Topical Human Growth Factors & Cytokines in Anti-Aging, Skin Rejuvenation and Procedure Recovery

George Taylor, MD
Chief Medical Officer
Cellese Regenerative Therapeutics

Human growth factors & cytokines are now mainstream

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The Skin Health and Beauty Pyramid: A Clinically Based Guide to Selecting Topical Skincare Products

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[a]Mayoral Dermatology, Coral Gables, FL
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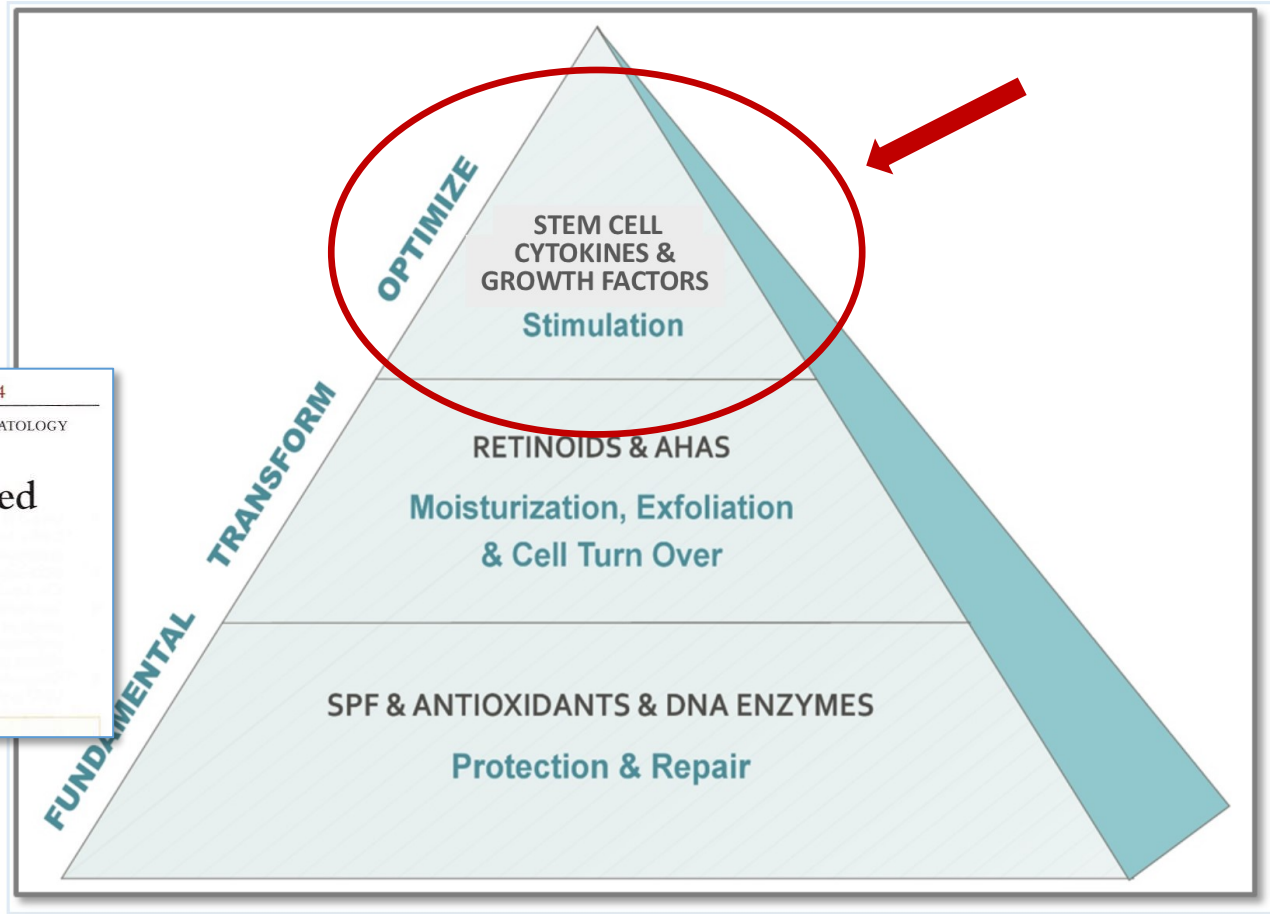
ABSTRACT



Recommended to optimize and stimulate skin health

Stem cells are bio-signal factories.

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The Skin Health and Beauty Pyramid: A Clinically Based Guide to Selecting Topical Skincare Products

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ABSTRACT

"There is a lot of discussion in the marketplace about **stem cells because these are factories for production of cell signaling peptides and growth factors** so they are often cultured in the lab to obtain the "broth" they live in that is rich in peptides and growth factors."

Bio-signals = { Cytokines, Growth Factors, Signaling Peptides

Early evidence of bio-signal efficacy

ENHANCEMENT OF WOUND HEALING BY TOPICAL TREATMENT WITH EPIDERMAL GROWTH FACTOR

GREGORY L. BROWN, M.D., LILLIAN B. NANNEY, PH.D., JOSEPH GRIFFEN, M.D., ANNE B. CRAMER, M.D., JOHN M. YANCEY, PH.D., LUKE J. CURTSINGER III, M.D., LARRY HOLTZIN, M.D., GREGORY S. SCHULTZ, PH.D., MAURICE J. JURKIEWICZ, M.D., AND JOHN B. LYNCH, M.D.

Abstract Experimental studies in animals have demonstrated that the topical application of epidermal growth factor accelerates the rate of epidermal regeneration of partial-thickness wounds and second-degree burns. We conducted a prospective, randomized, double-blind clinical trial using skin-graft–donor sites to determine whether epidermal growth factor would accelerate the rate of epidermal regeneration in humans. Paired donor sites were created in 12 patients who required skin grafting for either burns or reconstructive surgery. One donor site from each patient was treated topically with silver sulfadiazine cream, and one was treated with silver sulfadiazine cream containing epidermal growth factor (10 μg per milliliter). The donor sites were photographed daily, and healing was measured with the use of planimetric analysis.

The donor sites treated with silver sulfadiazine containing epidermal growth factor had an accelerated rate of epidermal regeneration in all 12 patients as compared with that in the paired donor sites treated with silver sulfadiazine alone. Treatment with epidermal growth factor significantly decreased the average length of time to 25 percent and 50 percent healing by approximately one day and that to 75 percent and 100 percent healing by approximately 1.5 days ($P<0.02$). Histologic evaluation of punch-biopsy specimens taken from the centers of donor sites three days after the onset of healing supported these results.

We conclude that epidermal growth factor accelerates the rate of healing of partial-thickness skin wounds. Further studies are required to determine the clinical importance of this finding. (N Engl J Med 1989; 321:76-9.)

EPIDERMAL regeneration is a complex process in which residual epithelial cells proliferate in an integrated manner to regenerate intact epidermis. Superficial wounds that do not result in total skin loss but that retain a portion of the dermis heal primarily by epidermal regeneration. The ability to stimulate this process could be of clinical benefit.

The molecular mechanisms that regulate normal epidermal regeneration are not fully understood, but it is probable that peptide growth factors acting through autocrine or paracrine mechanisms play an important part.[1,2] Many peptide growth factors are known to exist; one of the most widely studied is epidermal growth factor. Epidermal growth factor is a 53-amino-acid polypeptide that stimulates messenger RNA, DNA, and protein synthesis in many cell types.[3,4] In addition, it has been shown to stimulate keratinocyte division in vitro and epidermal regeneration in vivo.[5,6] Studies of partial-thickness burns and skin-graft–donor sites in animals demonstrated that treatment with epidermal growth factor significantly accelerated the rate of epidermal regeneration.[6] Epidermal growth factor also has been shown to have an effect on mesenchymal cells by producing marked proliferation of the dermis in partial-thickness wounds and increasing the tensile strength of surgical incisions.[6,7] On the basis of these studies, we conducted a prospective, randomized, double-blind clinical trial to evaluate the effect of topical therapy with epidermal growth factor on the rate of healing of skin-graft–donor sites.

