efficacy of the use of 1,450-nm diode laser as a treatment for SD. Using 1,450-nm diode laser with
cryogen cooling spray, Tay et al. treated 11 patients with SD and Fitzpatrick skin types IV to VI. Areas of treatment included the abdomen, arms, back, buttocks and thighs. When evaluated for safety and efficacy, 1,450-nm diode laser was deemed ineffective by physician assessment, showing no improvement in any lesions for all subjects after two months of treatment (Tay, Kwok, & Tan, 2006). Sixty-four percent of the patients (n = 7) also experienced transient erythema and significant postinflammatory hyperpigmentation following treatment. Based on these results, Tay et al. does not recommend the use of 1,450-nm diode laser for treatment of SD in similar skin types.

Nd:YAG laser was found to induce new collagen formation in a study evaluating treatment for facial wrinkles. Nd:YAG has a well-documented affinity for vascular targets. Due to these results, Goldman et al. (2008) conducted a small, single arm study targeting the dilated venules of immature SD in 20 patients with Fitzpatrick skin types of II to IV. Patients averaged 3.45 treatment sessions with a 3 to 6 week treatment interval. Results were described as excellent by fifty-five percent of study participants and only 40% of doctors. Yet some patients (n = 4) experienced no change in SD appearance.

The use of laser therapies for the treatment of SD, although popular, has been marred with uncontrolled studies and results that underscore their many limitations. Laser studies are understandably difficult to blind, in addition a significant proportion of the studies had small sample sizes, limited patient diversity, and a lack of control groups and randomization. Laser treatments are costly and the degree of improvement seems to be minimal to moderate and transient with potential adverse events such as erythema,
hyperpigmentation, hypopigmentation, blistering and crusting, scarring, purpura, secondary infection, and pain (Handley, 2006).

**Other Treatments**

Other treatments, including microdermabrasions, surgical excision, subcision, grafting procedures, cryotherapy, corticosteroid injections, pressure therapy, and radiation therapy have all been investigated as treatments for SD. None have shown significant benefit. Oftentimes the side effects and resulting scars were as severe as the original SD (Alster & Handrick, 2000).

Microdermabrasion is a skin resurfacing technique using inert aluminum oxide as an abrasive agent propelled at irregularities in the skin surface irregularities. Microdermabrasion has been thought to set in motion a cascade of molecular events capable of causing remodeling and repair of the dermal matrix for skin contour irregularities. In some indications it is reported to increase type-I collagen (Karimipour, Karimipour, & Orringer, 2010). It has proven effectiveness in skin conditions including acne scars, mottled pigmentation and fine wrinkles. Only a very limited number of studies have evaluated the use of microdermabrasion for treatment of SD, none with significant results. Karimipour et al. (2010) concluded that the use of microdermabrasion for SD was less effective than glycolic acid and chemical peels. Some reports suggest this technique may have a greater effect on striae alba than striae rubra (Elsaie, et al, 2009).

Surgery is an option meant to remove or relocate striae but has significant potential toxicity and cost (Baroudi, 1979). Subcision is a surgical technique utilized to
manage depressed scars. Its goal is to sever the fibrous attachments beneath the scar at the subdermal level in order to lift up the scar and induce the formation of connective tissues through normal physiological healing (Alsufyani & Alsufyani, 2012). A pilot study to determine if subcision is an effective treatment option for striae, showed a high percentage of striae treated in this manner developing necrosis (Luis-Montoya, Pichardo-Velázquez, Hojyo-Tomoka, & Domínguez-Cherit, 2005).

As evident from the information presented, a wide variety of treatments have been evaluated as treatment modalities for SD, however none has shown consistent results and thus there is no ‘gold standard’ treatment for improving the pathology of striae. This underscores the need to develop an effective and safe intervention that will modulate the wound healing process after striae scar development. A novel potential treatment, topical application of Pirfenidone, holds great promise in this indication.
PIRFENIDONE

Because established treatment modalities for SD have been determined inconsistent or ineffective, we propose the use of KitosCell, a topical application of Pirfenidone, as an effective and safe treatment for SD. Pirfenidone (PFD) [5-methyl-1-phenyl-2-(1H)-pyridone] (Figure 1) is a small molecule that has been shown to modulate the wound healing process and scar formation by regulating the action of a series of cellular factors. PFD is a white, odorless microcrystalline solid with a strong bitter taste. PFD is highly soluble in ethyl alcohol, chloroform, various lipid oils, and other lipid solvents, thus it is easily formulated to move through cell membranes (Macías-Barragán et al., 2010). Its characterization is well known by spectroscopic techniques such as gas chromatography, high-performance liquid chromatography (HPLC), infrared spectroscopy and magnetic resonance imaging.

![Figure 1. Structural formula and information on Pirfenidone.](image)

<table>
<thead>
<tr>
<th>IUPAC Name: 5-methyl-1-phenyl-2-(1H)-pyridone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
</tr>
<tr>
<td>Molecular Formula</td>
</tr>
<tr>
<td>XLogP3-AA</td>
</tr>
<tr>
<td>H-Bond Donor</td>
</tr>
<tr>
<td>H-Bond Acceptor</td>
</tr>
<tr>
<td>Rotatable Bond Count</td>
</tr>
<tr>
<td>Exact Mass</td>
</tr>
<tr>
<td>Mono Isotopic Mass</td>
</tr>
<tr>
<td>Topological Polar Surface Area</td>
</tr>
<tr>
<td>Heavy Atom Count</td>
</tr>
<tr>
<td>Formal Charge</td>
</tr>
<tr>
<td>Isotope Atom Count</td>
</tr>
</tbody>
</table>
Pharmacokinetic experiments in humans show a good safety profile with low toxicity. The acute toxicity and pharmacodynamics properties of PFD have been reported in multiple in vitro and in vivo animal studies. In addition, evidence from numerous published studies shows that PFD can modulate tissue remodeling and collagen metabolism. Data from published studies suggest that PFD may: (1) modulate tissue remodeling of fibrotic lesions, (2) remodel pre-existing abnormal lesions, and (3) prevent the formation of abnormal wound lesions following injury. Because of PFD’s documented low toxicity and its ability to modulate molecular effects involved in the wound healing mechanism, application of KitosCell shows great promise as a novel therapeutic treatment for SD.

