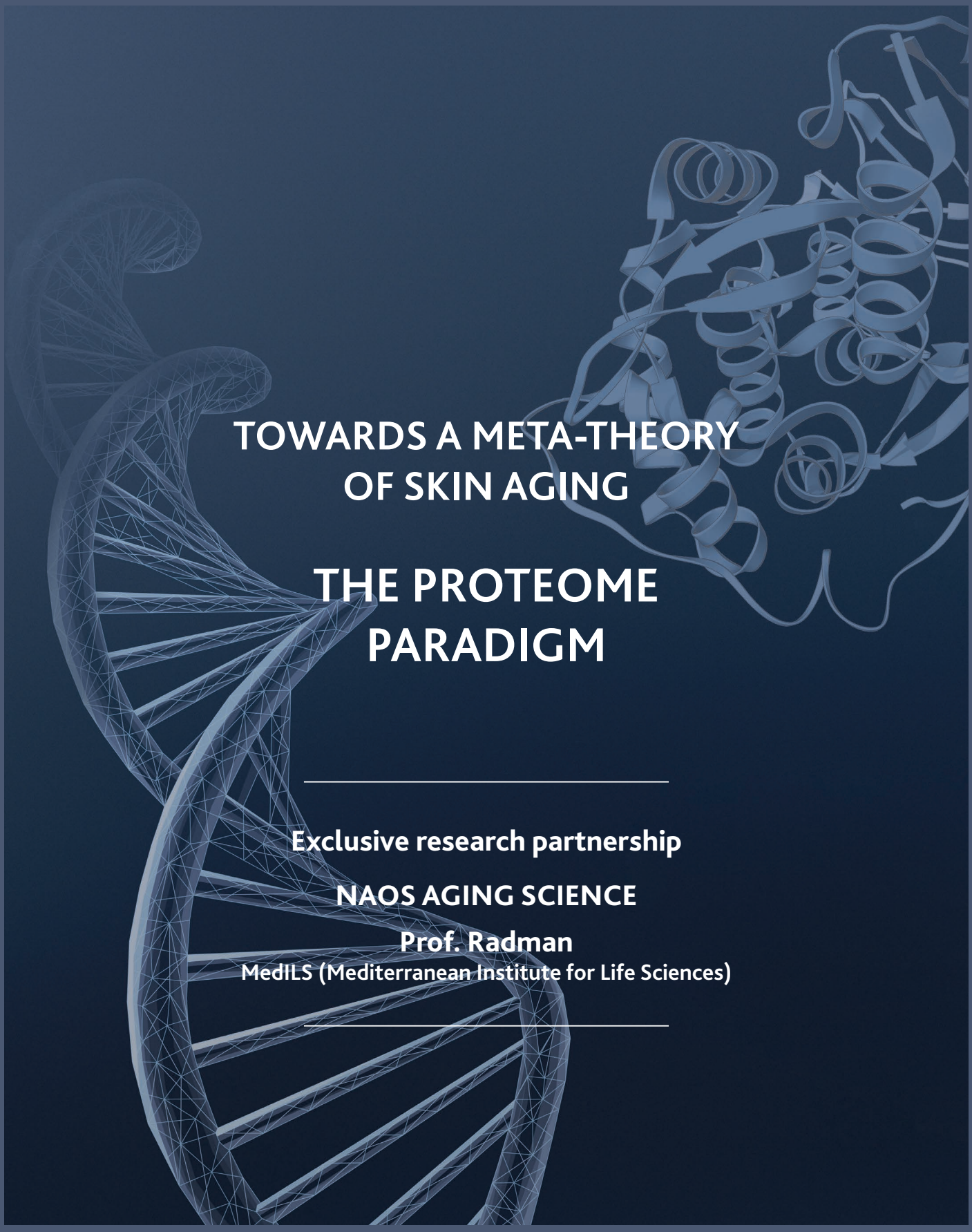
NAOS AGING SCIENCE

BIODERMA LABORATOIRE DERMATOLOGIQUE

INSTITUT ESTHEDERM PARIS

état pur



TOWARDS A META-THEORY OF SKIN AGING

THE PROTEOME PARADIGM

Exclusive research partnership

NAOS AGING SCIENCE

Prof. Radman

MedILS (Mediterranean Institute for Life Sciences)

CONTENTS

THE DISCOVERY

TOWARDS A META-THEORY OF AGING

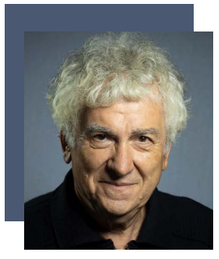
The biological evolution of some living beings is opening up a new path: understanding why and how we age

The inspiration comes from solutions found by nature, having had significantly more time than all the world's researchers in biology: performing billions of unsuccessful trials on a staggering number of living beings over billions of years.