From the Departments of Surgery and Biochemistry, Emory University, Atlanta (G.L.B., A.B.C., L.H., M.J.J.); Vanderbilt University, Nashville (L.B.N., J.G., J.B.L.); and the University of Louisville, Louisville, Ky. (J.M.Y., L.J.C., G.S.S.). Address reprint requests to Dr. Brown at the Department of Surgery, University of Louisville, Louisville, KY 40292.

Presented in part in abstract form at the UCLA Symposia on Molecular and Cellular Biology, Keystone, Colo., January 21, 1988, and the Plastic Surgery Research Council, San Francisco, May 20, 1988.

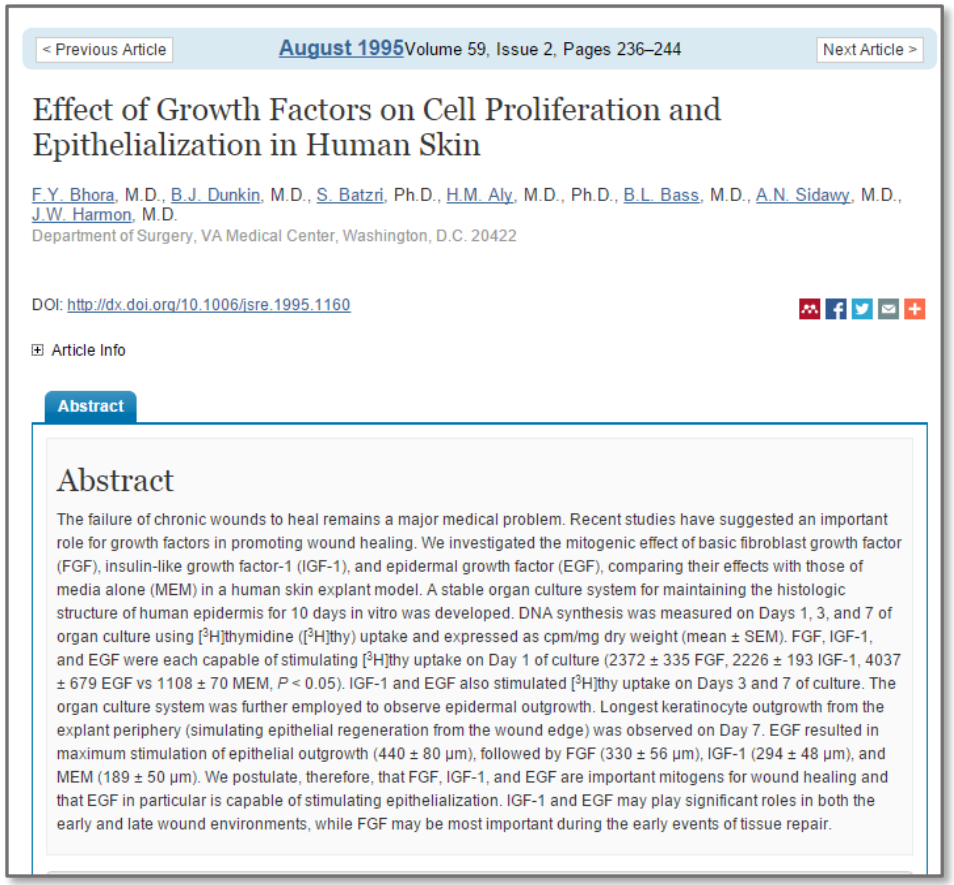
Supported in part by a contract (DMAD17-85-C-5197) from the U.S. Army Medical Research and Development Command Activity.

METHODS

Twelve patients (11 men and 1 woman) who required skin grafting for various reasons were studied at Emory and Vanderbilt universities. The patients ranged in age from 18 to 75 years (mean, 46)

New England Journal of Medicine

July 13, 1989



< Previous Article August 1995 Volume 59, Issue 2, Pages 236–244 Next Article >

Effect of Growth Factors on Cell Proliferation and Epithelialization in Human Skin

F.Y. Bhora, M.D., B.J. Dunkin, M.D., S. Batzri, Ph.D., H.M. Aly, M.D., Ph.D., B.L. Bass, M.D., A.N. Sidawy, M.D., J.W. Harmon, M.D.
Department of Surgery, VA Medical Center, Washington, D.C. 20422

