TOPICAL SKIN RESTORATION TECHNOLOGY
Advances in Age Management Strategies
TriHex Technology™ from Alastin Skincare powers effective skincare

Offered exclusively to health care professionals

Procedure Enhancement Systems

NEW Restore & Renew

Non-invasive System  Invasive System

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www.Alastin.com
The ALASTIN Skincare™ Restore and Renew line consists of products formulated to enhance production of collagen and elastin, recycle the extracellular matrix and volumize the skin for a more youthful appearance.

INTRODUCTION
Skin aging is the obvious external manifestation of a natural process occurring in tissues and organs throughout the body. Intrinsic processes (genetics, cellular metabolism and senescence, hormones) present with a gradually advancing loss of elasticity, fine lines and a slowed turnover of regenerating cells. Exposure to extrinsic factors (photodamage, sunlight exposure, pollutants, chemicals, toxins) exaggerates the aging response by aggravating and hastening aging manifestations in the skin such as discoloration, deep lines and a major loss of elasticity. Cumulatively, these present as a recognized pattern of structural and physiologic changes that manifest as aged skin.

In particular, the changes occurring within the extracellular matrix (ECM) have profound effects on cell-to-cell and cell-to-matrix signaling and cross talk. One of the main mechanisms responsible for intrinsic and extrinsic aging of the cells is the accumulation of damaged proteins in the cells and ECM. These proteins are modified by various post-translational mechanisms common with age, such as oxidation, glycation, and conjugation with products from lipid peroxidation. In young healthy skin, the proteolytic systems can effectively prevent the accumulation of damaged proteins both intracellularly and within the ECM, whereas in older, damaged skin the systems become inefficient and “clogged” with these protein fragments.

Very few skincare formulations in today’s market pay attention to these important background changes taking place after years of wear and tear and toxic exposures. ALASTIN Skincare™ has created the most comprehensive skincare products and regimen addressing ECM recycling in its entirety, by selecting agents that support both intracellular and extracellular protein renewal.
UV irradiation can reduce collagen production by approximately 80%, with fragmented collagen in the fibroblast environment thought to be the major cause of the reduced collagen production in both photoaged and chronologically aged human skin fibroblasts. In support of this concept, it has been demonstrated that when fibroblasts are removed from this fragmented collagen ECM milieu, they significantly improve their capacity to produce new collagen. This provides a foundation for anti-aging intervention.

**ALASTIN SKINCARE™ AND KEY INGREDIENTS**

The pathophysiologic background of skin damage related to sun exposure and aging has been well defined and presents an opportunity for a comprehensive restorative skincare regimen that encompasses all elements of the degenerative/regenerative sequence. This entails the following strategies:

- Modulation and clearance of metabolic byproducts of photodamage and aging both in the extracellular matrix and within the cells (ubiquitin-proteasome system or UPS system)
- Control of the corrosive damaging proteases (Matrix metalloproteinase-1 or MMP1)
- Stimulation of new collagen and elastin formation
- Volumizing the ECM and subdermis to optimize fibroblast function
- Incorporating antioxidant activity (against reactive oxygen species or ROS) and other cell regulating agents
- Eyelid nourishing and toning

**ALASTIN RESTORATIVE SKIN COMPLEX™**

Modulation and clearance of metabolic byproducts of photodamage and aging

Tripeptide (TP1), a matrikine (extracellular-derived peptides which regulate cell activity), simultaneously activates the production of metalloproteinases and anti-proteases that remove damaged proteins from the ECM macromolecules while activating the synthesis of new proteins for rebuilding the ECM. TP1 increased MMP-2 levels in conditioned media of cultured fibroblasts demonstrating increased MMP-2 proteolytic activity. MMP-2, a gelatinase, is important in digesting the gelatin fragments that remain after cleavage of normal collagen by MMP-1 related to sun damage. To counteract the MMPs, skin expresses natural inhibitors – tissue inhibitors of matrix metalloproteinases (TIMPs) that slow the process of collagen breakdown. The tripeptide -1 (TP1) also increased levels of MMP inhibitors TIMP-1 and TIMP-2 in cultures. Taken together, these results suggest that, by modulating MMP-2, and TIMPs expression and release, the tripeptide can modulate a large array of physiological processes, particularly those which require a rapid ECM clearance and turn over, such as cell migration, angiogenesis and tissue remodeling.

In addition, tripeptide has been shown to upregulate genes associated with the proteasome UPS system, activating the system and thus aiding in removing misfolded intracellular proteins. The biochemical uniqueness of tripeptide-1 resides both in its very small size, which would permit it to approach membrane receptors more easily than larger proteins, and its unique copper-binding characteristics that allows copper transfer into and from cells, both of which facilitate its entry into the cell. TP1 stops the release of oxidizing iron from ferritin and also has sun-protective properties blocking lethal ultraviolet radiation damage to cultured skin keratinocytes and reducing UV-induced erythema.

