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Original Article

Dual Core: A Mechanical, Biological, and Metabolic Model for Physiological Bio-regeneration with PEG-Crosslinked Hyaluronic Acid Fillers

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ABSTRACT

This proof-of-concept article introduces the “Dual Core Concept”, a novel facial rejuvenation model integrating complementary mechanical, biological, and metabolic processes within a single synergistic framework. The concept focuses on Neauvia Stimulate, a PEG-crosslinked hyaluronic acid (PEG-HA) filler enriched with calcium hydroxyapatite (CaHA), which intrinsically embodies two “cores”: the mechanical core providing immediate structural lift and the biological core inducing progressive dermal regeneration. To reinforce deep anatomical support, Neauvia Intense may be used concomitantly as a structural scaffold, optimizing the environment for superficial and mid-fat layer regeneration. Drawing on histological, clinical, and biochemical evidence, this model illustrates the evolution of aesthetic medicine from volumetric correction toward physiological bio-regeneration, emphasizing precise anatomical targeting and the “less-is-more” principle of natural tissue restoration. This integrative approach represents a paradigm shift from static correction to functional, multi-layered rejuvenation aligned with the physiology of facial tissues.

INTRODUCTION

Facial aging is now recognized not only as structural atrophy but as a progressive imbalance involving mechanical, cellular, and metabolic pathways. Recent understanding of skin aging emphasizes the role of mechanobiology, where cellular activity is governed by physical and biochemical cues within the extracellular matrix. Classical fillers corrected contours but did not restore the biological integrity of the skin.

PEG-crosslinked hyaluronic acid (PEG-HA) represents a new class of injectable biomaterials combining mechanical stability, biocompatibility, and immunomodulatory behaviour (1–3). Their unique chemistry enables integrated approaches such as Dual Core Protocol, which harmonize tissue support and regeneration through anatomical precision and controlled, physiological stimulation.

Concept Overview — The “Dual Core” Model

The Dual Core Model represents a novel framework for facial rejuvenation in which two synergistic biological mechanisms: mechanical support and biological stimulation – coexist within a single product – Neauvia Stimulate. This formulation, composed of polyethylene glycol–crosslinked hyaluronic acid (PEG-HA) enriched with calcium hydroxyapatite (CaHA) microspheres, simultaneously provides immediate structural reinforcement and long-term regenerative activation.

The PEG-HA matrix functions as Cuore che sostiene (“the heart that supports”), creating a cohesive, viscoelastic scaffold that restores contour, maintains localized tension, and provides instant volumetric lift. Embedded within this matrix, CaHA microparticles act as Cuore che stimola (“the heart that stimulates”), initiating a cascade of fibroblast activation, angiogenesis, and collagen remodeling that progressively enhances dermal density and elasticity. This intrinsic duality, mechanical and biological, embodies the essence of physiological bio-regeneration, in which immediate architectural support is seamlessly integrated with controlled tissue renewal. The interaction between the two cores within Stimulate ensures synchronized remodeling across both structural and cellular levels, promoting a stable and natural outcome consistent with the “less-is-more” philosophy.

To enhance the deep anatomical framework, Neauvia Intense can be used in combination with Stimulate. Its high elasticity and projection capacity strengthen deep support planes and improve lifting vectors, creating an ideal base for Stimulate’s regenerative activity. While Intense reinforces the deep structure, Stimulate remains the core therapeutic element that delivers both support and stimulation – the true manifestation of the Dual Core principle within a single product.

The Technique: Two Complementary Layers (“Cores”):

1. Cuore che stimola and Cuore che sostiene — Neauvia Stimulate

Superficial bio-regenerative and mechanical activation using PEG-crosslinked hyaluronic acid enriched with 1 % calcium hydroxyapatite (CaHA) microparticles (Neauvia Stimulate, Matex Lab, Geneva, Switzerland).