Many of these trials have had no effect, while others have turned out to be harmful to organisms; only very few changes have improved life performance under specific conditions.
Organisms capable of withstanding extreme conditions are examples of perfect evolution in terms of biological robustness: their genetic adaptation by selection has helped transform a hostile environment into an optimal environment.
These extremophiles such as *Deinococcus radiodurans* or *Arthrobacter agilis* bacteria inspired Prof. Radman's research, as their extreme resistance can be compared with resistance to aging, radioresistance and chronoresistance going hand in hand.
When exposed to radiation, they can transition from a "clinical death" state to a "resurrection" process through self-repair.
How can these living beings survive gamma ray doses 1,000 times the lethal dose for human beings? How is it possible that extreme damage to their DNA does not cause their death?
It is because, when they have multiple DNA fragments, "unoxidizable" proteins come into play to repair said DNA.

These two super-bacteria have "invented" systems that protect proteins against the corrosion normally caused by radiation.
This is how Prof. Radman began focusing on proteins, and therefore on the theory of the role of the proteome in the aging process. The survival of the organism depends on the activity of its proteins, as does its aging.
The skin ages because its cells age; the cells age because their proteome becomes oxidized, and ages.
If we target this cause—proteome alteration—common to all aging-related damage, action can be taken simultaneously on each of its consequences.
To this end, providing our cells with protective molecules that have been successfully tested by the evolution of living things is the most effective solution to combat the signs of time.

Increasing the use of biomimetism helps reduce the need to use molecules that have not been validated by nature, while giving us access to pure knowledge. And accessing knowledge gives us insight.



An internationally acclaimed geneticist and molecular biologist, Miroslav Radman is particularly known for his discovery of the SOS response to DNA lesions, and for revealing the importance of protecting the proteome in the cells' resistance to extreme conditions (radiation, temperature, dryness, etc.). His work has been the subject of more than 200 publications in the most prestigious international scientific journals, and has led to the filing of many patents.

His research on the role of proteome damage as a cause of age-related diseases such as Parkinson's, Alzheimer's and Charcot has helped pave the way for the most promising research strategies in aging therapies.

Prof. Miroslav Radman
Harvard – Inserm – CNRS
Member of the French Académie des sciences and the U.S. National Academy of Sciences
Founder of MedILS
(Mediterranean Institute for Life Sciences)
in Split, Croatia.

MEDITERRANEAN INSTITUTE FOR LIFE SCIENCES

MIROSLAV RADMAN AND JEAN-NOËL THOREL, TWO SCIENTISTS DRIVEN BY THE SAME PASSION FOR LIFE

Since the 2000s, Jean-Noël Thorel, pharmacist and founder of NAOS, has shared the vision and research of Professor Miroslav Radman, founder of MedILS *(Mediterranean Institute for Life Sciences)*, whose work on cell longevity and regeneration has revolutionized the understanding of aging and age-related pathologies *(diabetes, Parkinson's, Alzheimer's, Charcot, etc.)*.

A SHARED VISION OF THE SKIN AND AGE

The skin is a living ecosystem, the largest of our organs. As an interface between our inner being and the outside world, it is our reality, our face, our body, our emotions; it is the reflection of who we are. Its health is the result of a biological balance between our cells and their internal and external environment.

"Beauty is health that you can see, well-being is health that you can feel"
For Jean-Noël Thorel and Miroslav Radman, caring for and supporting the skin over time means looking after its health.

