Matrikine technology and barrier repair: the Ultimate in anti-age skin care?

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INTRODUCTION

Among all the demands the consumer makes to cosmetic products for skin care activity, a truly efficacious wrinkle treatment is still the most important benefit hoped for, ahead of simple moisturisation, elusive cellulite reduction and short term skin firming. The non negligible success of 'Botox®' treatment is proof of this fact. However, not all consumers are ready to undergo the procedure, to afford the cost at regular intervals and to affront the risk, however well it may be circumscribed.

Skin care from a jar is still preferable to most ladies, and as the population ages (or better, as the percentage of aged population increases), the demands for wrinkle reducing activity from cosmetic formulation gets stronger. Certainly, progress has been made over the years, from AHA's in the early 90's, to Retinol derivatives in the second half of the decade, for which measurable wrinkle reducing activity has been shown. The following generation of anti-wrinkle products, based on lipo-peptide technology [1], although introduced in 1992, took some years to find acceptance and widespread use; from 2000 onwards, however, the newly baptised "Matrikine concept" [2] gained followers and rapidly became a reference in wrinkle treatment around the world [3, 4]. The drawbacks of instability and irritation, often associated with previous wrinkle treatments, do not exist with this approach.

THE CONCEPT OF MATRIKINES

What is the secret behind the "soft" concept of Matrikines, how does it work and what can be done to improve it even further?

Horace in his Odes (vol. III) said it all when he spoke of the 'injuries of time'. Wrinkles and dry skin and all their consequences are the 'wounds' that time inflicts on our skin; the sun and the environment only accelerate the process. So wound healing became the focus of tissue research, and the skin is a wonderful model to study wound healing.

Nature is economical and we can always learn from her. During the wound healing process (the complexities of which are such that we cannot go into details here) macromolecules like collagen, elastin, glucosaminoglucanes, are broken down into smaller fragments by specific hydrolytic enzymes: collagenases (of the MMP type and others), elastases, hyaluronidases. The break-up of collagen or elastin is not random, however, as would occur in purely chemical (acid) hydrolysis; oligopeptide fragments of defined amino acid sequence are released, some of which have biological signalling activity, i.e. they play the role of 'local hormones' or paracrine secretion. Some specific fragments stimulate collagen neosynthesis in the nearby fibroblasts in order to speed the tissue repair process, others help attract fibroblasts to the site of the wound (chemotaxis), others again participate in interconnection and binding of macromolecules to their specific sites of attachment, all the while keeping the breakdown enzymes at bay [5]. Thus, the debris pieces, generated as a consequence of the traumatic event, are employed by nature to help in repairing the damage.

Peptides of this type are thus called Matrikines. The name derives from the well known concept of cytokines, trigger molecules (=kinins) within or without the cell (=cyte), but specifically destined to restore the Matrix of the broken tissue. These peptides are usually small, containing between 3 and 8 amino acids, seldom more, or less. They could not be used as such for cosmetic purposes, but the discovery that attaching a lipophilic fatty acid chain to these molecules lent them the bioavailability and ease of penetration [1] which they needed to be active in living human skin, all of a sudden opened the field of cosmetic skin treatment to peptide - and specifically to Matrikine technology [6]. Palmitoylated tri-, tetra-, penta- and hexapeptides, derived from collagen, immunoglobulin, laminin and elastin sequences as well as other sources, made headlines [7] as they showed wrinkle reduction in numerous human clinical trials, benchmarked against retinol, vitamin C, or neutral vehicles. Inevitably, many cosmetic brands formulated these first Matrikines in complex compositions, logically combining various actives together with the basic active wrinkle reducing agent for further, additive or, more difficult to prove, synergistic, effects. 1)

PROOF OF TRUE WRINKLE REPAIR

One such skin repair boosting effect was however discovered in a different context. In retrospect the logic appears sound, the observed results are coherent with what is known about some aspects of skin physiology.