**Molecular Mechanisms for Cytokine Signal Regulation**

Although knowledge of PFD is growing, its precise mechanism of action has yet to be clearly defined. Experiments evaluating PFD use in different pathological phenotypes have revealed clues of its actions in the wound healing process and have helped to broaden understanding of PFD’s molecular mechanism of action. Through various experiments, PFD has been determined to regulate wound repair by influencing cytokine signaling of growth factors including TGF-βs, connective tissue growth factor (CTGF), PDGF, and TNF-α, all important players in the wound healing process (Zhong, Sun, Lin, Wu, & Yu, 2011). Modulation of these signaling pathways can lead to changes in cellular function, including changes in collagen metabolism and inflammatory response. How PFD modulates cytokine signaling is the focus of current research, but
evidence that PFD can modulate transcriptional activity has been discovered. Whether cytokine signaling is influenced at a pre-transcriptional level is still debatable, but data collected from different experimental observations has helped to develop a more putative knowledge of the action of PFD.

**TGF-β**

PFD has been shown to modulate the activity of TGF-βs involved in collagen metabolism. A great deal of evidence suggests that TGF-βs is a central regulator of fibrosis. Several animal models over expressing the TGF-β family of cytokines have shown extensive progressive fibrosis, indicating that TGF-βs may play a predominant role in the progression of pulmonary fibrosis. Enhanced TGF-β gene expression in models of pulmonary fibrosis correlates with increased collagen and protein deposition. Likewise, human fibrotic lung tissue shows enhanced TGF-β gene and protein expression. The use of TGF-β antibodies resulted in the reduction of collagen deposition in murine bleomycin-induced lung fibrosis. Therapeutic efforts are therefore focusing on inhibition of TGF-β activities in indications with excessive fibrotic deposition. PFD modulates TGF-β gene expression and subsequent activity in vivo resulting in inhibition of TGF-β-mediated collagen synthesis. In bleomycin-induced lung injury hamster model PFD treatment resulted in the decrease TGF-β gene expression by 33% (S N Iyer, Gurujeyalakshmi, & Giri, 1999). For idiopathic pulmonary fibrosis (IPF) patients, PFD appears to slow progression of the disease process. In numerous other animal and human trials PDF has been shown to modulate the fibrotic composition at injury sites.
TNF-α

PFD has also been studied in multiple Phase 1, Phase 2 and Phase 3 clinical trials for its abilities to inhibit the synthesis and activity of tumor necrosis factor-alpha (TNF-α). Inhibition of TNF-α activity can eliminate edema, or vesicant responses (vesicles or blisters) caused by repeated trauma injury, injury caused by scalding or burns, skin injury caused by chemicals, products released by microbial infection (e.g. endotoxin), immunologic response to contact with a foreign biological product (e.g. contact dermatitis, insect bite), as well as classical allergic response and radiation exposure (e.g. sunburn). In each of these conditions, the initiating and dominating pathophysiologic action is directly a result of an immediate local release and/or synthesis of massive amounts of TNF-α from several types of cells at or adjacent to the injury site. The locally released TNF-α is followed by additional synthesis and release of TNF-α by invading macrophages drawn to the injury site by a cascade of chemotactic cytokines released locally from cells triggered by the greatly elevated TNF-α concentrations. PFD has been found to inhibit the synthesis of TNF-α or block the pathophysiological effects of TNF-α at injury sites. By inhibiting or blocking the synthesis, release, and the pathophysiologic actions of excessive levels of TNF-α, PFD indirectly inhibits the release of other biochemical products from cells such as histamines, prostaglandins, bradykinins, and peroxidases which can facilitate the arrest or resolution of the tissue or organ damage and aid in enabling the restoration of normal cellular function.
NF-κB

The ability of PFD to block the actions of several key cytokines suggests that it acts within the cell at a common molecular level within the nucleus. Iyer et al. (1999) demonstrated these actions occur at the pre-transcriptional level where an interface occurs between signals from specific genes or groups of genes. At this level, cellular responses to stimuli, such as injury, are transmitted to the transcription process by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-related proteins (Nakanishi et al., 2004). Almost every tissue depends upon these NF-κB proteins to initiate and influence the transcription process. These transmissions regulate:

1) mitotic events and exert control via the cyclins,

2) signals from genes which influence the transcription process and thereby implement
   a. the numerous biochemical synthetic processes which are normal for homeostatic (physiologic and biochemical) maintenance of the cytoplasm as well as nucleus of the cell,
   b. the synthesis and/or storage of a spectrum of biochemicals which are externalized by secretion from the cell so as to complement or regulate other cells in the adjacent environment;

3) regulate apoptosis or necrosis of cells and tissues,

4) regulate immunologic response of cells-type associated with synthesis or storage of antibodies to foreign substances or in generation of "autoimmunity" (Hoffmann, Natoli, & Ghosh, 2006).
Cytokines act as monitors of events connected with cellular injury and result in orchestrating the cellular proliferation and biochemical processes required to repair damaged cells or tissues. During normal tissue repair, the NF-κB related proteins are the common pathways of many of these cytokine signals. When excessive amounts of these cytokines are generated at the sites of injury, large amounts of the NF-κB related transcriptional proteins are synthesized and released. If the elevated NF-κB levels are not rapidly reduced to normal levels, adverse events may follow.