- **Plane**: superficial subdermal or mid-fat layer
- **Zones**: areas overlying the deep medial and lateral cheek fat pads (DMCFP/DLCFP), the pre-tarsal and pre-auricular regions
- **Purpose**: to restore dermal tension and elasticity by combining immediate mechanical support (Cuore che sostiene) with progressive fibroblast and angiogenic stimulation (Cuore che stimola). The resulting cohesive micro-depots provide gentle volumization and improve superficial structural integrity, enhancing facial contours without excessive filling.
- **Typical dose**: 0.1–0.2 mL per line or micro-depot (22G cannula, linear-retrograde technique).

2. Deep Structural Scaffold — Neauvia Intense

Deep volumetric reinforcement using a PEG-HA filler of high elasticity and projection capacity (Neauvia Intense, Matex Lab, Geneva, Switzerland).

- **Plane**: deep supraperiosteal or sub-SMAS
- **Zones**: deep medial and lateral cheek fat pads (DMCFP/DLCFP) (Fig. 1)
- **Purpose**: to re-establish deep facial support and optimize lifting vectors, creating a stable foundation for the regenerative activity of Stimulate.
- **Typical dose**: 0.2–0.3 mL per depot (2–3 depots per side, 22G cannula).

Together, these two layers create a coordinated dual-phase effect: immediate mechanical support combined with gradual biological regeneration, forming the basis of physiological tissue restoration (Fig. 2, Fig. 3).

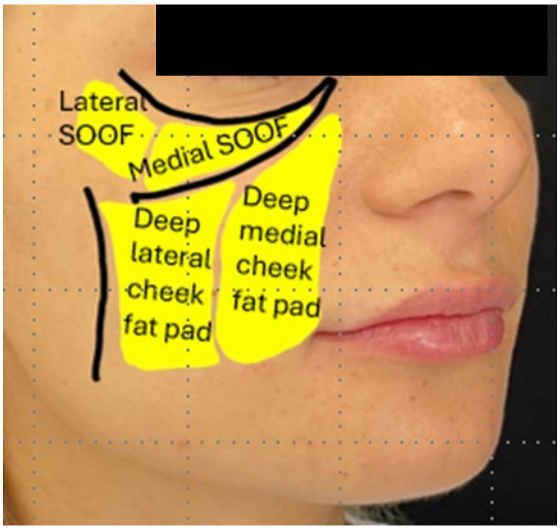

Fig. 1. *Treatment zones: deep medial and lateral cheek fat pads (DMCFP and DLCFP).*

BEFORE AFTER

Fig. 2. *Clinical photographs taken before and immediately after the Dual Core Protocol procedure.*

Fig. 3. *Clinical photographs taken before and immediately after the Dual Core Protocol procedure.*

Rationale

1. Mechanical and Biological Integration

Neauvia Stimulate exhibits a dual-phase mechanism of action, combining immediate mechanical reinforcement with long-term biological regeneration. This integrated behavior defines the essence of the Dual Core Model, representing a continuous transition from volumization to physiological tissue remodeling.

Upon injection, the PEG-crosslinked hyaluronic acid (PEG-HA) matrix provides an immediate lifting and contouring effect. Its optimized rheological balance between cohesivity and adhesivity enables the formation of stable micro-depots that integrate with the surrounding extracellular matrix, maintaining localized tension within the treated area. This mechanical anchoring contributes to instant skin repositioning and prevents relapse into pre-treatment laxity.

Simultaneously, low-concentration calcium hydroxyapatite (CaHA) microspheres remain evenly dispersed within the PEG-HA scaffold, creating a homogeneous three-dimensional bio-matrix characterized by stable viscoelastic properties and minimal inflammatory reactivity (4, 5). The controlled micro-strain applied to dermal fibroblasts triggers mechano-transduction cascades that upregulate collagen types I and III synthesis and stimulate neovascularization (6–9). This process results in gradual extracellular matrix (ECM) redensification and reinforcement of dermal architecture without fibrotic encapsulation or nodularity.