DOI: http://dx.doi.org/10.1006/jsre.1995.1160

Article Info

Abstract

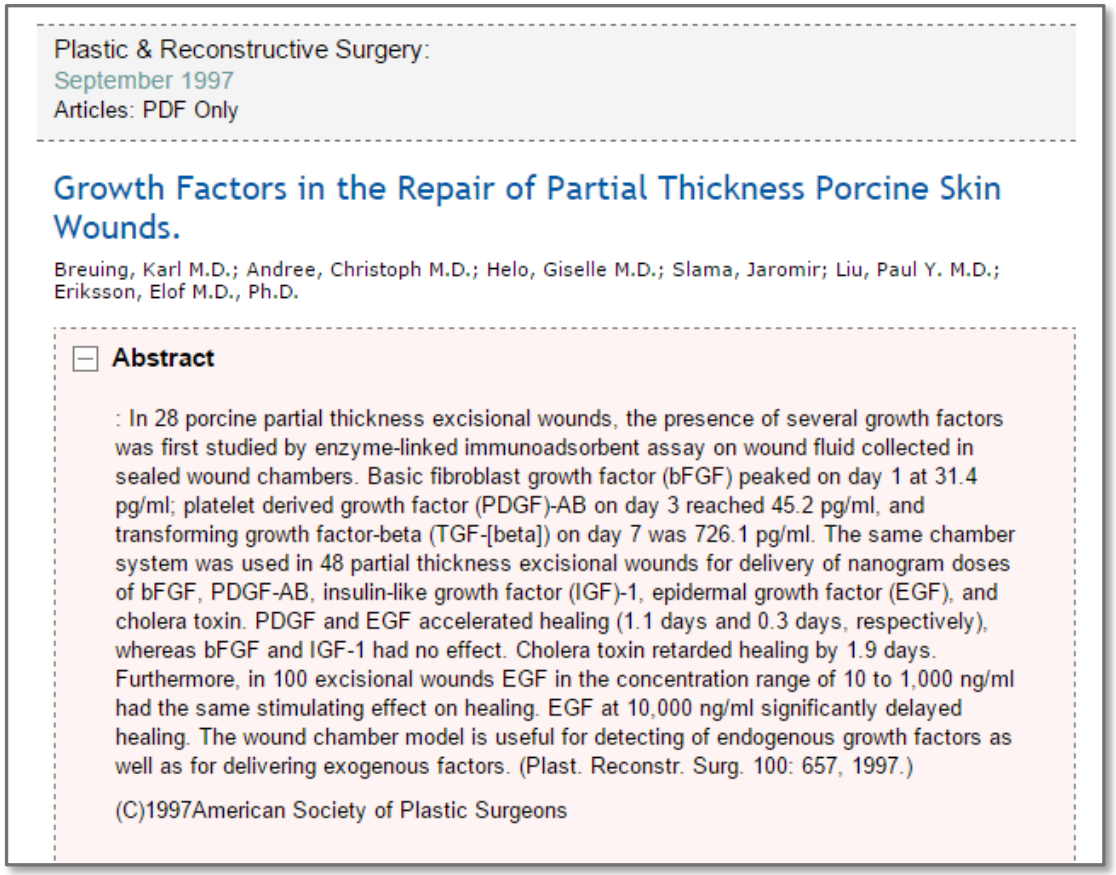
Abstract

The failure of chronic wounds to heal remains a major medical problem. Recent studies have suggested an important role for growth factors in promoting wound healing. We investigated the mitogenic effect of basic fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), and epidermal growth factor (EGF), comparing their effects with those of media alone (MEM) in a human skin explant model. A stable organ culture system for maintaining the histologic structure of human epidermis for 10 days in vitro was developed. DNA synthesis was measured on Days 1, 3, and 7 of organ culture using [^{3}H]thymidine ([^{3}H]thy) uptake and expressed as cpm/mg dry weight (mean ± SEM). FGF, IGF-1, and EGF were each capable of stimulating [^{3}H]thy uptake on Day 1 of culture (2372 ± 335 FGF, 2226 ± 193 IGF-1, 4037 ± 679 EGF vs 1108 ± 70 MEM, $P < 0.05$). IGF-1 and EGF also stimulated [^{3}H]thy uptake on Days 3 and 7 of culture. The organ culture system was further employed to observe epidermal outgrowth. Longest keratinocyte outgrowth from the explant periphery (simulating epithelial regeneration from the wound edge) was observed on Day 7. EGF resulted in maximum stimulation of epithelial outgrowth (440 ± 80 μm), followed by FGF (330 ± 56 μm), IGF-1 (294 ± 48 μm), and MEM (189 ± 50 μm). We postulate, therefore, that FGF, IGF-1, and EGF are important mitogens for wound healing and that EGF in particular is capable of stimulating epithelialization. IGF-1 and EGF may play significant roles in both the early and late wound environments, while FGF may be most important during the early events of tissue repair.

Journal of Surgical Research

August 1995

Early evidence of bio-signal efficacy



Plastic & Reconstructive Surgery:
September 1997
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Growth Factors in the Repair of Partial Thickness Porcine Skin Wounds.

Breuing, Karl M.D.; Andree, Christoph M.D.; Helo, Giselle M.D.; Slama, Jaromir; Liu, Paul Y. M.D.; Eriksson, Elof M.D., Ph.D.

Abstract

: In 28 porcine partial thickness excisional wounds, the presence of several growth factors was first studied by enzyme-linked immunoadsorbent assay on wound fluid collected in sealed wound chambers. Basic fibroblast growth factor (bFGF) peaked on day 1 at 31.4 pg/ml; platelet derived growth factor (PDGF)-AB on day 3 reached 45.2 pg/ml, and transforming growth factor-beta (TGF-[beta]) on day 7 was 726.1 pg/ml. The same chamber system was used in 48 partial thickness excisional wounds for delivery of nanogram doses of bFGF, PDGF-AB, insulin-like growth factor (IGF)-1, epidermal growth factor (EGF), and cholera toxin. PDGF and EGF accelerated healing (1.1 days and 0.3 days, respectively), whereas bFGF and IGF-1 had no effect. Cholera toxin retarded healing by 1.9 days. Furthermore, in 100 excisional wounds EGF in the concentration range of 10 to 1,000 ng/ml had the same stimulating effect on healing. EGF at 10,000 ng/ml significantly delayed healing. The wound chamber model is useful for detecting of endogenous growth factors as well as for delivering exogenous factors. (Plast. Reconstr. Surg. 100: 657, 1997.)

Plastic & Reconstructive Surgery

September 1997

Original Research

Reversal of photodamage with topical growth factors: a pilot study

Richard E Fitzpatrick & Elizabeth F Rostan

Authors:
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Cosmetic Laser Associates, Scripps – XIMED Medical Center, La Jolla, CA, USA

Received 18 June 2002
Accepted 18 November 2002

BACKGROUND: Interest in the reversal of facial photodamage has increased significantly among patients and physicians in the past decade. Though surgical procedures may be very effective, the associated healing time and potential risks have spurred the development of non-surgical treatments. There has also been an increasing depth of knowledge regarding wound healing and its control by growth factors as well as its modulation by the topical application of growth factors. Bioengineered tissue cultures have resulted in the ability to collect naturally occurring human growth factors in their tissue concentrations.
OBJECTIVE: The objective of this study is to determine if the twice daily application of a combination of multiple growth factors to photodamaged facial skin results in any evidence of improvement after 60 days.
METHODS: Fourteen patients applied a gel containing a mixture of eight different growth factors (Nouricel-MD) to photodamaged facial skin twice daily. Prior to the study and at 60 days there were clinical evaluations of photodamage (Fitzpatrick scale), 3 mm punch biopsies and optical profilometry. Patient questionnaires were answered at 60 days.
RESULTS: Eleven of 14 patients showed clinical improvement in at least one facial area. The peri-orbital region showed a statistically significant improvement ($p=0.0003$). Optical profilometry showed a statistically significant reduction in Ra measurement ($p=0.0075$) and shadowing ($p=0.02$), both indicating a decrease in the depth and number of textural irregularities or fine lines. Biopsies revealed new collagen formation in the Grenz zone (37% increase in thickness) and thickening of the epidermis by 27%. Eight of 14 patients felt their wrinkles were improved, while 12 of 14 felt their skin texture was improved.
CONCLUSIONS: The application of a mixture of topical growth factors may stimulate the repair of facial photodamage resulting in new collagen formation, epidermal thickening and the clinical appearance of smoother skin with less visible wrinkling. *J Cosmetic & Laser Ther* 2003; 5: 25–34

Introduction

Photoaging of the skin occurs in the outer layers of the skin, predominantly the epidermis and the upper 100–200 μm of the papillary dermis. This 'aging' of the skin is caused by ultraviolet (UV) light damage from both the UVA and UVB wavelengths and is a process distinct from chronologic aging.[1,2]

Histologically, this accumulation of UV damage manifests as solar elastosis – an amorphous, blue-staining mass in the papillary dermis which is comprised of abnormal collagen and elastin fibers.[3–12] Below the epidermis is a layer of pink-staining collagen that is always maintained even in severe photodamage. This layer is referred to as the Grenz zone. When new collagen is seen in the repair of photodamage, it first appears here as a thickening of this zone. Clinical manifestations of sun damage – loss of skin elasticity, rhytides, fine skin textural irregularities and papules – correlate with the degree of elastosis present in the dermis.[9,10,13–15]

Correspondence: RE Fitzpatrick, Cosmetic Laser Associates, Scripps – XIMED Medical Center, 9850 Genesee Avenue, Suite 480, La Jolla, CA 92037, USA. Email: aandrews@dermassociates.com

Journal of Cosmetic and Laser Therapy

Vol. 5, Issue 1, 2003

Confirming evidence

Efficacy of Novel Skin Cream Containing Mixture of Human Growth Factors and Cytokines for Skin Rejuvenation

J Drugs Dermatol. 2007 Oct;6(10):1018-23.

Human growth factor and cytokine skin cream for facial skin rejuvenation as assessed by 3D in vivo optical skin imaging.

Gold MH[1], Goldman MP, Biron J.

J Cosmet Laser Ther. 2008 Jun;10(2):104-9. doi: 10.1080/14764170701885392.

Clinical, histologic, and ultrastructural changes after use of human growth factor and cytokine skin cream for the treatment of skin rejuvenation.