Results from Nakanishi et al. (2004) describe the effects of PFD on NF-κB activity. In transfection experiments of cultured hepatocytes, a decreased transcriptional activation of inducible nitric oxide synthase (iNOS), a cellular signal for nitric oxide production, was exhibited in transfection experiments. Results also indicated that PFD inhibited transcriptional activation of the iNOS gene promoter, but had no effect on its nuclear translocation (Nakanishi et al., 2004). These observations support the hypothesis that the action of PFD must involve the NF-κB proteins since PFD repeatedly has shown a powerful inhibiting action against major cytokines, such as TNF-α and TGF-β.

Given the critical importance of these growth factors and their downstream signaling pathways, targeting TNF-α and TGF-β may lead to alterations in the scar formation of patients with SD. Topical administration of PFD has the potential to alter the disproportionate synthesis and degradation of matrix proteins in SD.
Pharmacokinetics of PFD in Human and Animal Models

Pharmacokinetic parameters of PFD have been explored in numerous animal and human studies. Shi et al. (2007) designed a study to evaluate the pharmacokinetics of single escalating doses and multiple oral doses of PFD in healthy patients. A total of 48 subjects were included in the study and randomized into groups for the dose-escalation (n = 12, 6 women and 6 men in each group). PFD was rapidly absorbed through the stomach and cleared from plasma following single oral doses. The maximum plasma concentrations occurred at 0.33 to 1 hour after administration. The pharmacokinetic parameters of the multiple doses were similar to those from single doses under fed conditions, indicating no significant accumulation of PFD with repeated dosing. All participants tolerated the drug doses well, completed the study and there were no significant pharmacokinetic differences found between genders. All participants completed the study without serious adverse events, requiring intervention, the most frequent being dizziness and nausea. It was also determined that the consumption of food significantly affected the absorption of PFD, helping to improve tolerability and reduce adverse events incidence.

To investigate the modulatory effects of PFD in the wound healing process of glaucoma and pharmacokinetics of topical PFD application, Sun et al. (2011) instilled a PFD solution (0.5%) into a rabbit model’s conjunctival sac. After administration the rabbits were sacrificed and the concentrations of PFD from the conjunctive, sclera, cornea, aqueous humor, and vitreous were quantified by HPLC. The rapid absorption was followed by fast clearance. The maximum concentration was achieved in all the ocular
tissues within 20 minutes. Sun et al. concluded that topical administration of PFD might be an effective approach to modulating wound healing after glaucoma surgery due to the inhibition of fibrotic accumulation in rabbit eyes.

In a sheep model, Bruss et al. (2008) administered a 30 mg/kg intravenous (IV) dose of PFD to observe the plasma clearance of PFD. Four sheep received $^{14}$C-pirfenidone; plasma and urine samples were collected from all subjects ($n = 6$). Once in the bloodstream PFD is converted to its main metabolite, hydroxypirfenidone (OH-PFD). However, the collection of additional metabolites and conjugated metabolites makes the liver the most probable site of metabolism. Overall, PFD, OH-PFD, OH-PFD glucuronide, carboxypirfenidone, and acetoxypirfenidone were discovered from urine samples. Results confirmed that PFD and its metabolites disappear with first order kinetics with a clearance of 1.2 l/kg/h, half-life of 24 minutes, and distribution volume of 0.71 l/kg. Organ distributions after 48 hours of IV administration were as follows, in descending order of presence: lung, kidney, brain, liver, lymph node, and adipose tissue, consistent with wide distribution in higher irrigated organs. Urine samples contained approximately 80% of tracer, of this less than 1% was in the form of the parent drug and 50% was in the form of identifiable PFD metabolites. Therefore, PFD was shown to be rapidly absorbed and completely metabolized in animal model studies.

Similarly, Braim et al. (2008) administered a single dose of PFD intravenously to horses to investigate plasma pharmacokinetics of PFD and major metabolites and temporal effects of PFD infusions. Mild clinical effects, including tachycardia and muscle fasciculation, were observed during drug administration, yet stopped at the end of
infusion. No additional adverse events were noted after the termination of infusion. PFD metabolites were detected 5 minutes after infusion and no parent drug or metabolites were detected after 24 hours in the plasma. Ultimately, only transient adverse events were noted during the administration and drug metabolism, with rapid clearance.

In summary, PFD has a simple chemical structure that is soluble in alcohol and chloroform allowing it to easily translocate through the cell membrane without requiring a membrane-bound receptor. When administered orally, it is absorbed readily in the gastrointestinal tract and reaches the blood stream rapidly. After topical application in the rabbit eye, ocular tissues absorbed PFD within 20 minutes. After IV infusion, the half-life of this drug was calculated to be 24 minutes. PFD was shown to rapidly diminish in plasma concentration and accumulate in tissues with a higher concentration in more irrigated organs. Complete metabolism was accomplished, most likely in the liver, to a variety of metabolites and finally eliminated through the kidney in the urine. In samples of sheep urine, it started to appear after 48 hours. Due to these results, application of PFD in a topical form for SD appears to be safe and submit patients to low toxicity.

**Use of PFD for Fibrotic Diseases in Humans**

PFD has been shown to regulate key growth factors and fibrotic cytokines when tested in animal and clinical trials to evaluate its effects on inflammation and fibrosis. It has shown a pharmacologic ability to treat excessive collagen formation in hypertrophic scars and in removing or preventing scar tissue found in fibrosis associated with injured tissues or various organs (skin, lung and liver). (Schaefer, Ruhrmund, Pan, Seiwert,
Kossen, 2011). All of these diseases share a pathological irregularity in which collagen deposition exceeds its degradation.