**Control of the corrosive damaging proteases**

A key objective in altering the destructive ECM milieu is to prevent the destructive enzymes and end products from causing protein fragmentation, misfolding, abnormal cross linkages and amorphous elastin clumps. To this end, phosphatidylserine (PS), a highly enriched membrane phospholipid component, is known to have several physiological roles, such as activating signaling enzymes and antioxidant activity. It has been found to decrease MMP-1 in a dose dependent manner, to increase pro-collagen formation and may act as a substrate for AGE targets thus reducing the damage from glycation effects.

**Stimulation of new collagen and elastin formation**

When stimulating new collagen formation, TP1 also increases levels of lysyl oxidase, the beneficial enzymatic cross linker. In addition, during this regenerative process, the alignment of collagen fibers into uniform structures of appropriate length is important. Proteoglycans of the dermis – decorin and dermatopontin, both stimulated by tripeptide – are vital to this process. Our gene marker studies have confirmed that elastin production is also stimulated by TP1, particularly fibrillin-1, the component that is most severely affected by solar elastosis.

One of the Hexapetides (Hex) in our formulation has the repeating amino acid sequence found in tropoelastin and the key sequence found at the binding site for the elastin protein to its cell surface receptor. Matrikines that predominantly activate elastin formation, elastokines, are among the most important matrikines yet described. This is because these elastin-derived peptides are chemotactic for fibroblasts and monocytes and have the capacity to stimulate the generation of elastin.

**Volumizing the ECM and subdermis to optimize fibroblast function**

Volumizing of the dermis and subdermal areas improves the density of these areas allowing stretching of the fibroblast at its focal adhesion sites resulting in spindle shaped functional cells. This heralds new collagen, elastin and GAG production. Volumizing results from this neocollagenesis, GAG and elastin
production but can also be contributed to in large degree by fatty tissue, the process of adipogenesis.

Our proprietary formulation includes a PGC1α stimulator. PGC1α (peroxisome proliferator-activated receptor-gamma – PPARγ - coactivator 1 alpha) is a transcriptional coactivator that plays a central role in adipogenic activity. It is intimately involved in thermogenesis conserving and donating energy as heat in response to environmental conditions such as cold stress. The formulation incorporates a phospholipid delivery system to facilitate penetration and absorption of the materials through the stratum corneum.

In the process of adipogenesis, PGC1α expression is strongly induced in differentiation of preadipocytes of mesenchymal origin into white adipocytes. This differentiation of preadipocytes to white adipocytes occurs under the influence of PPARγ. The young adipocytes formed under these conditions appear to be small and active and this size and activity has been seen to be synergistic and in line with good elastin formation. In other words, large, mature adipocytes have been associated with diminished elastin—manifesting as aged sagging skin—whereas younger, smaller, newly synthesized adipocytes are accompanied by increased elastin levels. In addition, adiponectin, secreted by small adipocytes (found in normal non-obese subjects) increase hyaluronic acid synthesis, whereas palmitic acid secreted by enlarged adipocytes (obese subjects) decrease collagen and elastin and fibroblast function. Fibroblasts cultured with enlarged adipocytes have shown decreased elastin gene expression.

PGC1α stimulators, such as those used in ALASTIN Skincare™ formulations, are thus useful candidates for increasing adipogenesis, providing small active adipocytes through this PPARγ activation pathway. In addition, expansion of compressed fat tissue has been observed to take place through the Hypoxia Inducible Factor (HIF-1α) pathway. Via this pathway, our active amino acid additions to the formulation have been observed to increase induction of target genes such as GK/Glycerol Kinase, FABP3 and FABP4, all involved in adipogenesis.

**ALASTIN RESTORATIVE EYE TREATMENT™**

Sagging of eyelid skin, wrinkles, dark circles and under eye bags are the primary patient concerns related to aging of the upper and lower eyelid areas. The eyelid skin, being four times thinner than other parts of the body, manifests with earlier, more apparent, signs of aging. ALASTIN Restorative Eye Treatment™ incorporates botanicals and other actives in addition to TriHex Technology™ to help address signs of the aging eye.
ALASTIN RENEWAL RETINOL .5™

ALASTIN Renewal Retinol 0.5™ has a number of differentiating aspects to its formulation. Retinol, being among the first recognized cell regulators, has obvious positive effects on cell renewal and regeneration. ALASTIN Renewal Retinol 0.5™ is encapsulated with a solid lipid nanoparticle ceramide delivery system providing a membrane structured nanosphere. This ensures quicker delivery, stability of retinol within the capsule and less irritation. This is achieved by film formation of these spheres on the surface of the skin, ensuring less transepidermal water loss, more skin lipid mobility and optimized lipid exchange between the stratum corneum and the film. The system provides more stability, fewer side effects, quicker penetration and increased efficacy to the retinol than traditional liposome technology. Additionally, the product provides moisturization via synergistic natural potent HA activity28,29 countering the dryness usually induced by retinol.