The synergistic interplay between the mechanical and biological cores within Stimulate defines its unique regenerative capacity where immediate structural stabilization of the superficial and mid-dermal layers is seamlessly followed by physiological regeneration. Clinically, this leads to improved midface projection, restoration of natural tension lines, and visible correction of superficial volume loss. To optimize treatment outcomes, Neauvia Intense may be used concomitantly as a deep structural support, reinforcing the facial framework and enhancing the lifting vectors that facilitate the regenerative activity of Stimulate. This layered approach ensures full 3-dimensional harmony between deep mechanical stability and superficial biological renewal.

2. Immunomodulation and Safety

In vitro and clinical evidence consistently demonstrates that PEG-HA fillers have been shown to reduce macrophage recruitment, CD4+/CD8+ lymphocytic infiltration, and the expression of pro-inflammatory cytokines such as TNF-α and IL-8 (3, 7-9). These findings indicate that PEG crosslinking minimizes immune cell activation and reactive oxygen species formation under both resting and stimulated conditions, thereby lowering the risk of immune-mediated adverse reactions, including granuloma formation or cellulitis, while promoting a more anti-inflammatory immune phenotype (3, 7-9).

Histological and in vivo studies further confirm this effect, showing diminished antigen presentation and lower counts of CD4+, CD8+, and B cells, as well as macrophages in the surrounding tissue. Importantly, stable antibody levels have been observed even in autoimmune patients, supporting the notion that PEG-HA combined with low-concentration CaHA acts as an immunomodulatory and well-tolerated system (3, 7-9). Long-term clinical experience reinforces these data, with no reports of granulomas, foreign body reactions, or related complications over more than three years of follow-up (9). Altogether, these findings establish PEG-HA as a physiologically compatible, immunologically stable, and clinically safe filler platform suitable for long-term regenerative applications.

3. Metabolic Dimension — The "Third Core"

Beyond fibroblast activation, emerging data indicate that both hyaluronic acid (HA) and calcium hydroxyapatite (CaHA) may influence adipocyte metabolism and dermal–subdermal communication. Turkevych (2022) highlighted the potential influence of CaHA on the structure and physiology of subcutaneous white adipose tissue (sWAT), suggesting a mechanical and metabolic interaction between adipocytes and dermal fibroblasts (10). He proposed that low-concentration CaHA (1–3%) could modulate the formation and secretion of exosomes from surrounding cells, mediating long-range biochemical signalling and contributing to the prolonged improvement of skin quality observed clinically. This hypothesis implies that the benefits of CaHA extend beyond neocollagenesis, involving metabolic crosstalk between dermal and adipose compartments.

Building upon this concept, it can be hypothesized that CaHA and HA fillers may also affect adipocyte-related regulatory pathways such as leptin receptor, PPAR-γ, or lipoprotein lipase (LPL), which govern lipid turnover, cellular energy balance, and local tissue homeostasis. By modulating these pathways, injectable biomaterials could normalize the dynamic equilibrium between dermal fibroblasts and subdermal adipocytes, enhancing extracellular matrix turnover and stabilizing long-term tissue tone and elasticity.

Recent clinical and histological evidence further supports this metabolic dimension. Kubik et al. (2024) demonstrated that treatment with PEG-HA + 1% CaHA (Neauvia Stimulate) led to a 27.3% increase in collagen fluorescence intensity after 21 days ($p = 0.0313$), together with a visible reduction in CD4+/CD8+ inflammatory infiltration and normalization of tissue architecture (3). These findings suggest a coordinated process of immuno-metabolic remodelling, where improved collagen organization parallels a more quiescent, energy-balanced microenvironment. This integrative model positions adipocytes not merely as passive fat-storage cells but as active modulators of skin physiology through their interaction with fibroblasts, endothelial cells, and immune mediators. Modifying this dermal–adipose signalling loop through bio-compatible fillers such as PEG-HA + CaHA may thus open new perspectives for metabolic rejuvenation and long-term tissue homeostasis.