Skin

Hypertrophic and keloid scars result from a regeneration-regulating mechanism gone awry in the wound healing process. They are characterized by an excessive formation of fibrous scar tissue at the wound site. This collagen overproduction can be attributed to a strong proliferating activity of the fibroblasts. The cytokine signaling related to keloid and hypertrophic scar formation is still being investigated, however recent studies are focusing on the influence of various growth factors such as TGF-β and PDGF. These growth factors have been shown to be overexpressed in keloid formations (Wolfram, Tzankov, Pülzl, & Piza-Katzer, 2009). Patients also have pruritus, pain, or pressure in addition to the fibrous growths. Adding to their complexity, treatment is often stifled by disfiguration during treatment and frequent recurrence.

Armendariz-Borunda et al. (2012) evaluated the efficacy and safety of KitosCell® (topical PFD), 8% in pediatric patients with hypertrophic scars caused by burns of different etiologies. Pediatric patients with hypertrophic scars between the ages of 3 to 16 years of age were enrolled in this trial. Thirty-three patients were enrolled in the study group to receive the pirfenidone treatment and 30 patients were enrolled in the control group to receive pressure therapy. From the first month of treatment, patients in the PFD group showed statically significant scar regression in comparison with their initial Vancouver score measurement ($P \leq 0.001$). This was continuous and progressive
until the 6th month of treatment. When comparing the two groups, the PFD group experienced significantly higher improvement in the Vancouver Scar Scale (VSS) and Visual Analog Scale (VAS) scores at every month’s determination. At the end of the 6 months, the PFD group had significantly higher improvement than the pressure therapy treatment group ($P \leq 0.001$). In the PFD group, 9 of 33 patients (27%) showed a decreased in their VSS score of more than 55%, 22 patients (67%) decreased it from 30% to 45%, and only 2 patients had a 30% decrease or less in their VSS score. Patients in the control group showed a slight improvement of 16% on the average ($P=0.001$). It was concluded that topical administration of 8% PFD gel 3 times a day is more effective and safe in comparison to standard pressure therapy for the treatment of hypertrophic scars caused by burns in pediatric population. Only minor adverse events such as rash and local erythema were reported.

Lung

The effects of PFD to treat pulmonary fibrosis has been evaluated in interstitial pulmonary disease, lung fibrosis resulting from bleomycin, and several other types of acute lung injury (Macías-Barragán et al., 2010). Interstitial pulmonary diseases have many different etiologies and encompass many pathological processes, yet all affect the pulmonary interstitium. This group of disorders is characterized by deep scarring of the lung, resulting in shortness of breath and ultimately death if no effective intervention is determined.
The most common form of interstitial pulmonary disease, IPF, poses a significant management challenge to patients and health care professionals. The natural progression of IPF is fatal, secondary to respiratory failure (Azuma, 2012). Conventional anti-inflammatory treatment, involving corticosteroids and some immunosuppressants, focuses on suppressing inflammation within pulmonary tissues and is effective in delaying disease progression in 23% of cases. For patients who have struggled with IPF for extended periods of time and are past the initial inflammatory stage of the disease, an agent to modulate the fibrotic deposition in interstitial tissue was hypothesized to be a more effective form of treatment.

The tolerability and efficacy of PFD was evaluated for the first time in a clinical setting by Raghu et al. (1999) in terminally ill patients with advanced IPF. The study enrolled late-stage IPF patients, regardless of illness or physical limitations. Enrolled patients had exhibited progressive deterioration or not tolerated conventional therapy prior to study enrollment. Fifty-four patients participated in the study and were followed for mortality, change in lung function, and adverse events. The drug was well tolerated in patients who reported non-threatening adverse events due to treatment, but these subsided after a decreased dose or discontinuation of PFD. After treatment, 38 of 46 patients were able to suspend conventional treatment of prednisolone within two months of study enrollment. Eight were able to reduce their daily prednisolone dose and 8 had no conventional treatment to begin with. The 1- and 2-year survival rates were 78% and 63%, respectively.
Because the study enrolled a small number of patients with significant co-morbidities, lacked randomization and controls, and had inconsistent historical data, there was insufficient data to substantiate the efficacy of PFD as a treatment for IPF. However, the study results are still promising. In addition to the absence of serious adverse events, PFD did not result in blood count or blood chemistry abnormalities. Pulmonary function test (PFTs) measurements stabilized following PFD treatment. An inhibition in the decline of forced vital capacity (FVC)/vital capacity (VC) was seen after administration leading researchers to believe that the results may correlate with a decrease in mortality rate.

In 2005 Azuma et al. published results of a double-blind, placebo-controlled, randomized, prospective clinical trial to evaluate the efficacy and safety of PFD in adult patients with IPF. A total of 109 patients were enrolled in this study and randomly assigned either to PFD or placebo treatment arms in a 2:1 ratio. Twenty-five different clinics in Japan participated in the trial and enrolled subjects who demonstrated adequate oxygenation at rest and oxygen saturation (SpO₂) of 90% or less during exertion while breathing air within 1 month before enrollment. The primary endpoint was defined as the change in the lowest SpO₂ by pulse oximetry during a 6-minute steady-state exercise test (6MET), secondary endpoints were changes in resting PFTs while breathing air, disease progression by high-resolution computerized tomography (HRCT) patterns, episodes of acute exacerbations if IPF, changes in serum markers of pneumocyte damage, and changes in quality of life measurements. This study demonstrated no difference in primary endpoint results but a significant difference in secondary endpoints including
change in VC and acute exacerbation incidence after 9 months of treatment. Whereas there was no significant difference in the primary endpoint between the two groups when the data were analyzed for all patients, a positive trend was noted after 9 months of treatment in the PFD group. However, PFD treatment suppressed the decrease in oxygenation during exercise in a subset of patients who did not demonstrate SpO2 less than 80% during baseline assessment. During the 9-month follow-up study, the most important findings noted were that the episodes of acute exacerbation of IPF manifested exclusively in the placebo group and there was a lesser decline of change in VC in patients receiving PFD (Azuma et al., 2005).