J Drugs Dermatol. 2009 May;8(5 Suppl Skin Rejuenation):4-13.

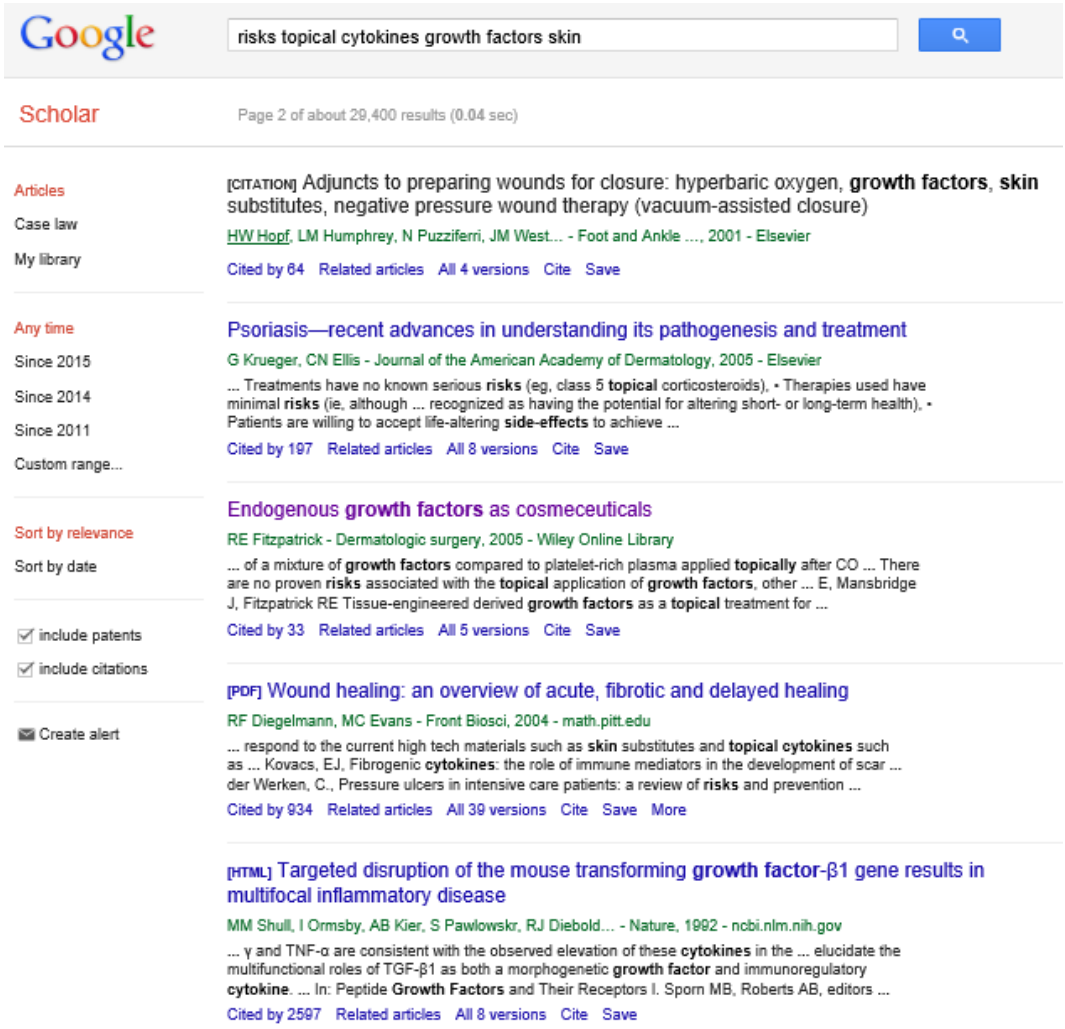
Topically applied physiologically balanced growth factors: a new paradigm of skin rejuvenation.

Sundaram H[1], Mehta RC, Norine JA, Kircik L, Cook-Bolden FE, Atkin DH, Werschler PW, Fitzpatrick RE.

J Clin Aesthet Dermatol. 2010 Dec;3(12):37-42.

Human growth factor cream and hyaluronic Acid serum in conjunction with micro laser peel: an efficient regimen for skin rejuvenation.

Long pristine history of safety



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HW Hopf, LM Humphrey, N Puzziferri, JM West... - Foot and Ankle ..., 2001 - Elsevier

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Psoriasis—recent advances in understanding its pathogenesis and treatment

G Krueger, CN Ellis - Journal of the American Academy of Dermatology, 2005 - Elsevier

... Treatments have no known serious **risks** (eg, class 5 **topical** corticosteroids), • Therapies used have minimal **risks** (ie, although ... recognized as having the potential for altering short- or long-term health), • Patients are willing to accept life-altering **side-effects** to achieve ...

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Endogenous **growth factors** as cosmeceuticals

RE Fitzpatrick - Dermatologic surgery, 2005 - Wiley Online Library

... of a mixture of **growth factors** compared to platelet-rich plasma applied **topically** after CO ... There are no proven **risks** associated with the **topical** application of **growth factors**, other ... E, Mansbridge J, Fitzpatrick RE Tissue-engineered derived **growth factors** as a **topical** treatment for ...

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[PDF] Wound healing: an overview of acute, fibrotic and delayed healing

RF Diegelmann, MC Evans - Front Biosci, 2004 - math.pitt.edu

... respond to the current high tech materials such as **skin** substitutes and **topical cytokines** such as ... Kovacs, EJ, Fibrogenic **cytokines**: the role of immune mediators in the development of scar ... der Werken, C., Pressure ulcers in intensive care patients: a review of **risks** and prevention ...

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[HTML] Targeted disruption of the mouse transforming **growth factor**-β1 gene results in multifocal inflammatory disease

MM Shull, I Ormsby, AB Kier, S Pawlowskr, RJ Diebold... - Nature, 1992 - ncbi.nlm.nih.gov

... γ and TNF-α are consistent with the observed elevation of these **cytokines** in the ... elucidate the multifunctional roles of TGF-β1 as both a morphogenetic **growth factor** and immunoregulatory **cytokine**. ... In: Peptide **Growth Factors** and Their Receptors I. Sporn MB, Roberts AB, editors ...

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Hypertrophic scars and keloids—a review of their pathophysiology, **risk factors**, and therapeutic management

D Wolfram, A Tzankov, P Pülzl... - Dermatologic ..., 2009 - Wiley Online Library

... Imiquimod 5% cream, a **topical** immune response modifier, is approved for the treatment of ... Furthermore, the use of interferons is also associated with severe **side effects**, including fever ... and scars: a review of keloids and scars, their pathogenesis, **risk factors**, and management. ...

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The epidermal **growth factor** receptor system in **skin** repair and inflammation

S Pastore, F Mascia, V Mariani... - Journal of Investigative ..., 2008 - nature.com

... A human wound-healing study also demonstrated that **topical** application of recombinant EGF ... The **cytokines** released by these cell populations, mainly represented by IL-1, TNF-α ... Andrade C, Busam KJ, Myskowski P, Halpern AC (2006) Dermatologic **side effects** associated with ...

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[HTML] Smoldering and polarized inflammation in the initiation and promotion of malignant disease

F Balkwill, KA Charles, A Mantovani - Cancer cell, 2005 - Elsevier

... Polymorphisms thought to enhance IL-1β production confer an increased **risk** of chronic ... The proinflammatory **cytokines** signal to initiated and/or otherwise damaged epithelial cells to ... et al., 2004); neither do the **skin** carcinogenesis studies, where a single **topical** application of ...