It started with the observation that in frequent cases, the application of a foundation (pigmented) cream has an unintended side effect: the unevenness of the skin surface (fine lines, wrinkles) appear to be worse rather than better after the application of the foundation, especially around the eyes (cf. pictures 1 and 2). Although this is not true for all foundations, the purpose of which, after all, is to smooth the surface and to physically 'fill' the lines, it is nevertheless an often recognised phenomenon. Furthermore, foundations have a tendency to dry out the skin, to augment trans-epidermal water loss (TEWL), probably due to the large surface of the pigment particles. Would it be possible to counteract these effects in a skin care foundation?

Fig. 1: subject R, day 1, without foundation

Fig. 2: same subject, same day, with foundation (5 minutes later)

We expected we would need to combine a powerful skin repair agent, a Matrikine of a new nature with a moisture preserving concept. Simple humectants would not help, as their moisture mostly stays at the surface and might interfere with the foundation, or dry out too quickly. We turned to the well known, although meanwhile somewhat overshadowed technology of ceramides, as their barrier repair activity had been described in numerous papers [8, 9]. We formulated a base that contains high amounts of synthetic, skin identical ceramide 2, the skin's most abundant ceramide, and of a synthetic fragment of elastin, palmitoylated for the purpose, called Pal-Val-Gly-Val-Ala-Pro-Gly. This peptide represents the most frequently encountered repeat sequence of elastin, coils up in a helix type conformation and is responsible for the elasticity of youthful skin. Yet, as a fragment, it plays the role of a special type of Matrikine: it is chemotactic and has the, almost magic, property of attracting fibroblast cells towards itself, like pheromones attract insects to each other. This of course is highly useful in tissue repair and healing, making sure that more "construction units", churning out the needed macromolecules, are present at the repair site. DNA array experiments have then shown that this peptide, next to its wound healing activities in general is likely to stimulate cell proliferation, thus increasing the fibroblast concentration in the skin. (table I: activated genes). Preliminary clinical trials on the Pal-VGVAPG peptide had shown that increased skin firmness resulted from topical application over one month.

TABLE I

CHANGE IN GENE EXPRESSION IN PRESENCE OF PAL-VGVAPG	% / BASELINE
Granulocyte chemotactic protein GCP2	227%
Ephrin receptor	179%
Plasminogen inhibitor protein	166%
EGF response factor(ERF1)	154%
Calmodulin	150%

CLINICAL RESULTS:

Thus a clinical study on 25 volunteers, aged 42 to 66, was set up. Although classical end points such as wrinkle depth, wrinkle volume, wrinkle density and the like, were used to measure the expected effect in quantitative terms, the real test would be the effect of the foundation. Only photographic pictures would give us this answer. It was thus necessary to take pictures of each volunteer on day 1 of the test, before she put on the foundation; then, under identical conditions of light, angle, head positioning and exposure, we took a second picture (see above, 1 and 2). In many cases indeed, an aggravating effect of the foundation could be observed by the trained eye. Of course, no instrumental method, not even contact-less fringe projection which measures true surface changes, would detect this, as it is essentially an optical effect, but badly perceived nevertheless by consumers.

The panellists then were given 4 preparations, containing the ceramide 2 and Pal-VGVAPG base at 2% in a fluid foundation; the four creams differed only in the type and amount of pigment they

contained so as to give the ladies some choices in the color, depending on the occasion; the fourth cream actually contained no pigment at all, to be used for instance, on weekends or such days. It imported however that the ladies did use this skin care formula (cf. table II) daily, and NOT use any other skin care product on the face, not even before application of the foundation, for all of the two months.

The results after two months of application of these foundations are astounding. Pictures 3 and 4 show the same lady, now without (3) and with (4) foundation, and the "aggravating" effect has disappeared: why? Because the wrinkles have decreased so much that there is less to "aggravate". And she is not alone. Pictures 5 to 8 are a further selection of the observed anti-wrinkle effect of this powerful combination of Matrikine and barrier repair concept.