Taniguchi et al. (2010) developed a study after obtaining encouraging results from the previous Phase II clinical trial. The objective of this trial was to further investigate the therapeutic effects and safety of oral PFD on lung functional deterioration and disease progression in IPF patients. The aim of this study was to determine the change from baseline VC when compared to placebo. Results indicated that those treated with PFD improved VC, and the distribution of progression-free survival was better than in the placebo group.

Oral PFD is approved for marketing in 29 European countries and Canada under the InterMune trade name Esbriet® for IPF and in Japan and South Korea where it is marketed by Shionogi & Co. Ltd under the trade name Pirespa®. Under different trade names, PFD is also approved for the treatment of IPF in China, India, and Argentina. PFD has been granted Orphan Drug and Fast Track designation by the Food and Drug Administration (FDA), and also has been granted Orphan Drug status in Europe.
InterMune is currently conducting an additional Phase III study, ASCEND, in the United States to confirm the efficacy of PFD and support the regulatory registration of Esbriet® for the treatment of IPF.

Before the introduction of PFD, the prognosis of patients suffering from IPF was grim. The fatal progression and lack of effective treatments for this disease presented a management challenge to clinicians and patients. Because of the immuno-modulatory and anti-inflammatory properties of PFD, researchers hoped that it could fill the unmet medical need of patients with IPF. In numerous studies of PFD treatment for IPF, the drug has a well-documented track record of safety. No significant adverse events and only transient adverse events which subsided after cessation or dose modification, were documented during studies. PFD has documented success in slowing the decline in lung function, slowing the accumulation of scar tissue, and shows great promise as a safe, well tolerated treatment for IPF.

Liver

Liver fibrosis occurs in many different types of liver diseases. It is a consequence of collagen and ECM protein accumulation in response to liver injury. Hepatic stellate cells (HSC) are activated by fibrogenic cytokines such as TFG-βs, angiotensin II, and leptin to change to a myofibroblast-like phenotype (Bataller & Brenner, 2005). These activated cells have been identified as major collagen-producing cells in patients with liver fibrosis. Advanced liver fibrosis can be the result of a variety of etiologies.
Due to the high collagen deposition in effected liver pathology, the use of antifibrotic therapies has been explored to inhibit or prevent the formation of ECM proteins. A pilot study to evaluate the safety and efficacy of PFD in 15 patients with established liver disease caused by hepatitis C virus chronic infections was performed by Armendariz-Borunda and colleagues (2006). Color Doppler biopsies obtained at baseline and after 12 months of treatment showed improvements in the following liver histology: necrosis, inflammation, steatosis, fibrosis, and cell regeneration to pathologists who were blinded to the sequence and clinical biochemical characteristics of the patients. Gene expression of key molecules involved in collagen turnover was quantified using real time polymerase chain reaction. Similarly, mRNAs coding for profibrogenic molecules such as collagen, type I, alpha 1 (Col1A1), TGF-β and TIMP-1 were markedly down-regulated at the end of treatment.

PFD has shown evidence of benefit in a wide variety of fibrotic diseases where it has been shown to modulate fibrotic deposition. Most clinical trials describe that PFD is generally well tolerated with mild adverse events. The most common adverse effects include gastrointestinal discomfort, anorexia, fatigue, sedation, and photosensitivity rash. Often these symptoms are temporary and resolve completely once the drug is withdrawn. Overall, the results from multiple pilot studies of PFD in the treatment of other indications provides a significant rationale that PFD appears to be safe in a variety of patient populations and provides an effective means of altering the cytokine-mediated processes involved with fibrosis. PFD may also show evidence of benefit to patients of
many fibrosis-related diseases, such as multiple sclerosis (MS), Harmansk-Pudlak syndrome, focal segmental glomerulosclerosis, idiopathic pulmonary fibrosis (IPF), hypertrophic cardiomyopathy, kidney disease in patients with diabetes, neurofibromatosis type 1, plexiform neurofibrosis, and fibrosis caused by radiation therapy for cancer (Macías-Barragán et al., 2010). Although pathological manifestation of fibrotic disorders and SD is dichotomous, the pathway in their formation shares many of the same elements. The cytokines and downstream pathways that regulate mechanisms resulting in excessive fibrosis are the same pathways that lead to a loose ECM and low collagen deposition in SD. Thus, PFD may prove to be a safe and effective treatment for SD.
PROPOSED CLINICAL TRIAL PROTOCOL

- Recruitment
- Randomize
- Select treatment area
  - KitosCell TID with monthly evaluations (mo 1-6)
  - Placebo TID with monthly evaluations (mo 1-6)

Study Assessment (6 mo)

Optional: KitosCell TID with monthly evaluations (mo 6-12)

Study Assessment (12 mo)

Course #1

Course #2

Primary Endpoint
Determine safety and efficacy of Pirfenidone, 8% topical gel composition (KitosCell®) as treatment for steroid induced striae.

Figure 2: Protocol Schema.
Table 1. Study Time and Events Table.

<table>
<thead>
<tr>
<th></th>
<th>KitosCell/Placebo Treatment</th>
<th>Optional KitosCell Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Course #1 (mo 1-6)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patient Registration</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biopsy&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Photographic Assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory Studies</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>(CDC/differential)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Visual Analog Scale (VAS)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vancouver Scar Scale (VSS)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>(Expert dermatologist review of photographs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Assessment Scale (POSAS)(Investigator and patient review)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Inventory</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Case Report Forms/Data Collection</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1. KitosCell Treatment offered to patients regardless of initial treatment.
2. Course #1 Treatment can start same day as Baseline assessment with confirmation of patient eligibility.
3. Second biopsy will be obtained at completion of treatment, either at the completion of 6 months of treatment, or at the completion of 1 year of treatment (not both).