Cited by 1178 Related articles All 8 versions Cite Save

New and established **topical** corticosteroids in dermatology

B Brazzini, N Pimpinelli - American journal of clinical dermatology, 2002 - Springer

... The **risks** associated with the use of corticosteroids 'parallel' the ben- ... It is noteworthy that the **risk** of sensitization to corticosteroids is increased in long term dermatoses ... petrolatum), and hydrocortisone-17-butyrate (1% ethanol).[42,43] Long term use of **topical** corticosteroids may ...

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Antioxidant activity, lipid peroxidation and **skin** diseases. What's new

S Briganti, M Picardo - Journal of the European Academy of ..., 2003 - Wiley Online Library

... However, the usefulness of this drug is diminished by toxic **side-effects**, including **skin** ... in cell redox environment induces the gene expression of pro-inflammatory **cytokines**, such as IL ... Thus antioxidant oral supplementation or **topical** application may be an effective approach in ...

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Pilot trial using BM-MSC conditioned media

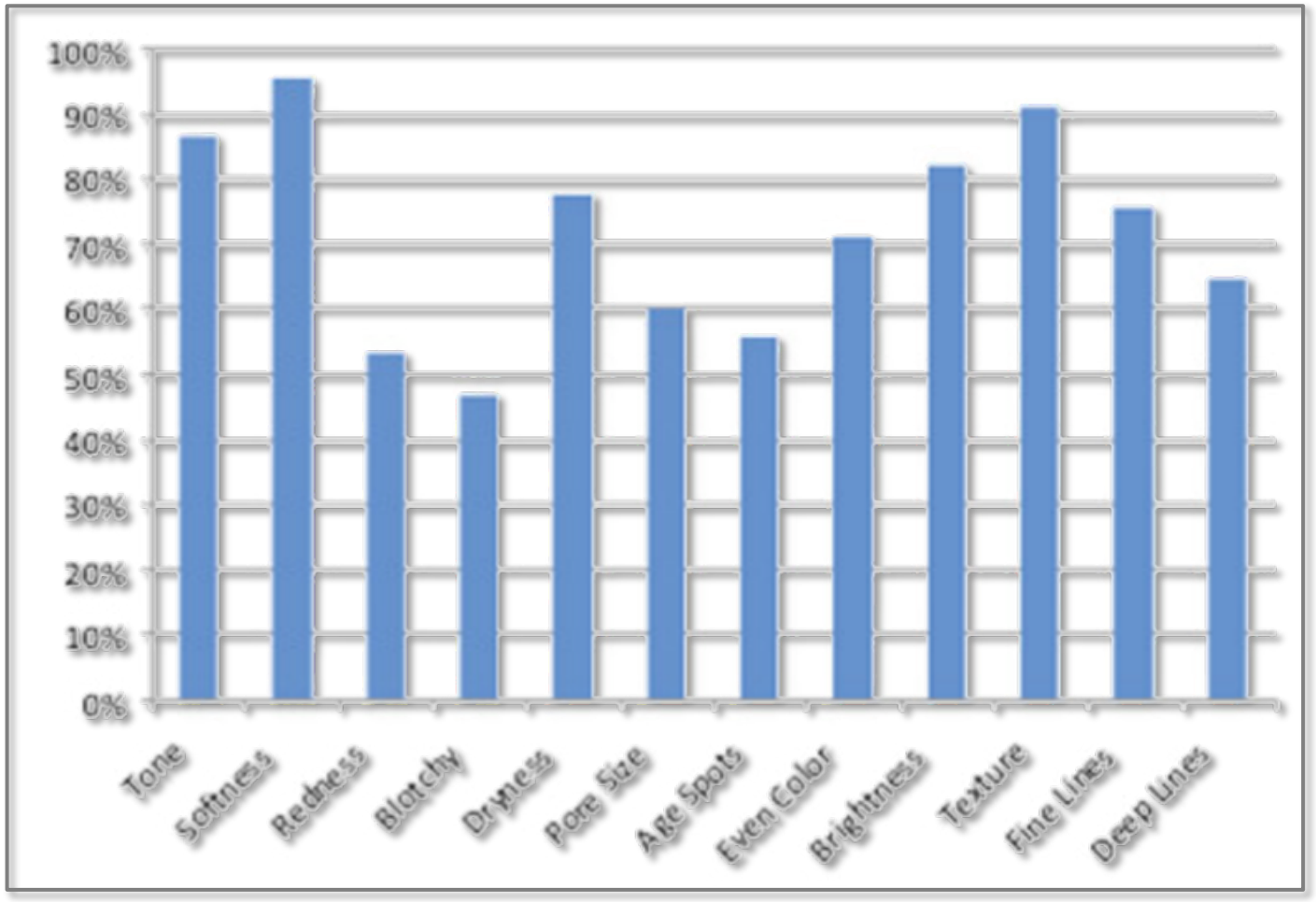
Pilot trial:
24 days duration
Fourteen subjects (12f/1m)
36 to 72 yrs. of age

Measured:
Course lines, fine lines, reflectivity, texture, tone, coloration

Results:
All subjects improved in at least one criterion.
11 of 14 (86%) observed improvement in four criteria.

