Discovering novel small molecules to modulate signal transduction imbalances.
Signum’s Core Technology

Creating Innovations in Dermatology to Combat Aging

Image: https://www.niehs.nih.gov/research/atniehs/labs/stl/
1. Dr. Stock joined the faculty of Princeton University in 1982.
   - Elected Fellow, American Academy of Microbiology
   - Winner of The Humboldt Prize
   - Elected Fellow, American Association for the Advancement of Science (AAAS)

2. 150 peer reviewed publications in top scientific journals.


4. In 1998 Dr. Stock and Max began to work together at Princeton University to apply the results of these scientific breakthroughs toward the development of products with direct applications for human health.
Signum’s research and development have yielded novel anti-aging agents that can protect our skin.

Common causes of premature aging of our skin cells:
1. Chronic inflammation
2. Oxidative stress
3. DNA damage

Signum has developed proprietary molecules and extracts that are:
1. Anti-inflammatory
2. Anti-oxidant
3. Modulate cell signaling
Signum’s Technology is Patent Protected

**Signum’s patents** have been exclusively licensed to Nerium International

**Licensed Patents:**

1. Isoprenyl compounds and methods thereof  
   **US 8372884 B2**

2. Compositions and methods for enhancing cognitive function  
   **US 7923041 B2**
Why Nerium International?

1. Perfect marriage with “Real Science, Real Results.”
2. Developing novel products that work and are affordable
3. Bringing innovative research to consumers faster than anyone
4. A family business with a set of core values in alignment with our own
SIG-1273™ : A Novel Anti-Aging Cosmetic Ingredient
## Causes of Skin Aging

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>FACTOR(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photo-aging</td>
<td>UVA, UVB</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Chemicals, pollution, metals, etc...</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Free radicals</td>
</tr>
<tr>
<td>Breakdown of ECM</td>
<td>MMPs</td>
</tr>
<tr>
<td>(e.g. collagen, elastin)</td>
<td></td>
</tr>
<tr>
<td>Delayed skin repair</td>
<td>Intrinsic aging</td>
</tr>
</tbody>
</table>

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![Skin Composition Diagram](image)

**Younger Skin**
- Epidermis
- Dermis
- Hypodermis
- Hyaluronan and water
- Elastin
- Collagen

**Older Skin**
- Deep wrinkle
- Fibroblast
- Oxytalan
- Capillary vessel
Novel Technology Platform: IPCs

Isoprenylcysteine (IPCs) molecules modulate cell signaling

Studies by Dr. Jeffry Stock of Princeton University discovered and demonstrated that IPC molecules target inflammation:

How do IPC’s Work?

G-Proteins can bind to GPCR, creating downstream signaling pathways which lead to inflammation, oxidative stress, and aging.
The Discovery: Novel Library of Molecules

Screened for novel molecules that were safe and had anti-aging properties

1. ~1400 well-characterized molecules generated.

2. Series of phytol-derived molecules (phytol is a naturally occurring oil found in plants and vegetables) to create a novel, patent protected series of new functional ingredients.
1. SIG-1273™ chemical modulating cell signaling pathways through EGFR channels.
Next Generation IPC, SIG-1273

Novel, Proprietary Anti-aging molecule: SIG-1273™

1. Built on the research performed by Dr. Jeffry Stock at Princeton University over 20 years ago.

2. Signum scientists discovered SIG-1273™ in 2008. Since then we have demonstrated it is a multi-action anti-aging molecule.

3. Nerium International has obtained the exclusive rights to SIG-1273™, which is now available in Nerium’s Optimera Formula line.
How Does SIG-1273™ Work?

SIG-1273™ targets not just the signs of aging, but also the causes

1. Acts as a powerful anti-oxidant reducing oxidative stress and free radical damage from sun, pollution and other environmental factors.
2. Mimics and boosts the skin’s natural age-fighting mechanisms.
3. Protects against collagen breakdown.
4. Targets the causes of inflammation, the main factor of aging.
SIG-1273™: Peer Reviewed Publications

1. **JOURNAL OF COSMETIC DERMATOLOGY**
   *In vitro* and clinical evaluation of SIG1273: a cosmetic functional ingredient with a broad spectrum of anti-aging and antioxidant activities.

2. **INTERNATIONAL JOURNAL OF COSMETIC SCIENCE**

3. **JOURNAL OF COSMETIC DERMATOLOGY**
   SIG1273: a new cosmetic functional ingredient to reduce blemishes and *Propionibacterium acnes* in acne prone skin.
SIG-1273™ Targets Cellulite in the Skin

SIG-1273™ targets 3 causes of cellulite to help promote the appearance of smooth skin

- Decrease in oxidative stress
- Increase in lipolysis by adipocytes
- Increase in dermal ECM proteins
SIG-1273™ Combats Cellulite

1. SIG-1273™ demonstrates strong antioxidant activity in both cell free and cell based oxidative stress assays
2. SIG-1273™ in adipocytes shows lipolytic properties (destroys fat cells)
3. SIG-1273™ formulated in Optimera® Firming Body cream applied topically produced positive effect in the expression of both skin aging (COL4A1, HAS2) and anti-cellulite (HIF1A) related genes
Optimera Containing SIG-1273™ Improves Appearance of Cellulite