1.0 Objective

The overall objective of this proposed study is to evaluate the safety and efficacy of Pirfenidone, 8% topical gel composition (KitosCell®) in the resolution of striae distensae.
2.0 **Hypothesis**

KitosCell® can be efficiently and safely administered as a topical gel to steroid induced dermatologic striae and will lead to healing of the skin lesions as measured by minimized color and diminished size of the striae.

3.0 **Patient Selection**

All trial patients must meet the following inclusion and exclusion criteria.

3.1 **Inclusion Criteria**

3.1.1 Patient is at least 12 years old.

3.1.2 Patient has diagnosis of striae.

3.1.3 Patient has completed active oncologic treatment (chemotherapy and/or radiation) for greater than 6 months.

3.1.4 Patient is not neutropenic (must have Absolute Neutrophil Count ≥ 1,000/µl)

3.1.5 Patient or guardian has signed informed consent according to institutional guidelines.

3.2 **Exclusion Criteria**

3.2.1 Patient does not have underlying genetic connective tissue disorder that increases the risk for striae (such as rheumatoid arthritis, Marfan syndrome, lupus erythematosus, scleroderma or similar disorders).
3.2.2 Patient does not use immunosuppressive drugs (including systemic corticosteroids, unless being used for acute symptoms (i.e. asthma exacerbation).

3.2.3 Patient does not have diagnosis of immunodeficiency.

3.2.4 Patient does not have active dermatologic infections in area to be treated for study.

3.2.5 Patient is not pregnant or breast-feeding. Female patients of childbearing age must have negative serum or urine pregnancy test within 1 week prior to enrollment.

4.0 Registration and Pretreatment Procedures

This is a blinded, placebo controlled trial. Clinical site personnel will determine eligibility of prospective subjects. Eligible patients must be registered prior to treatment to verify eligibility and obtain the dose assignment. When a patient has signed informed consent, then the Eligibility Checklist form should be sent to study sponsor. The patient will be assigned a case number and randomized to receive KitosCell study drug (topical pirfenidone) or placebo. Following registration, subjects may begin protocol treatment.

4.1 Registration Process

4.1.1 Obtain written informed consent from the subject/guardian/parent prior to performing any study specific assessments.
4.1.2 Confirm eligibility of patient (subject must meet each inclusion and exclusion criteria list in protocol).

4.1.3 Submit the supporting documentation (laboratory report, History and physical results, met eligibility criteria) and the consent to study sponsor.

4.1.4 Study sponsor will verify eligibility, register the subject on the study, assign a protocol case number, and be randomized to receive study drug (pirfenidone) or placebo.

4.2 Pretreatment Evaluation

The following should be performed as the pre-treatment assessment:

4.2.1 History and physical examination.

4.2.2 Obtain baseline laboratory studies (complete blood count and differential; urine/serum pregnancy test if indicated).

4.2.3 Obtain baseline digital photographs (3) of ROI.

4.2.4 Completion of Patient Assessment Scale (POSAS) by the subjects.

5.0 Treatment Plan

5.1 Overview

- Eligible patients will be randomized to receive KitosCell (topical pirfenidone) or placebo.

- Patients will undergo a pre-assessment visit including physical examination and laboratory evaluation.
• Prior to treatment, the patient will have baseline photographs taken of striae and a region of interest (ROI) will be defined (measured and mapped).

• Patients will be instructed how to measure dose of study drug/placebo, how to apply it to ROI, and the frequency of application. The treatment area for each patient will be the same dimensions, but may vary with regard to where on the body the ROI is located. Patients will apply daily doses of study drug/placebo and return at one month intervals for physical examinations and repeat photographs of ROI.

After 6 months of treatment, the following parameters will be evaluated: photographs of ROI, laboratory studies (complete blood count and differential), Investigator Assessment (VAS and VSS), Patient Assessment Scale (POSAS) and Adverse Event Inventory. At this point patients will be given the option to stop treatment.

OPTIONAL:

1. If patients opt to continue treatment beyond 6 months, they will receive study drug (KitosCell) regardless of which group—study drug or placebo—they were randomized to in the first 6 months of treatment. Patients will be directed to administer the study drug to the ROI in the same manner and frequency for an additional 6 months. Monthly physical examinations and pictures of ROI will continue during the second 6-month period of treatment. After a full year of
treatment is complete, a final assessment will occur with the same parameters as at the initial 6-month treatment completion.

2. Patients will be given the option to have skin biopsies at the beginning and at the end of their study treatment. The ‘end of treatment’ is defined as either after 6 months of receiving study drug or placebo, or after 1 year (if they opted to receive an additional 6 months of treatment). The final biopsy will be obtained within 4 weeks of completion of treatment. Testing that will be collected include:

a. H&E Stain (to assess the characteristics of skin, epidermal and dermal thickness).

b. Masson Trichrome (to assess collagen and its conformational arrangement).

5.2 KitosCell/Placebo Administration

Investigators will advise patients how to measure and administer KitosCell/placebo gel.

6.0 Patient Assessments

6.1 Evaluation During and After Treatment

6.1.1 Treatment Assessment

The following will be performed monthly as patient receives study drug or placebo. They should occur every 3-5 weeks from the date of the baseline/previous assessment:
6.1.1.1 History and physical examination.

6.1.1.2 Obtain digital photographs (3) of ROI.

6.1.1.3 Completion of Patient Assessment Scale (POSAS) by the subjects.

6.1.1.4 Adverse Event Inventory.

6.1.2 Post-completion of Treatment Evaluation

The following will be performed at the 6-month completion of treatment of study drug and/or placebo, and after one year of treatment if the patient elects to continue treatment (optional phase of study).