Four examples of skin improvements seen

Clinical trial of BM-MSC product for market

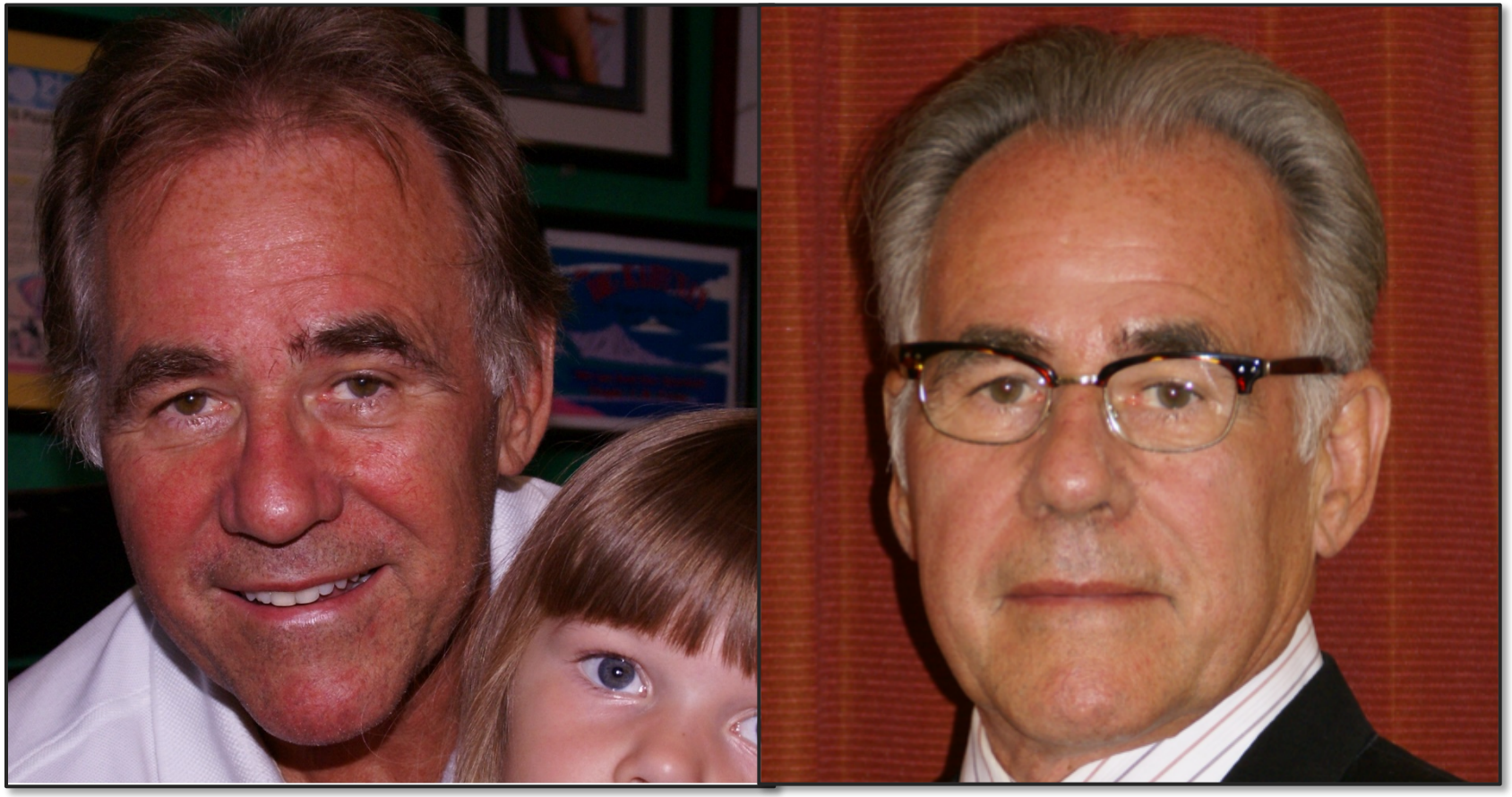


Clinical Trial:
6 to 8 weeks duration
Forty-nine subjects (44f/5m)
30 to 75 yrs. of age

Skin parameters evaluated:
Tone, softness, redness, blotchiness, dryness, pore size, age spots, evenness of color, brightness, texture, fine lines, deep lines.

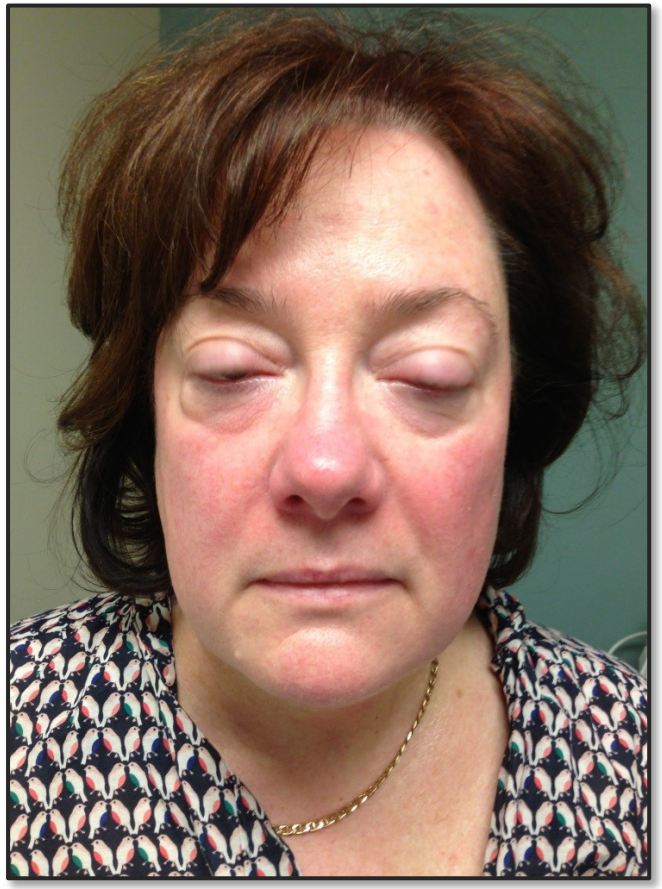
Results:
Graph shows percent of subjects noticing improvement in their skin.

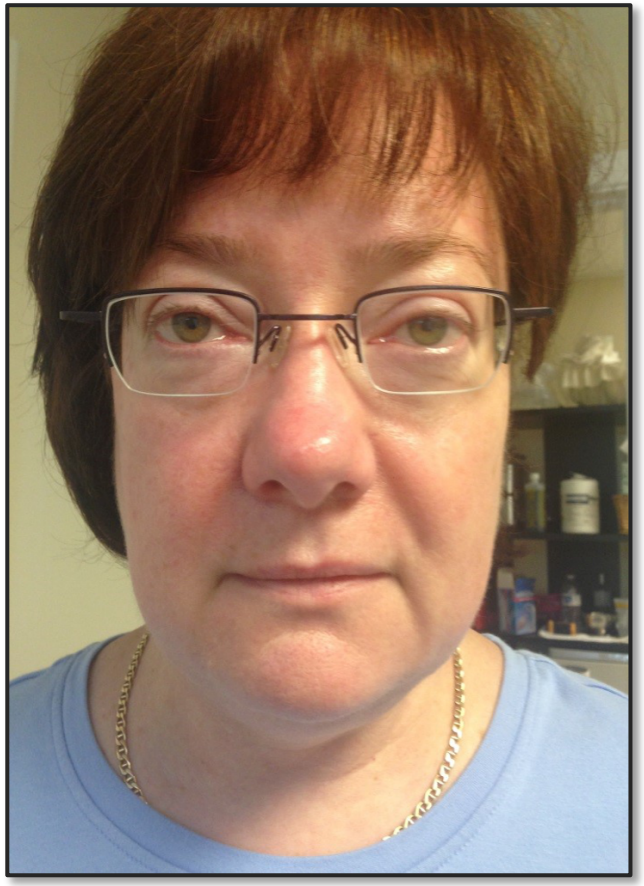
Anti-inflammatory effect on patient # 1



- Decades of **rosacea** symptoms
- Managed for years with low dose **oral doxycycline** q.d., topical **Metrogel** b.i.d., and topical steroids prn
- **Several flare ups per month** from all usual triggers
- Stopped meds and **started AnteAGE (consumer version) 7.1.11.**
- **Not a single flare up to date** despite complete disregard for all triggers and no meds.