Altogether, the "third core" extends the Dual Core Protocol paradigm from mechanical and biological repair toward a broader, metabolic regulation of skin vitality representing a potential new frontier in regenerative aesthetics. In this framework, the metabolic core acts as a silent regulator, maintaining the bioenergetic balance required for sustained dermal regeneration.

Preliminary Observation (Proof of Concept)

The Dual Core Model was applied as an anatomically guided midface rejuvenation concept using Neauvia Stimulate and with Neauvia Intense employed to reinforce the deep structural scaffold. Immediate outcomes included visible midface elevation and contour enhancement, followed by progressive improvement in skin texture, density, and elasticity observed within 4–6 weeks. No adverse effects, palpable nodules, or irregularities were reported during follow-up.

Future evaluations will include quantitative assessment of dermal remodeling using high-frequency ultrasound (HF-USG) and 3D photometric imaging to objectively document volumetric and structural changes over time.

The Dual Core mechanism reflects the shift from "simple" correction toward functional and physiological regeneration, integrating three complementary layers of biological activity:

- The mechanical core – provides immediate lift and structural support through PEG-crosslinked HA micro-depots.
- The biological core – activates fibroblasts, stimulates angiogenesis, and promotes controlled collagen remodeling for long-term dermal renewal.
- The metabolic core – modulates adipocyte–fibroblast communication and extracellular matrix homeostasis, stabilizing tissue architecture and local metabolic signaling.

Together, these synergistic processes embody the concept of physiological bio-regeneration, the controlled activation of endogenous fibroblastic, vascular, immune, and metabolic pathways that promote durable tissue renewal (3, 6, 9).

Clinically, this integrated model achieves measurable rejuvenation with reduced product volumes, effectively translating the "less is more" principle into a structured, anatomy-driven protocol that bridges precision correction and true tissue regeneration.

CONCLUSIONS AND FUTURE PERSPECTIVES

The Dual Core Model, centred on Neauvia Stimulate and supported by Neauvia Intense, represents a new-generation approach to facial rejuvenation, integrating mechanical support, biological activation, and metabolic modulation within a cohesive, layered bio-regenerative framework.

It embodies the principle of "from restoring shape to restoring biology", shifting the focus from aesthetic correction toward functional, physiological tissue regeneration.

The success of this model relies on profound anatomical understanding, enabling precise placement of the material within functional fat compartments and retaining ligaments while ensuring complete vascular safety. A key element of clinical practice remains adherence to the code *MAT* principle:

M – Material (awareness of the properties and behavior of the implant)

A – Anatomy (knowledge of the structures in the treated area)

T – Technique (selection of the appropriate injection method according to tissue characteristics).

In clinical application, Neauvia Intense serves as the deep mechanical scaffold, providing elasticity, projection, and vectoral lift within deep and sub-SMAS planes.

This foundation optimizes the anatomical environment for the biological and metabolic regenerative effects of Neauvia Stimulate, which acts in the superficial and mid-dermal layers as a true Dual Core system, combining immediate structural reinforcement with long-term physiological renewal. The synergy between these two fillers one mechanical, one bioactive allows restoration of 3D facial harmony with reduced product volumes and enhanced precision. Emerging evidence also highlights the involvement of immunological regulation and vascular homeostasis in bioregenerative processes, reinforcing the importance of combining mechanical, biological, and metabolic actions within a single therapeutic ecosystem. Ultimately, the Dual Core Model moves aesthetic medicine beyond visual correction, toward the restoration of biological harmony and skin function. Future research, including high-frequency ultrasound (HF-USG) imaging, histological evaluation, and molecular biomarker analysis should further validate and quantify this mechanical–biological–metabolic synergy and its long-term influence on skin health and regenerative dynamics.

This integrated concept opens the way for more predictable, evidence-based, and personalized regenerative protocols, merging anatomical precision with a deep understanding of tissue physiology.

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