6.1.2.1 History and physical examination.

6.1.2.2 Laboratory studies (complete blood count and differential).

6.1.2.3 Obtain digital photographs (3) of ROI.

6.1.2.4 Completion of Patient Assessment Scale (POSAS) by the subjects.

6.1.2.5 Completion of Investigator Assessment Scale (VSS) by the investigators.

6.1.2.6 Adverse Event Inventory.

6.1.2.7 Optional: Biopsy at completion of treatment: either after completion of 6 months of treatment or after one year of treatment (not both) depending upon whether patient opted to continue treatment (optional phase of study).
6.2 Photographic Documentation of Target Striae:

Investigators will define an area of skin to be studied/evaluated as the ROI. Digital photographs of the treatment area will be taken by the provider using a computer-controlled digital camera under standardized illumination conditions.

Three digital photographs will be taken of the ROI with each assessment. Investigators will analyze and compare photographs with baseline, measuring striae size, area and grading color changes.

6.2.1 Photographic evaluation

Standardized photographs will be taken of the region of interest (ROI). A measurement scale and color scale card will be included in the photograph in an effort to maintain consistency of photos. The ROI will be outlined and the area of the most pronounced striae will be calculated. Future assessments should be performed in an effort to repeat the baseline photograph. Erythema and melanin index (EI and MI) will be calculated using the method described in Yamamoto, et al. (2008).

6.3 Investigator Assessment Scales

Clinical experts will perform a blinded review to analyze and compare photographs obtained at baseline, with those obtained at the completion of Course #1 and, if applicable, Course #2. Two assessment scales will be utilized to achieve this review: Vancouver Scar Scale (VSS) and Visual Analog Scale (VAS).
6.3.1. Vancouver Scar Scale (VSS)

VSS, shown in Table 2, is the most widely used outcome measure in burn and similar scarring studies. It assesses 4 variables: vascularity, height/thickness, pliability, and pigmentation, using a 0 to 13 scoring system.

Table 2. Vancouver Scar Scale.

<table>
<thead>
<tr>
<th>Scar Characteristics</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascularity</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Pink</td>
<td>1</td>
</tr>
<tr>
<td>Red</td>
<td>2</td>
</tr>
<tr>
<td>Purple</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pigmentation</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>1</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>2</td>
</tr>
<tr>
<td><strong>Pliability</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Supple</td>
<td>1</td>
</tr>
<tr>
<td>Yielding</td>
<td>2</td>
</tr>
<tr>
<td>Firm</td>
<td>3</td>
</tr>
<tr>
<td>Ropes</td>
<td>4</td>
</tr>
<tr>
<td>Contracture</td>
<td>5</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td></td>
</tr>
<tr>
<td>Flat</td>
<td>0</td>
</tr>
<tr>
<td>&lt;2 mm</td>
<td>1</td>
</tr>
<tr>
<td>2–5 mm</td>
<td>2</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>13</td>
</tr>
</tbody>
</table>

6.3.2. Visual Analog Scale (VAS)

The VAS is a photograph-based scale derived from evaluating standardized digital photographs in 4 dimensions (pigmentation, vascularity, acceptability, and observer comfort). It sums the individual scores to get a single overall score ranging from “excellent” to “poor”. It has demonstrated high observer reliability and internal consistency when compared to expert panel evaluation.
6.4 Patient and Observer Scar Assessment Scale (POSAS)

Patients and observer will complete a questionnaire during each visit and a score will be calculated. The POSAS is a scar assessment scale that includes subjective symptoms of pain and pruritus with an expansion on the objective data captured in the VSS. It consists of two numerical scales: the Patient Scar Assessment Scale and the Observer Scar Assessment Scale, utilizing a scoring system from 5-50. It assesses vascularity, pigmentation, thickness, relief, pliability, and surface area, and it incorporates patient assessments of pain, itching, color, stiffness, thickness, and relief.

6.5 Measurements and Evaluations to be Obtained

Assessments will be obtained according to the timeline presented in Table 1.

7.0 Off-Study Criteria

Patients can be withdrawn from the study for the following reasons:

- Patient or family withdraws consent.
- Removal from protocol therapy by the principal investigator if patient unwilling or able to comply with protocol requirements.

8.0 Ethical and Regulatory Considerations

8.1 Consent Procedure

All patients and/or their parents or legal guardians must sign an approved informed consent form in order to be eligible for this study.
8.2 Confidentiality

Confidentiality of patients’ records will be maintained within legal limits. The data from this study may be published; however no patients will be named or identified. A list of patients and their randomization results (receiving study drug or placebo) will be kept locked at study sponsor location.

8.3 Risk-Benefit Ratio

The present study may have no benefit to the study subjects. Previous oral and topical studies of pirfenidone demonstrate improvements of scarring similar to striae. Clinical and non-clinical data has shown its efficacy in the treatment of hypertrophic scarring and chronic ulcers. Important information will be gained regarding the efficacy of pirfenidone for treatment of striae.

8.4 Adverse Event Reporting

Adverse events should be reported to the study sponsor. Adverse Events will be monitored and graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAEv3.0). Adverse events not included in the CTCAEv3.0 should be reported and graded under the Other adverse event within the appropriate category.

Adverse events, which are unexpected and associated with the use of this product, will be reported to the FDA and the National Institutes of Health (NIH) Office of Biotechnical Activities (OBA) according to the schedule shown below in Table 3:
Table 3. Adverse Event Reporting Schedule.

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Timing of Report (relative to when the person responsible for making the report becomes aware of the event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or life-threatening</td>
<td>As soon as possible, no later than 7 calendar days</td>
</tr>
<tr>
<td>Serious adverse event resulting in one of the following:</td>
<td>As soon as possible, no later than 15 calendar days</td>
</tr>
<tr>
<td>1. Inpatient hospitalization</td>
<td></td>
</tr>
<tr>
<td>2. A persistent or significant disability or incapacity</td>
<td></td>
</tr>
<tr>
<td>3. A congenital anomaly or birth defect</td>
<td></td>
</tr>
<tr>
<td>4. Important medical event that, based on the medical judgment of the investigator, may require medical or surgical intervention to prevent one of the outcomes listed above</td>
<td></td>
</tr>
<tr>
<td>Any other unexpected adverse experience associated with the use of the product</td>
<td>In the annual report</td>
</tr>
</tbody>
</table>

Reporting to the IRBs and IBCs will be done according to the requirements of the relevant IRBs and IBCs.