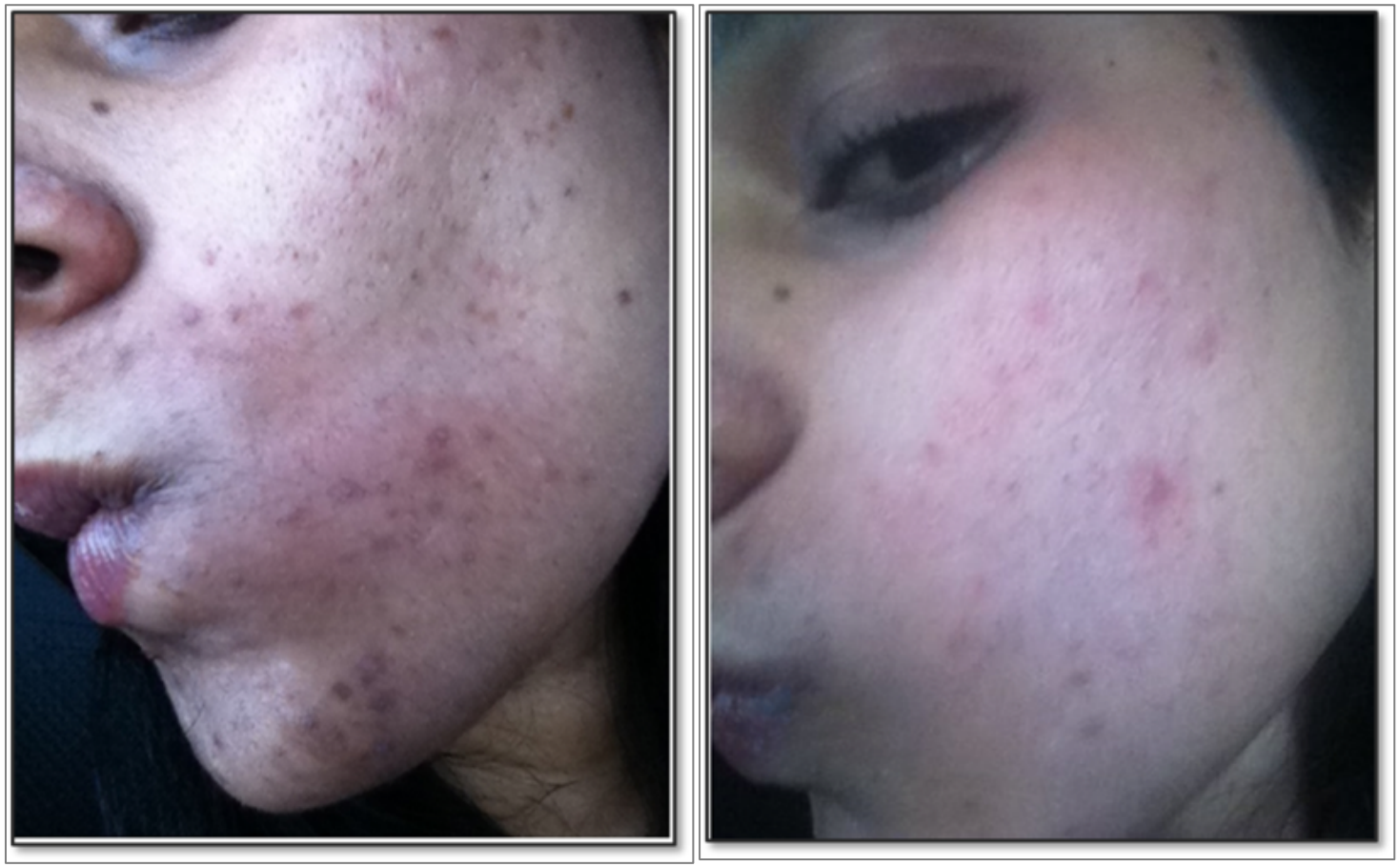
Anti-inflammatory effect @ one month





- **Chronic red face** for years
- **Reduced redness and more even skin tone** at end of first month

Benefits on Acne & PIH

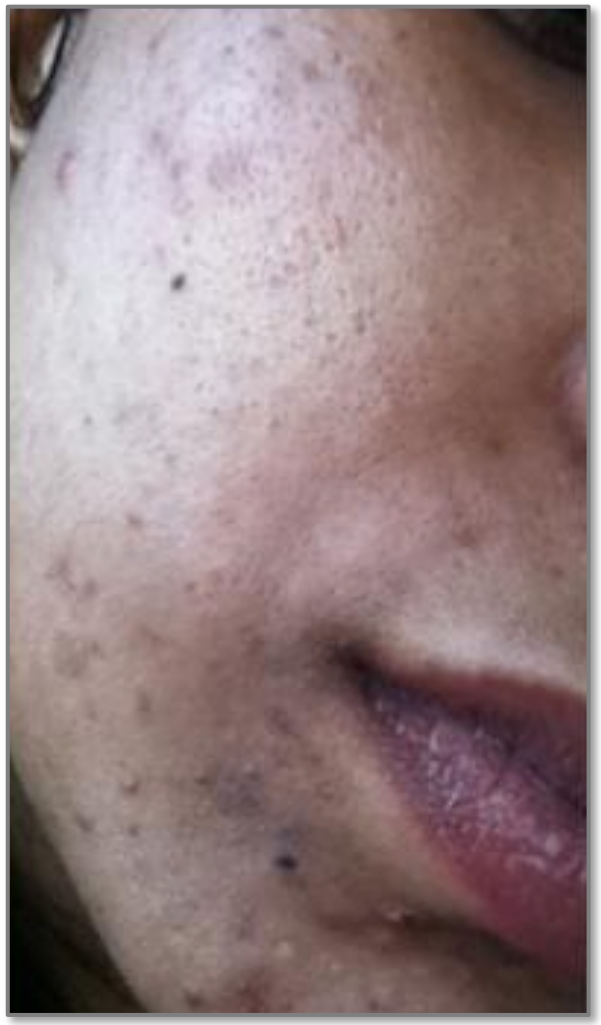


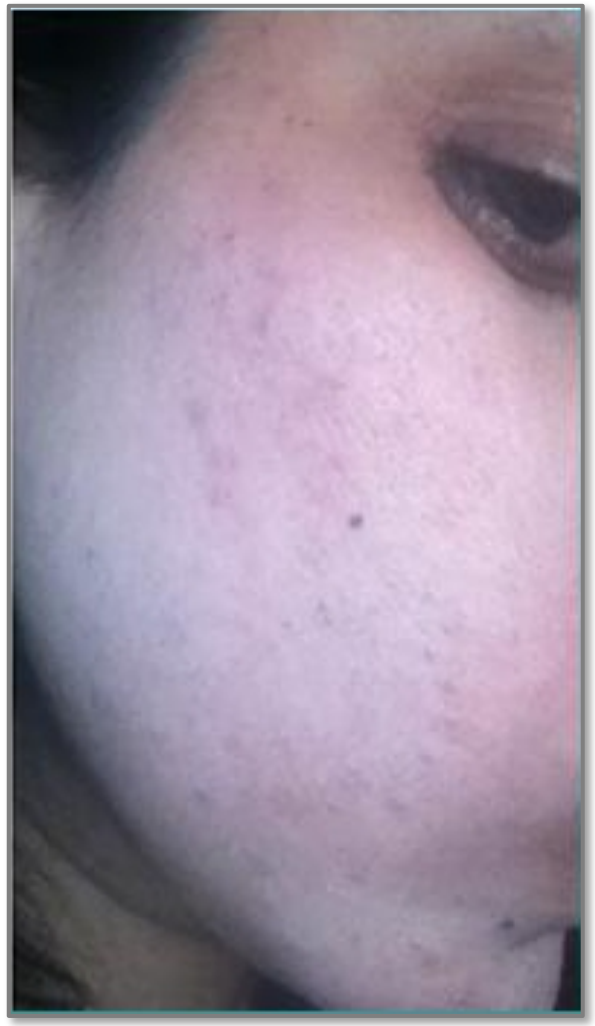
An **early online purchaser** of AnteAGE consumer version

Used product for **8 weeks** b.i.d.