Life expectancy has doubled in one century. Our skin has the ability to adapt to this longevity, as it has natural mechanisms inherited from the billions of trials Nature has performed over the course of our evolution. We now understand how to slow down aging processes to take advantage of the time we save, while staying healthy.
The skin's biological age is not necessarily related to the individual's chronological age: if we protect and optimize the biological robustness of our proteins, and consequently that of our cell repair systems, the entire functionality of youth is preserved.

The partnership between NAOS AGING SCIENCE and MedILS has made it possible to implement this powerful and revolutionary scientific approach.

Bioderma's dermatological expertise and the cosmetic know-how developed by **Institut Esthederm** for over 40 years have been combined to develop one of the most promising biological pathways: **protecting the proteome as a response to skin aging**.

Miroslav Radman
Doctor in molecular biology, geneticist.
Founder of MedILS
(Mediterranean Institute for Life Sciences)

Jean-Noël Thorel
Pharmacist, expert in cell biology,
Founder and CEO of NAOS
(Institut Esthederm - Bioderma - Etat Pur)

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40 YEARS OF RESEARCH
IN PROTEOME SCIENCE

Hero of longevity, *deinococcus radiodurans*, the immortal bacterium

Understanding longevity mechanisms through extremophile bacteria

To understand the keys to a long and healthy life, Miroslav Radman focused on living organisms that have extraordinary longevity: **extremophile bacteria** [1].

These organisms, whose biology was optimized by billions of years of evolution, manage to survive and thrive in extreme conditions (temperature, pH, salinity, radiation, etc.) close to the physical and biological limits of life [7].

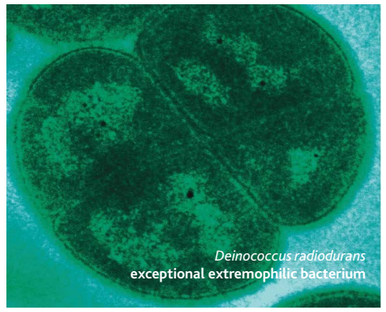
Studying their defense and resilience systems against a harsh environment is key to understanding stress tolerance and aging resistance mechanisms.

Some life forms are quasi-immortal

Deinococcus radiodurans is one of the most resistant known bacteria: it is capable of surviving extreme levels of irradiation intensity, hydrogen peroxide, acid, temperature, dryness, etc.

A major scientific discovery

As *Deinococcus radiodurans* is extremely resistant thanks to its perfectly protected proteome, a long and healthy life in human beings depends on protecting the proteome.



Deinococcus radiodurans
exceptional extremophilic bacterium

As proteins perform all life functions, the initial cause of age-related diseases and aging itself must be found in the functioning of the proteins.

A NEW SCIENTIFIC PARADIGM:
BEYOND THE GENOME, THE PROTEOME

Towards a new understanding of aging

Proteins: the body's 2nd largest component but the primary source of longevity

The proteome refers to all the proteins of a cell or organism. Proteins (from the Greek *protos* meaning "first" [6]) are the body's second greatest component after water [5], i.e., more than 20% of weight.

As a genuinely vital asset, they provide many key functions in all organs and are effectors of the entire cell mechanism.

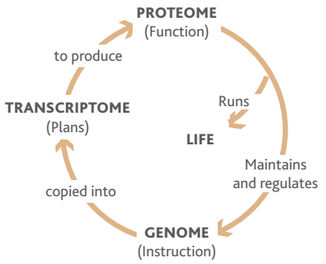
Why target the proteome rather than the genome?

While genes constantly carry all biological information *(= what could happen)*, not all our genes are expressed everywhere in our body at all times.

It is only when a gene is translated into a protein that it is fully expressed *(= what really happens)*.

The proteome is a dynamic entity that constantly adapts to the needs of the cell and its environment [22]. **It is therefore the starting point of all the vital functions of the skin. Its alteration is the main cause of aging.**

The importance of the causality of the proteome, the new meta-theory of aging, **includes most previously identified theories.** For example, the telomere shortening theory is explained by the protection of telomerase, which is a protein.



A new understanding of aging: the proteome, responsible for longevity.

In the same way as in the organism, the thousands of proteins essential to the skin's physiology play a structural as well as functional role [7].

They constitute the fabric, frame and density of skin layers, like **elastin or collagen**.
They also make sure that all vital physiological processes such as breathing, **repair, communication** and cell waste **disposal** work properly.