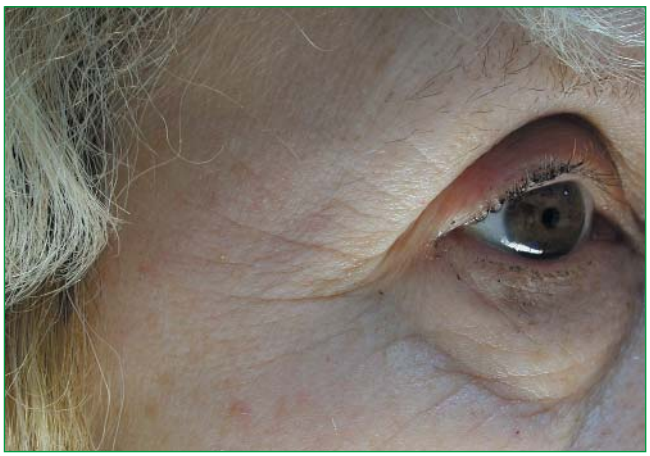

Fig 3: subject R, Day 56, w/o foundation

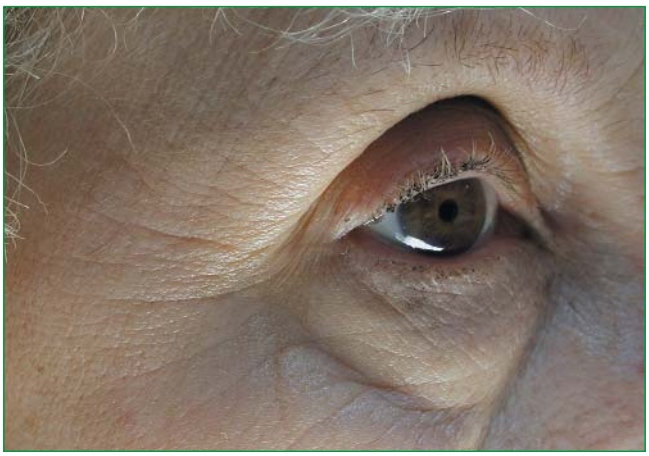

Fig. 4: with foundation

Fig. 5: subject N, Day 1, with foundation

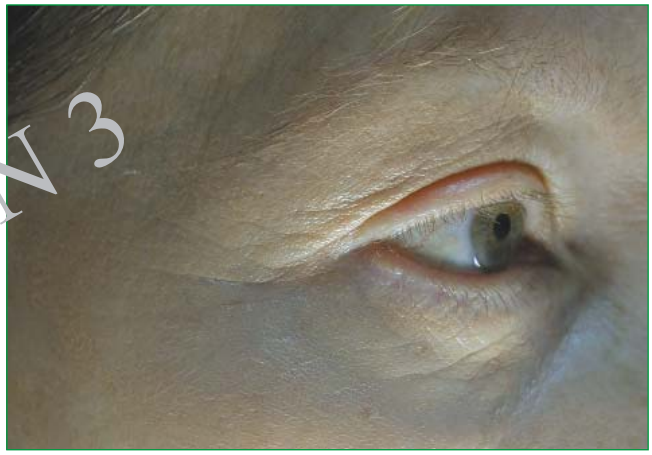

Fig. 6: subject N, Day 56, with foundation

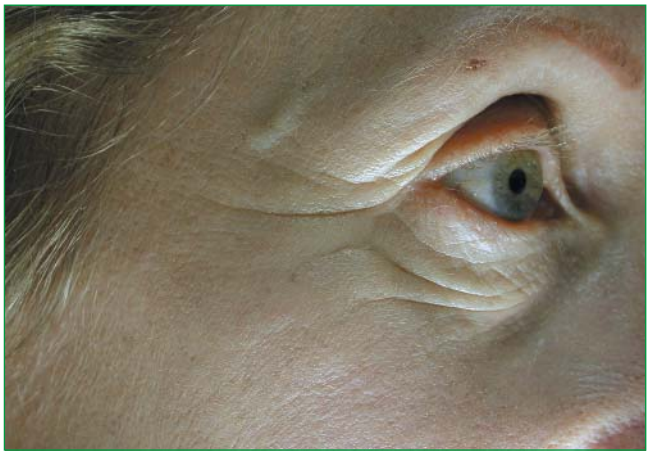

Fig. 7: subject L, Day 1, with foundation

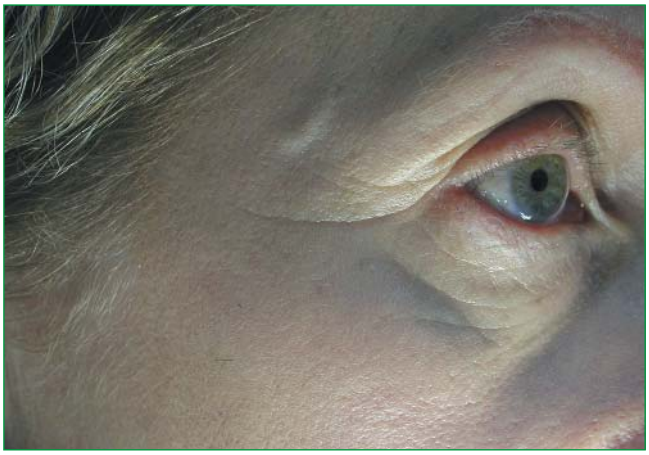

Fig. 8: subject L, Day 56, with foundation

TABLE II: FOUNDATION FORMULA EMPLOYED IN THE TEST:

RAW MATERIALS	INCI	SUPPLIER	%
Phase 1			
Demineralized water	Water (Aqua)		q.s. 100
KOH (10% aq.)	Potassium Hydroxide		1.30
Crillet 4	Polysorbate 80	Croda	0.10
Phase 2			
Propylene glycol	Propylene Glycol		4.00
Veegum R	Magnesium Aluminum Silicate	Vanderbilt	1.00
Phase 3			
Cromollient DP3-A	Di-PPG-3 Myristyl Ether Adipate	Croda	12.00
Crodamol ISNP	Isostearyl Neopentanoate	Croda	4.00
Crodafos CS 20 acid	Cetearyl Alcohol (and) ceteth-20 Phosphate (and) Dicetyl Phosphate	Croda	4.00
Volpo S10	Steareth-10	Croda	2.00
Crodacol C-70	Cetyl Alcohol	Croda	0.62
Volpo S-2	Steareth-20	Croda	0.50
DERMAXYL™	-	Sederma	2.00
Phase 4			
Preservatives			q.s

CONCLUSION:

Is this the end of wrinkle research? Certainly not. There is always room for improvement, although there are limits to the speed with which older skin can recover and restore its appearance. Too powerful ingredients of novel nature, or used at too high concentrations, might have undesirable opposite effects, a reaction by the organism, irritation, inflammation, and the like. True tissue repair does need time to be safe, well tolerated, well organised on a biochemical/biological scale, and thus effective.

It is of course entirely easy and self evident to imagine further combinations of the Matrikine technology described here and elsewhere with all the other hundreds of active skin care ingredients listed in the CTFA catalogue or promoted in scientific papers, cosmetic trade journals or company literature 1). Although synergistic effects cannot be excluded, most likely these combinations will lead to additive results, thus boosting the anti-wrinkle effect or improving skin condition by treating complementary skin deficiencies (i.e. dryness + wrinkles, oil secretion + wrinkles and thinning, age spots and flaccid skin etc.) with appropriate, more or less classical combinations of actives.

But then, maybe entirely new classes of substances are just around the corner, waiting to be discovered to advance once more on the path to 'eternal youth'?

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1) As usual, combinations of the Pal-VGVAPG peptide alone or together with the ceramide with all types of "anti-age" actives, especially with AHAs and BHAs, polyphenols, all vitamins (A, C, E) and their derivatives, isoflavones and flavonoids of all sorts, anti-inflammatory agents such as bisabolol, farnesol, phytantriol, as well as combinations with other Matrikines and active peptides, oligosaccharides, mono-, oligo- or polynucleotides, with antioxidants, enzymes and sun filters, among other actives, can be realised by formulators skilled in the art of cosmetic creation.

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