IMUDILIN®

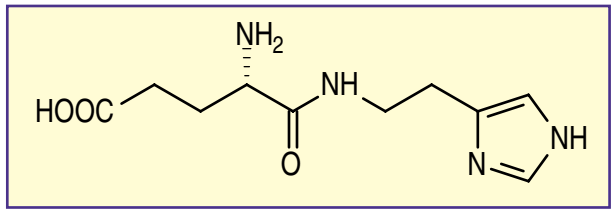
EXSYMOL

Aqueous solution of L-glutamyl-amidoethylimidazole (GAEI)

INCI name : GLUTAMYLAMIDOETHYL IMIDAZOLE (and) WATER

Chemical family

IMUDILIN® is a stable aqueous solution of a synthetic pseudodipeptide.



Analytical composition

L-Glutamyl-amidoethylimidazole	1.00 %
Sodium methyl paraben	0.14 %
Water sq	100.00 %

Technical characteristics

Limpid, colorless liquid

pH : about 5

Density at 20°C : about 1.0

Miscible with water, alcohols and glycols.

Availability

1, 5 or 30 kg drums

Uses

Skin protection through cytokine-like immunostimulation
(restores the immune defense and stimulates cell metabolism)

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Anti-aging and anti-stress

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Anti-pollution

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Men's care, after-shave

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Night products

RESTORATION OF THE IMMUNE DEFENSE AND STIMULATION OF THE IMMUNE DEFENSE

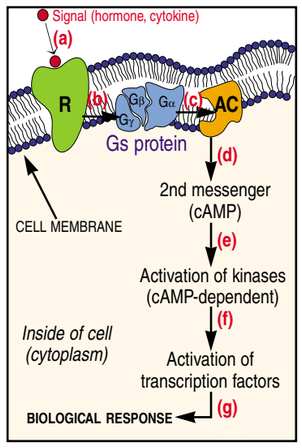
Homeostasis, cell communication, immune response

Skin homeostasis depends on a communication network that takes place between all the different constituents of the cutaneous tissue.

The communication between the cells that involves a number of signalling molecules such as hormones, cytokines, growth factors, is also essential for the repairing (tissue regeneration) and defense system (inflammation, immune response) of the skin.

With aging and repeated environmental stresses (pollution, UV exposures…), cell communication is impaired and this results in reduced immune defense, altered metabolic activity characterized for instance by a feeling of dry skin.

All biological signals elicit a cellular response through a mechanism called "signal transduction", which transfers the external signal to a biological target located inside the cell.



SIGNAL TRANSDUCTION PATHWAY

(a) Signal (hormone, cytokine) moves towards the target cell membrane.

(b) The receptor protein (R) initiates the transduction of the signal to the inside of the cell by interacting with intermediate Gs protein (G_γ, G_β, G_α).

(c) The Gs protein activates the adenylate cyclase (AC).

(d) (e) (f) The activated adenylate cyclase produces an intra-cellular «second messenger» that diffuses through cAMP-dependent protein kinases, that finally activate the transcription factors.

(g) The biological response includes cell multiplication, gene activation and production of biomolecules.

IMUDILIN® is able to stimulate the signal production, at the origin of the signal transduction.

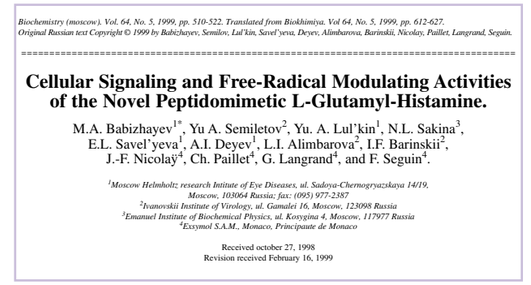
Free radicals are biological messengers for signal transduction

Free radicals are generally considered as toxic species for biological organisms but it has been evidenced that some of them positively take part to essential physiological processes. Some free radical species (e.g. $NO^\bullet$, $O_2^{-\bullet}$, $OH^\bullet$) are also communication messengers produced by numerous cells, in particular in the skin. As an example, fibroblasts and lymphocytes continuously produce small quantities of superoxide anion ($O_2^{-\bullet}$) that regulate the cells growth. A common characteristics in the process of transduction is that the quantities of free radicals involved are always very low (sub-toxic).

Even if the exact mechanism is still unknown, free radicals have already been described in the literature as modulator of the kinases activity, which are key intermediates in the signal transduction pathway.

A unique cytokine like activity : IMUDILIN® stimulates the signal transduction

IMUDILIN® has the unique property of being an anti-oxidant at high concentration (like ALISTIN® and EXSY-ARL®), while at very low concentration, it releases small quantities of superoxide anion ($O_2^{-\bullet}$).
Far from being damaging, these sub-toxic amounts of free radicals improve the immune cells' response, by stimulating their signal transduction pathway.
Thus, IMUDILIN® mimics the effects of cytokines at concentrations similar to these natural signals.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Cellular Signaling and Free-Radical Modulating Activities of the Novel Peptidomimetic L-Glutamyl-Histamine.