These proteins, which are essential to cell life, are limitless: DNA repair enzymes, **hormones, connexins,** which mediate cell communication, **aquaporins**, which carry water through various epidermal layers… all these roles are performed by multiple specialized proteins that ensure the health and balance of our largest organ: the skin.

Protecting the integrity of the proteome in the long term will help preserve the skin's youthfulness.

AND IN THE SKIN?

Main cause of skin proteome alteration: carbonylation, biological marker of aging

The aging chemistry of any cell, including skin cells, involves the oxidation of proteins, responsible for all vital functions. With time and harsh external factors, skin proteins are subject to various alterations, the biggest threat being carbonylation, an irreversible phenomenon linked to oxidation.

Carbonylated proteins lose their three-dimensional structure and can no longer perform their biological functions, which is why they must be recycled or eliminated.

With age, they are more difficult to eliminate and accumulate in the form of toxic aggregates [12] which hinder cell physiology. These **protein aggregates [11] are both aging markers and accelerators.** By clogging up cell detoxification systems, they transform proteostasis, essential to balanced life, into proteotoxicity, which accelerates aging [10].

What are the visible consequences for the skin?

These irreversible changes in the proteins result in the appearance of **wrinkles**, **dull and uneven complexion, loss of firmness or density.**

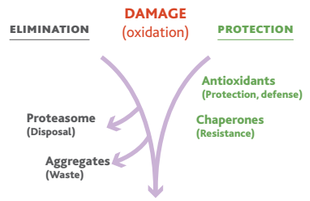
CARBONYLATION, THE BIGGEST OXIDATIVE THREAT TO THE PROTEOME

As we age, the level of carbonylated proteins in the body increases considerably *(up to 30% of all body proteins, in particular in the skin)* [13][14][15].

CONSEQUENCES FOR THE SKIN

In the horny layer, carbonylation causes a decrease in the water retention capacity and **skin dehydration. In the epidermis**, the keratins (particularly sensitive proteins) are a prime target of carbonylation, which disrupts light transmission [18], **altering the radiance and evenness of the complexion.**

In the dermis, it triggers morphological changes in the fibroblasts, while altering the dermal matrix [19], breaking down collagen and elastin fibers, resulting in premature skin aging. The skin loses **density, firmness and elasticity.**



Traditional antioxidants have a protective role that is not specific to proteins, as they are either lipophilic or hydrophilic.

The ideal protein-protecting active ingredient should be **both lipophilic and hydrophilic** for specific affinity with proteins, and should have two modes of action:

- **"chaperone," to physically protect the functional structure of proteins, and considerably reduce their sensitivity to alteration [20].**
- **antioxidant, to provide a biochemical shield that protects proteins from carbonylation.**

It is thanks to this type of molecule that some microorganisms are quasi-immortal, as they make their proteins unoxidizable.

THIS NEW CATEGORY OF PHYSICAL-BIOLOGICAL PROTECTION ACTIVE INGREDIENTS IS A MAJOR BREAKTHROUGH THAT SUPERSEDES ALL PREVIOUS ANTIOXIDANT APPROACHES.

Preserving the functionality of proteins and reducing their level of carbonylation thanks to antioxidant chaperones is therefore the key strategy to combat aging: it results in better cell and tissue functionality, and consequently helps reduce signs of aging.

12 YEARS OF RESEARCH
FOR AGE PROTEOM™ TOPICAL APPLICATION

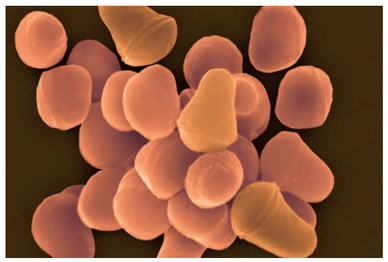
Inspired by Prof. Radman's work, NAOS research teams selected an extremophile bacterium capable of durably protecting the skin proteome.

Exploiting the extremes: *Arthrobacter agilis*, a bacterium with unique properties

Some of the molecules of this extremophile bacterium have a specific affinity with skin proteins. They have a physical shield function similar to that of natural chaperones, combined with powerful antioxidant properties.