Clinical Grade Evaluation from week 2 to 12

<table>
<thead>
<tr>
<th>Assessment Measured</th>
<th>Mean % Improvement from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thigh Contour</td>
<td>21 - 49%</td>
</tr>
<tr>
<td>Skin Tone</td>
<td>16 - 42%</td>
</tr>
<tr>
<td>Firmness</td>
<td>21 - 48%</td>
</tr>
<tr>
<td>Elasticity</td>
<td>19 - 42%</td>
</tr>
<tr>
<td>Cellulite</td>
<td>6 - 44%</td>
</tr>
</tbody>
</table>

Baseline

2 weeks after
Benefits of SIG-1273™ Age Defying Optimera Formula

1. Protects against photo aging
2. Improves skin elasticity & firmness
3. Antioxidant, reduces oxidative stress
4. Improves fine lines and wrinkles
5. Protects against collagen breakdown
6. Boosts skin repair mechanisms
SIG-1191™: A Novel Anti-Aging Cosmetic Ingredient
1. SIG-1191™ chemical modulating cell signaling pathways through specific Aquaporin 3 channels (AQP3).
How Does SIG-1191™ Work?

SIG-1191™ targets the causes of skin dehydration and chronic inflammation

1. Possesses unique skin hydration potential by modulating the expression and production of Aquaporin-3 (AQP-3) water channels, which is responsible for water transport and hydration in the human skin epidermis.

2. Mimics and boosts the skin’s natural age-fighting mechanisms.

3. Protects against fibroblast cellular senescence.

4. Targets the causes of inflammation, the main factor of aging.
What are Aquaporins?

Aquaporins are a family of transmembrane proteins forming water channels in the basal layer of the epidermis and are responsible for water transport and hydration in the human skin epidermis.

Aquaporin-3 (AQP3) is the major aquaporin found in the skin.

Dr. Z. Draelos, J Clin Aesthet Derm, 5(7):53-6 2012
Aquaporin-3 (AQP3) as a new skin care target

1. “AQP3 role in skin is to increase glycerol and water content which results in increased hydration/moisturization, barrier recovery, and wound healing (aka skin repair).”
   AS Verkman JID 2008

2. “Altering the expression of AQP3 may be a potential mechanism for treating some of these dry skin conditions. The search is currently under way for compounds that can be used to pharmacologically stimulate AQP3 expression, thereby improving the hydration state of the skin by endogenous means.”
   Z Draelos JCAD 2012

3. “The potential exists for AQP3 levels to be manipulated thus presenting interesting possibilities for AQP3 modulators to be developed and incorporated into future generations of skin care products.”
   Z Draelos JCAD 2012
SIG-1191™ stimulates AQP3 expression in Keratinocytes

Dose-dependent increase in aquaporin-3 (AQP3) by SIG-1191™

*statistically significant P value > 0.05
<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>FACTOR(S)</th>
<th>SIG-1191</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Leaky” capillaries</td>
<td>Free heme</td>
<td>✔️</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>UVB, Inflammation</td>
<td>✔️</td>
</tr>
<tr>
<td>Puffiness (Edema)</td>
<td>Inflammation</td>
<td>✔️</td>
</tr>
<tr>
<td>Dryness</td>
<td>Decrease in moisture</td>
<td>✔️</td>
</tr>
</tbody>
</table>
**Under eye-Dark circles: SIG-1191™ and HDMECs**

**SIG-1191™ increase HO-1 expression in HDMECs by 70% above vehicle**

“One of the main causes of dark circles under the eye is the accumulation of heme resulting from blood leakage. The free heme produced in this manner is highly cytotoxic, pro-inflammatory and pro-oxidative…”

J Cosmet Sci 2014 65(2):103-113

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>HO-1 EXPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>0%</td>
</tr>
<tr>
<td>Vehicle</td>
<td>+20%</td>
</tr>
<tr>
<td>EGCG*</td>
<td>+40%</td>
</tr>
<tr>
<td>SIG-1191</td>
<td>+90%</td>
</tr>
</tbody>
</table>

*Epigallocatechin Gallate


3. December 2016 - N-Acetylglutaminoyl-S-Farnesyl-L-cysteine (SIG-1191): an anti-inflammatory molecule that increases the expression of the aquaglyceroporin, aquaporin-3, in human keratinocytes
Benefits of SIG-1191™ Eye Serum

1. Delivers an immediate reduction in the appearance of fine lines and wrinkles.

2. Supports the skin’s natural structure.

3. Fights the appearance of:
   • Dark circles
   • Puffiness
   • Lines and wrinkles

4. Matches your skin’s natural pH level, ensuring optimal skin health.

5. Firms and brightens the appearance of the eye area.

6. Ideal for all skin types; dermatologist and ophthalmologist tested.
Research Pipeline for Mind, Body & Face

Developing new anti-aging technology distributed exclusively through Nerium International

FACE
Hydration/Moisture
Skin aging
Acne

MIND
Neuro-inflammation
Mental focus/Memory
Oxidative stress

BODY
Micro-inflammation
Metabolic
Cardiovascular

SIGNUM BIOSCIENCES: THE SCIENCE OF STAYING HEALTHY®
Thank You