M.A. Babizhayev[1*], Yu A. Semiletov[2], Yu. A. Lul'kin[1], N.L. Sakina[3], E.L. Savel'yeva[1], A.I. Deyev[1], L.I. Alimbarova[2], I.F. Barinskii[2], J.-F. Nicolay[4], Ch. Paillet[4], G. Langrand[4], and F. Seguin[4].

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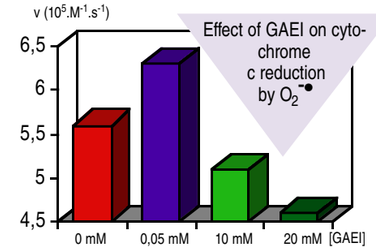
IMUDILIN® is pro-oxidant at low concentrations and anti-oxidant at higher concentrations

This unique property of IMUDILIN® has been evidenced in the study of cytochrome c reduction by $O_2^{-\bullet}$, generated by xanthine oxydase.

The graph shows that a very low concentration of L-glutamyl-amidoethylimidazole (GAEI) is able to speed-up the kinetics of cytochrome c reduction, which is the consequence of a higher production of superoxide anion $O_2^{-\bullet}$. At higher concentrations, this effect is replaced by the anti-oxidant property : the kinetics of cytochrome c reduction is slower than the reference.

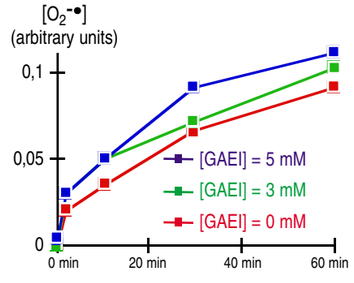


A confirmation of this property was obtained with the study of liposomes peroxidation by iron/ascorbate when incubated with IMUDILIN® : at low concentration (0.042 mM) more lipid peroxides are produced and at higher concentration (10 mM) IMUDILIN® displays its anti-oxidant capacity by reducing the lipid peroxides.

IMUDILIN® can generate $O_2^{-\bullet}$

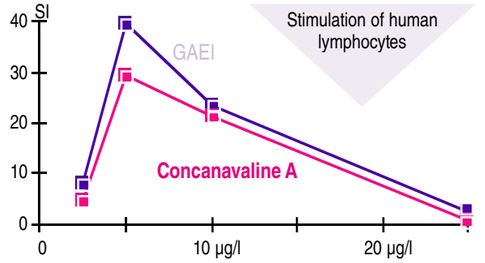
The capacity of IMUDILIN® to stimulate the prodution of free radicals has been exemplified by the study of $O_2^{-\bullet}$ formation, by the phenantroline test, during the oxidation of ferrous ion :

$$Fe^{2+} + O_2 \longrightarrow Fe^{3+} + O_2^{-\bullet}$$



IMMUNOSTIMULATION

The immunostimulating capacity of IMUDILIN® has been evidenced in the stimulation of immune cells (murine splenocytes, human lymphocytes).
The graph here below illustrates the cytostimulation eficiency of L-glutamyl-amidoethylimidazole on human lymphocytes.
The immunostimulation effect is characterized by the stimulation index "SI" (amount of tritiated thymidine incorporated in the living cells).
The activity is compared to that of concanavaline A, a reference immunostimulator.



At low concentrations, $O_2^{-\bullet}$ is produced and IMUDILIN® displays lymphocites-stimulating activity similar to a reference immunostimulator (concanavaline A).

Tolerance study

The tolerance of L-glutamyl-amidoethylimidazole has been studied *in vitro* by alternative methods either on cell culture or reconstituted epidermis. The ocular tolerance is evaluated by studying the cytotoxicity on fibroblasts culture isolated from rabbit cornea. The cutaneous tolerance is evaluated on reconstituted epidermis by evaluation of cell viability after a contact period of 24 hours with the product. The results observed indicate that :

- IMUDILIN® is non irritant according to the procedure of **ocular irritation**,
- IMUDILIN® is non irritant according to the procedure of **primary cutaneous irritation**,
- IMUDILIN® is **not phototoxic**.

The tolerance was completed by *in vivo* studies of **skin sensitizing, iritability, phototoxicity and photoallaergy potential on human volunteers** :

- IMUDILIN® does not provoke skin irritations or sensitizing and it does not produce phototoxicity or photoallergy, after exposure to the UVA/UVB radiation.

The potential mutagenic activity of L-glutamyl-amidoethylimidazole has also been studied and **no mutagenic activity** has been induced on the 6 selected bacterial strains

Formulation

IMUDILIN® is a very stable solution. The product can be formulated in the aqueous phase without restriction nor constrain. It has no incompatibilities of common knowledge.

The suggested use level is around 0.1%.

Existing studies

(Available upon request)

Cellular Signaling and Free-Radical Modulating Activities of the Novel Peptidomimetic L-Glutamyl-Histamine. M.A. Babizhayev, Yu A. Semiletov, Yu. A. Lul'kin, N.L. Sakina, E.L. Savel'yeva, A.I. Deyev, L.I. Alimbarova, I.F. Barinskii, J.-F. Nicolaÿ, Ch. Paillet, G. Langrand, and F. Seguin.
Biochemistry Vol.64, No.5, 1999, pp 510-522.

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Technical document

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IMUDILIN®, a new "cytokine-like" active ingredient for the stimulation of the natural defense of the skin.

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Toxicity - Tolerances

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