Discovered in snowflakes in 2010 by a researcher from NAOS laboratories, the *Arthrobacter agilis* bacterium, native to Antarctica, has an amazing ability to survive, which allows it to withstand the most extreme temperatures, UV rays and oxidative stress.

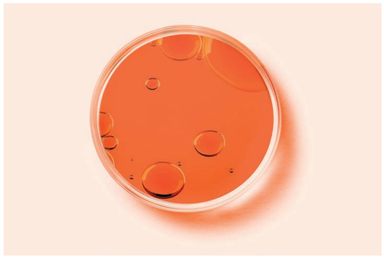
An *A. agilis* extract has much more powerful antioxidant properties than the reference bacterium used in Prof. Radman's research, *Deinococcus radiodurans*.



Largely unexplored thus far, it appears to provide skin cells with the best possible protection, due to the presence of red biological pigments that mimic the skin's natural defense systems: bacterioruberins.

Its ability to survive in extreme conditions is thanks to the presence of an arrangement of highly specific molecules, i.e., 6 more or less glycosylated forms of bacterioruberin (such diversity cannot be found in any other species known to date), powerful antioxidants with a chaperone effect, capable of durably protecting its proteome.

The NAOS applied research laboratories managed to extract these bacterioruberins to create the Age Proteom™ patented biotechnology.



Targeting the cause of skin aging, to optimize cell longevity

The Age Proteom™ patented biotechnology is the first antioxidant chaperone ever described.
By lowering proteins' carbonylation level, it prevents irreversible damage and helps restore better cell and tissue functioning.
This new approach is a first-rate response to long-term care for skin aging.

IT USHERS IN A GENERATION OF "HEALTHY AGING" SKINCARE PRODUCTS, DEDICATED TO LASTINGLY PRESERVING THE SKIN'S HEALTH AND HOMEOSTASIS.

AGE PROTEOM™ PATENTED BIOTECHNOLOGY:
PROOF OF EFFICACY

1st proteome protection active ingredient, with an "antioxidant chaperone" mechanism

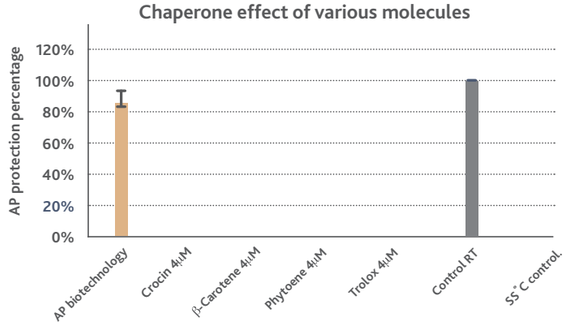
As a result of the NAOS ecobiological approach, bacterioruberins from *Arthrobacter agilis* have demonstrated a strong affinity with skin proteins and a unique "chaperone-like antioxidant" activity.
They are capable of protecting the skin proteome to tackle aging at source:

- Protection of structural proteins: elastin
- Protection of functional proteins: DNA repair
- Protection against harsh environmental factors: UV, blue light, pollution
- Protection against carbonylation, irreversible damage to proteins

1 Protein protection CHAPERONE-LIKE ACTIVITY (physical shield)

With more than 80% protective efficacy, this active ingredient creates a genuine physical shield that preserves the structure of proteins, allowing them to remain functional over the long term.

Chaperone efficacy - Specific protection of proteins

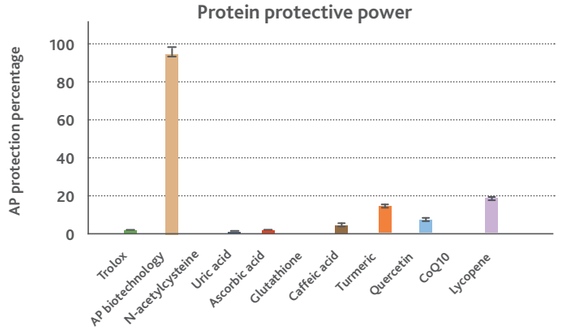


AP-Heat test / uses heat to destabilize the alkaline phosphatase protein (AP) (specific chaperone effect test).