ALASTIN RESTORE AND RENEW SKIN CARE LINE WITH TRI-HEX TECHNOLOGY™

By combining this group of potent peptides, lipids, and botanicals in ALASTIN Restorative Skin Complex™ and the Restore and Renew line, a comprehensive strategy of ECM clearance and replacement has been established with the aim to achieve dermal and subdermal restoration. As detailed above, the peptides operate as cell regulators as well as anti-oxidants to clear the ECM of protein fragments, balance the inflammatory protease milieu, stimulate intracellular protease function and stimulate replacement of collagen, elastin, decorin and dermatopontin. PS acts as a false substrate to reduce AGE products, decrease MMP-1 and stimulate procollagen. The adipogenic and volumizing components create a denser healthy dermis and subdermis. Other active agents that provide synergy to the described dermal restorative process are also included in the formulation. Thus, all elements of toxic degeneration and restorative regeneration along with ECM recycling are addressed in the design of the ALASTIN Skincare Restore and Renew product regimen. Importantly, our active agents have also been carefully selected to include those with small molecular sizes, enhancing stratum corneum penetration and absorption. This strategy has been evidenced histologically below.

Most importantly, validation has been achieved by demonstrating and confirming the desired histological changes in the ECM (Figure 2). Clinically, improvement in lines and wrinkles, texture, pigmentation and quality of the skin are observed (Figure 3) while the patient experience has been overwhelmingly and dramatically positive (Figure 4).

CONCLUSION

Skin photodamage and aging is characterized by a simultaneous sequence of degenerating events occurring over a period of time. This cumulatively presents as well defined changes in the dermis and subdermal areas. The accumulation of the byproducts of metabolism secondary to photodamage precipitate fragmentation of structural proteins with inefficient clearing of these byproducts. This accumulation of byproducts, together with age-related atrophy of subcutaneous adipose tissue, typically manifests as thin, atrophic, lined and pigmented skin.

The ALASTIN Restore and Renew skincare line, and its flagship product, ALASTIN Restorative Skin Complex™ with TriHex
In a recent survey of ALASTIN Restorative Skin Complex™ users after 8 weeks of twice-daily use
Percent of Subjects Who Somewhat or Strongly Agreed with Assessment Statements (N=14)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>My fine lines and wrinkles are less visible</td>
<td>92</td>
</tr>
<tr>
<td>My deep wrinkles are less visible</td>
<td>92</td>
</tr>
<tr>
<td>My face feels more firm</td>
<td>92</td>
</tr>
<tr>
<td>My face looks like it has more volume</td>
<td>92</td>
</tr>
<tr>
<td>My face has better elasticity</td>
<td>85</td>
</tr>
<tr>
<td>My skin tone is more even and clear</td>
<td>92</td>
</tr>
<tr>
<td>My skin looks more radiant and luminous</td>
<td>92</td>
</tr>
<tr>
<td>My pores appear less visible</td>
<td>85</td>
</tr>
<tr>
<td>My face feels smoother and softer</td>
<td>100</td>
</tr>
<tr>
<td>My skin looks healthier</td>
<td>100</td>
</tr>
<tr>
<td>My skin looks more youthful</td>
<td>85</td>
</tr>
</tbody>
</table>

I am satisfied with the overall results the product provides                | 100     |
I will continue using the product to treat my skin                          | 100     |
I would recommend this product to a friend                                   | 100     |

NEW! ALASTIN™ Restore and Renew skincare for daily use

Put TriHex Technology™ to work for patients in a simple yet comprehensive daily regimen

**STIMULATES** clearing of fragmented elastin & collagen in the ECM and enhances the production of new elastin and collagen, resulting in optimal skin restoration

**STRENGTHENS** and thickens the skin with specific ingredients targeted to provide a youthful, more volumized appearance

**SUPPORTS** a long-term healthy skin journey with cell-communicating ingredients designed to strengthen, smooth, and brighten skin

Patients currently using Alastin Skin Nectar can switch to daily use Restorative Skin Complex™ following re-epithelialization of their post-procedure skin or after their final treatment in a series

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