8.4.1 Definition of Adverse Events (AE’s)

Adverse events (AE’s) will be defined as any treatment related toxicity(s).

In other studies utilizing topical pirfenidone (Armendariz-Borunda et al., 2012; Cell Therapy and Technology, 2008) the most common side effects noted were transient, mild pruritis and erythema.

8.5 Risks

The risk to health care workers and close contacts is extremely low, so no additional precautions are indicated.
9.0 Statistical Analysis

Statistical comparison between study arms will be assessed using Student’s *t*-test following confirmation of normality of the sample distribution. Statistical significance will be considered $P < 0.05$. 
CONCLUSION

SD affects a substantial proportion of the global population. Although SD is not usually an impairing medical problem, it can cause significant psychological distress and decrease quality of life. Diverse varieties of treatments have been proposed for SD, including diet and exercise, pharmaceutical agent, and laser treatments. However these treatments have yielded inconsistent and limited results. In the absence of successful treatment option, the goal of this study is to demonstrate that topical PFD can diminish the color and size of SD for affected patients. PFD is a small non-peptide with its ability to modulate the cytokines and downstream pathways that are responsible for inflammation and fibrosis. PFD offers a new hope in the management of SD which currently only has limited treatment options.

Clinical and non-clinical studies have shown that PFD can modulate the wound healing process through and is generally well tolerated with minimal adverse effects. Possibly related effects noted were mild or transient, and included pruritus, desquamation, erythema and/or rash; all resolved independently after treatment cessation. Regulation of TGF-β and TNF-α by PFD has shown significant effects on the reparative process in many different diseases. As an oral drug, PFD has been approved for treatment of IPF in multiple countries outside of the United States. A randomized, double-blind, placebo controlled, Phase III trial of PFD for the treatment of IPF is currently underway in the United States. In addition, an 8% topical gel formulation of PFD is approved in Mexico and other Latin American countries for the treatment of hypertrophic and keloid scars as well as acute burns and wound. Clinical data in hypertrophic and keloid scars
indicates PFD is effective in the modulation of collagenase and fibroblast activity, which lead to effective collagen remodeling.

These encouraging results support the evaluation of PFD as an agent to stimulate the remodeling of the pathological collagen structure found in SD. KitosCell®, topical PFD, has been tested and approved for application three times a day as treatment of pre-existing scars. The goal of this study is to evaluate the safety and efficacy of this same schedule and formulation on patients with SD.
REFERENCES


VITA

JEREMY PARCO KOONTZ

Address: 27819 SE 400th Place
Enumclaw, WA 98022

Email: jeremykoontz@gmail.com

Year of Birth: 1983

Education:
Boston University School of Medicine, Boston, MA
Master of Science in Medical Sciences, May 2014

Brigham Young University, Provo, UT
Bachelor of Science in Neuroscience, December 2009

Relevant Experience:

Clinical Research Intern,
Advantagene, Inc.  
Auburndale, MA 2013-Present
Developed expanded knowledge of experimental design while evaluating the results of study drugs advancing through clinical trials. As a project manager, gained first-hand experience formulating and establishing study protocol and design for potential disease treatments. Collected and verified study data of research subjects from various treatment institutions.

Ophthalmic Medical Assistant,
Retina & Vitreous Surgeons of Utah, LLC  
Provo, UT 2008-2010
Developed strong relationships with patients suffering from various eye disorders and injuries. Proficiently conducted preliminary exams, reviewed medical history, conducted diagnostic tests, and measured vision and ocular pressure. Learned the uniqueness of this specialized branch of medicine—the great depth of understanding of a specific region of the body applied to a vastly diverse patient population—while working side-by-side with surgeons as first-assistant during surgery and while performing optical coherence tomography (OCT) and direct fundus photography.

Organic Chemistry Research Assistant  
Provo UT 2005-2010
Strengthened problem-solving skills while isolating and identifying chemical compounds from human and bovine eye dissections to understand the progression of age-related macular degeneration (ARMD). Also, exploited the photosensitivity of these compounds to develop a chemotherapeutic agent to selectively target and kill cancer cells with light. Through hard work was awarded grants, served as a BYU Cancer Research Center Fellow (2006) and composed Honors theses titled *Synthesis, Photochemistry, and Folate*
Conjugation of A2-1,6-Diaminohexane (A2DA). Learned to work as a team member, think on my feet, and apply knowledge from many different facets of study.

President, BYU Cancer Research Awareness Group Provo UT 2005-2008

Responsible for orchestrating all club activities, service projects, and campus and community events to raise awareness about cancer, and cancer prevention. Learned to listen and provide comfort to others through personal experiences. Enhanced leadership qualities as I oversaw the organization of the annual Rex Lee Run, a run to raise money for cancer research. Our efforts raised the participation from 1,200 to over 3,000 participants in three years.

Additional Experiences


Honors, Awards, and Accomplishments

Fulfilled rigorous requirements to graduate with Brigham Young University Honors
Published thesis titled, *Synthesis, Photochemistry, and Folate Conjugation of A2-1,6-Diaminohexane (A2DA)*
2006 Brigham Young University Cancer Research Center Fellow
Recipient of twelve scholarships including the BYU Office of Research and Creative Activities Scholarship (2006) and Enumclaw Community Hospital Scholarship (2001)
Strong academic student often selected to Dean’s List
Asked to remain an unprecedented addition year as intern at Retina and Vitreous Surgeons of Utah