2 Protein protection ANTIOXIDANT ACTIVITY (biochemical shield)

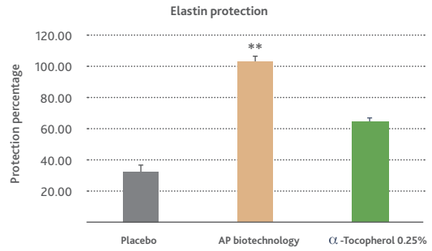
Its protein protective power is largely superior to that of reference antioxidant molecules (CoQ10, glutathione, ascorbic acid, lycopene).

Superior antioxidant efficiency to reference antioxidants



APox test / uses the activity of alkaline phosphatase (AP) as a marker of protein protection against oxidative stress. The more significant AP activity is, the higher the protection against free radicals.

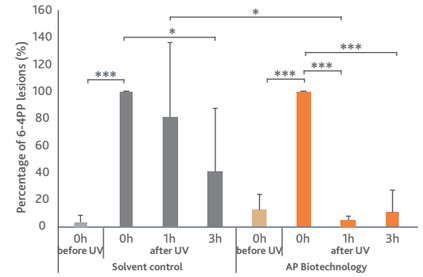
Ex vivo TEST: PROTECTION OF STRUCTURAL PROTEINS (ELASTIN) AGAINST UVA RAYS AND POLLUTION



***significant according to Dunnett's test (p<0.1)*

The Age Proteom™ patented biotechnology effectively protects dermal elastin from all major harsh environmental factors (103% protection largely superior to α-tocopherol, the reference molecule).

In vitro TEST: PROTECTION OF FUNCTIONAL PROTEINS INVOLVED IN NATURAL DNA REPAIR MECHANISMS, FOLLOWING DAMAGE CAUSED BY UV RAYS

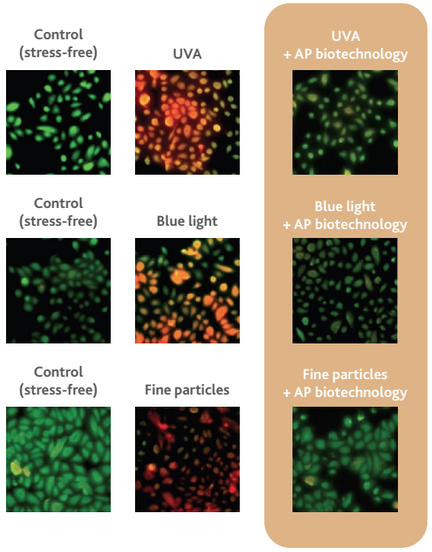


*Student's test: *p≤0.05; ***p≤0.001*

UV absorption leads to different types of DNA damage, in particular pyrimidine-pyrimidone (6-4) photoproducts (6-4PP). If this damage is not repaired, it can result in mutations, apoptosis (programmed cell death) or carcinogenesis.

The Age Proteom™ patented biotechnology significantly accelerates the repair of DNA lesions in normal human keratinocytes, 1 hour after exposure to UV stress.

In vitro TEST: PROTECTION OF SKIN PROTEINS AGAINST CARBONYLATION CAUSED BY UVA RAYS, BLUE LIGHT AND PARTICULATE POLLUTION



In vitro test on normal human epidermal keratinocytes (NHEK) cultured before being brought into contact (or not) with the active ingredient, and then subjected to stresses (UVA, blue light or fine particles).

The Age Proteom™ patented biotechnology protects keratinocytes against all major harsh environmental factors.

STRESS	PROTECTION FACTOR
UVA	63.8%
Blue light	73%
Fine particles	96.2%

BEYOND THE GENOME, THE PROTEOME
A NEW VISION FOR THE SCIENCE OF AGING.

THE CELL LONGEVITY SERUM

AGE PROTEOM™

The AGE PROTEOM serum ushers in a new generation of dermatological skincare products based on Bioderma's expertise combined with the science of cosmetics acquired by Institut Esthederm over the past 40 years.

AGE PROTEOM™

ADVANCED SERUM

FORMULATED ACCORDING TO NAOS'S ECOBIOLOGICAL CRITERIA

Formulatory synergies designed to reduce the use of conventional preservation systems and improve skin affinity.

Use of biomimetic ingredients that respect the cutaneous ecosystem, active ingredients interacting with the skin's natural mechanisms, incorporated in the right dose.

Perfect skin and eye tolerance.

Formulation

Highly moisturizing emulsion: glycerin, xanthan gum, natural polyol derived from corn sugar.

Light, allergen-free fragrance.

Galenic formulation that encourages compliance

This serum-emulsion is the result of the NAOS research laboratories' formulation expertise. Unlike the watery, film-forming textures of traditional serums, its fresh, moisturizing texture provides long-lasting comfort for all skin types, with or without the addition of a skincare cream.

Indications: all ages, all skin types.

Dosage: morning and evening, alone or in addition to a skincare cream.

Packaging: 30ml "self-dosing" dropper bottle (1 month's use, to be renewed for permanent use).

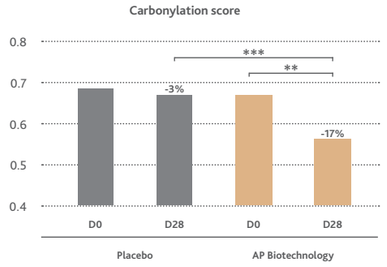
A VIRTUOUS PRESERVATION SYSTEM

Our formulators have selected polyols in affinity with oil and water. These multi-purpose polyols are both moisturizing and naturally antimicrobial. Their ability to bind to the water in the formula is not conducive to the development of microorganisms.

Associating them with the acidic pH in affinity with the skin's pH made it possible to do without a conventional preservation system.

In vivo TEST: reduction in carbonylation, responsible for irreversible damage relating to skin aging

In vivo evaluation of the protein protective effect against carbonylation



*Student's test: **p<0.01*

AFTER 28 DAYS

The carbonylation of epidermal proteins is reduced by 17%.

Test on 23 women aged 38 to 69, phototypes II to III, smokers, with a dull complexion. Application in the morning & evening onto half of the face.

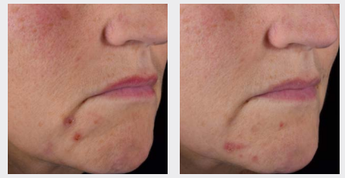
DERMATOLOGICAL AND COSMETIC EFFICACY 6-MONTH CLINICAL TRIAL

Clinical scoring of 5 parameters: wrinkles, radiance, density, firmness, complexion evenness.

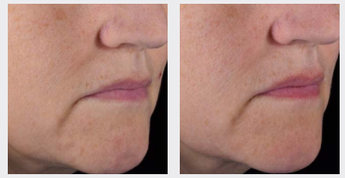
The efficacy of the AGE PROTEOM™ serum on skin aging was assessed after 1 month, 3 months and 6 months of twice-daily application under normal conditions of use in the morning and evening.

55 Caucasian women, aged 42 to 65, phototypes II to IV, all skin types, urban environment, signs of fatigue (wrinkles, fine lines and/or dark circles and/or puffiness) and pigmentation disorders (dark spots, uneven complexion). 8 volunteers are smokers.

RADIANCE

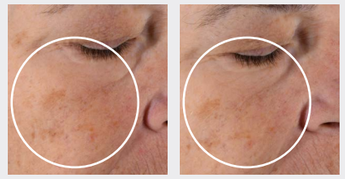


T0 — 1 MONTH

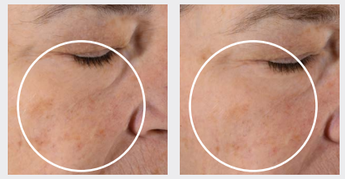


3 MONTHS — 6 MONTHS

COMPLEXION EVENNESS

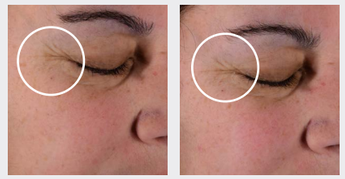


T0 — 1 MONTH

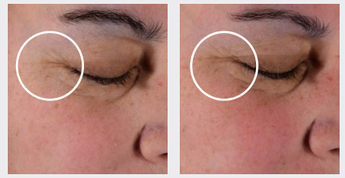


3 MONTHS — 6 MONTHS

WRINKLES (CROW'S FEET)



T0 — 1 MONTH



3 MONTHS — 6 MONTHS

AFTER 28 DAYS, THE SKIN AGES TWO TIMES SLOWER

NEW: MEASURING OVERALL CHANGES IN THE AGING PROCESS

For each of the volunteers, the improvement measurements of signs of aging are added up.

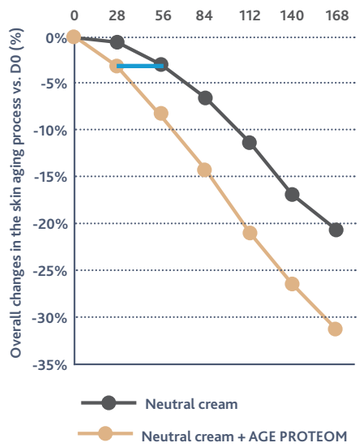
[wrinkles] + [radiance] + [complexion evenness] + [pigmentation marks] + [firmness] + [density]

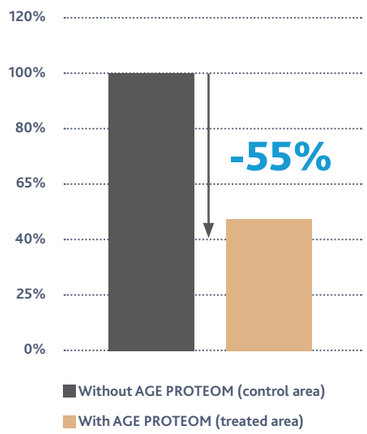
The average gives us an aging slowdown speed curve between the treated side and the untreated side.

CLINICAL STUDY ON ONE HALF OF THE FACE

Measurement of changes in the aging process after 6 months between the SIDE TREATED with AGE PROTEOM and the UNTREATED SIDE

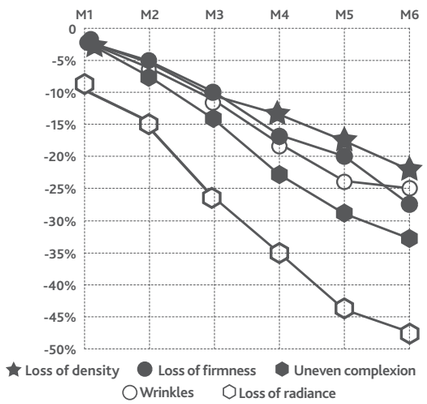
SLOWDOWN IN SKIN AGING*





CLINICALLY PROVEN EFFICACY AGAINST ALL AGING PARAMETERS**

SUSTAINABLE REDUCTION IN SIGNS OF AGING



Wrinkles	**-26%**
Loss of radiance	**-47%**
Uneven complexion	**-32%**
Sagging	**-28%**
Loss of density	**-24%**

** Average improvement in the 5 signs of aging after 1 month, versus a placebo with no biological effects after 2 months – clinical study, 6 months, 55 volunteers.*
*** Clinical test (scoring), 55 volunteers aged 42 to 65, stressful lifestyle, showing signs of fatigue & pigmentation disorders. Twice-daily application (morning & evening) for 6 months. Randomized application onto one half of the face: on one side Age Proteom™ + neutral cream (treated area), on the other neutral cream alone (control area).*

PATIENT SELF-ASSESSMENT

Characteristics that encourage compliance

TEXTURE*

Overall assessment	**90%**
Pleasant to use	**93%**
Rapid absorption	**97%**

IMMEDIATE EFFICACY*

HYDRATION	**93%**

PERCEIVED EFFICACY ON D28

Caucasian skin*

COMPLEXION EVENNESS	**90%**
RADIANCE	**87%**
FIRMNESS	**83%**
REGENERATION	**83%**
SKIN QUALITY	**83%**

Asian skin**

COMPLEXION EVENNESS	**94%**
FIRMNESS	**88%**
SKIN QUALITY	**97%**

*30 women, aged 40 to 54, all skin types. 73% smokers, 23% short sleepers, 67% urban dwellers, 63% exposed to pollution, 3% party goers.
**32 Asian women (Chinese), aged 35 to 55, who say they are short sleepers, live in an urban environment exposed to pollution and are party goers, 50% of whom are smokers.

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