Two episodes of dermarolling with .25 mm device three weeks apart

Benefits on Acne & PIH





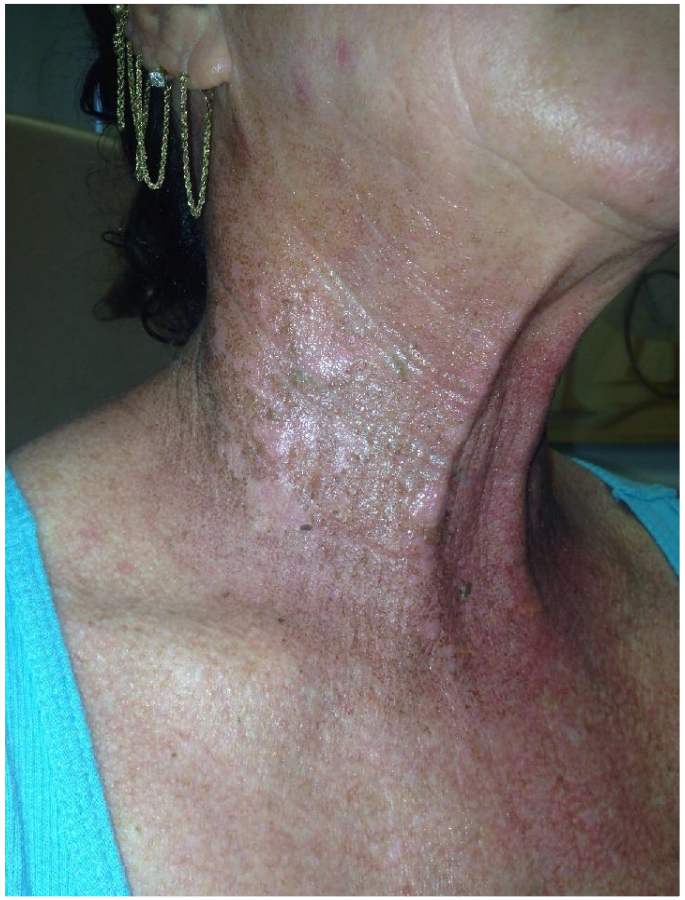
An **early online purchaser** of AnteAGE consumer version

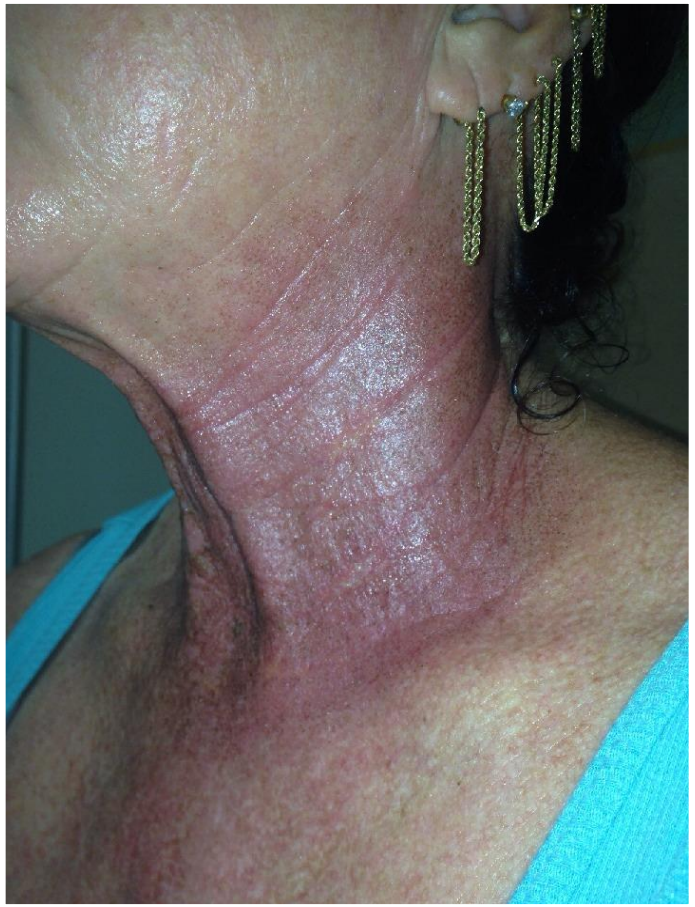
Used product for **8 weeks** b.i.d.

Two episodes of dermarolling with .25 mm device three weeks apart

Recovery after fractional CO_2 laser

"Less pain, less redness, less swelling, more peeling"

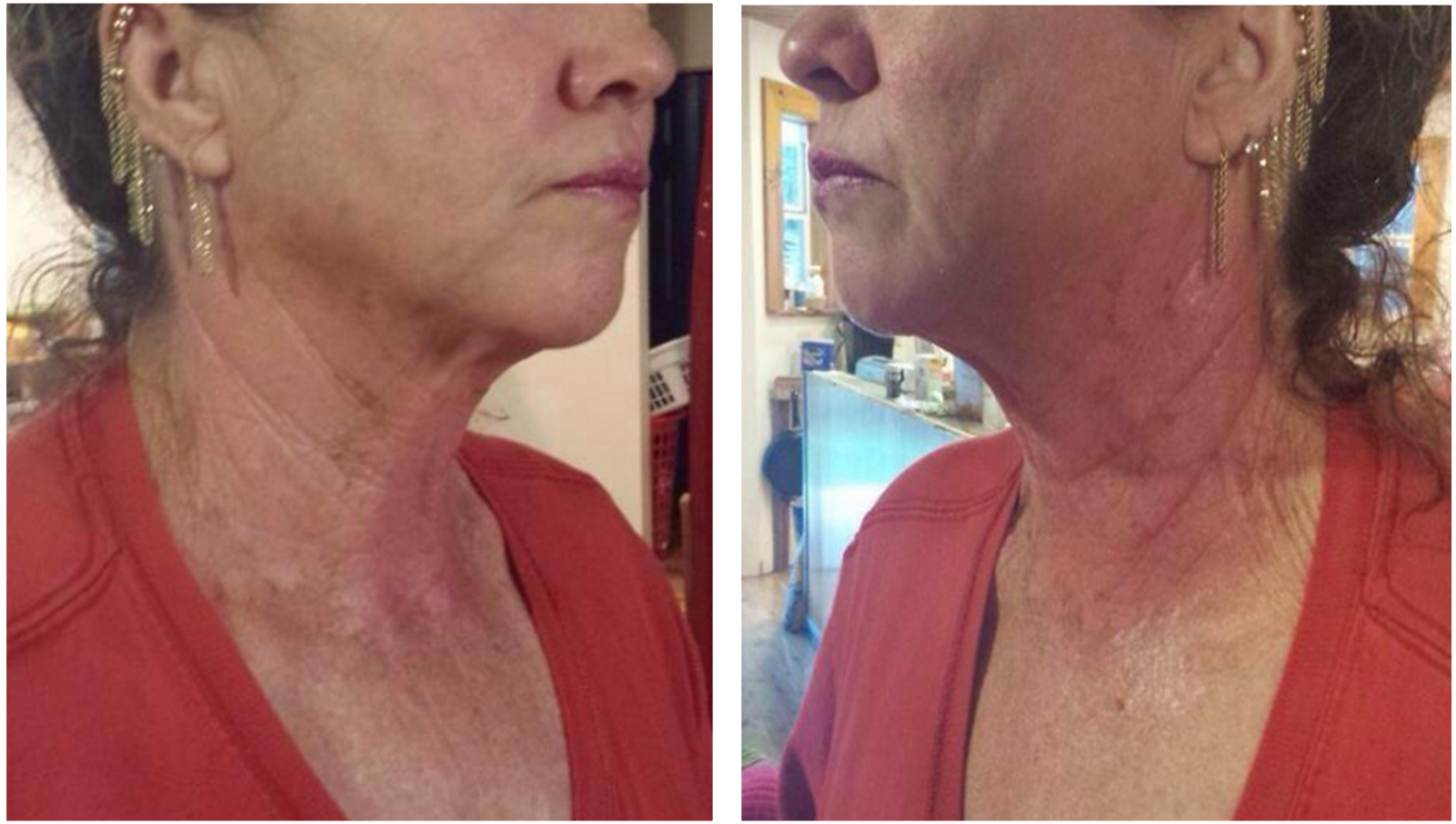




"More pain, more redness, more swelling, less peeling"

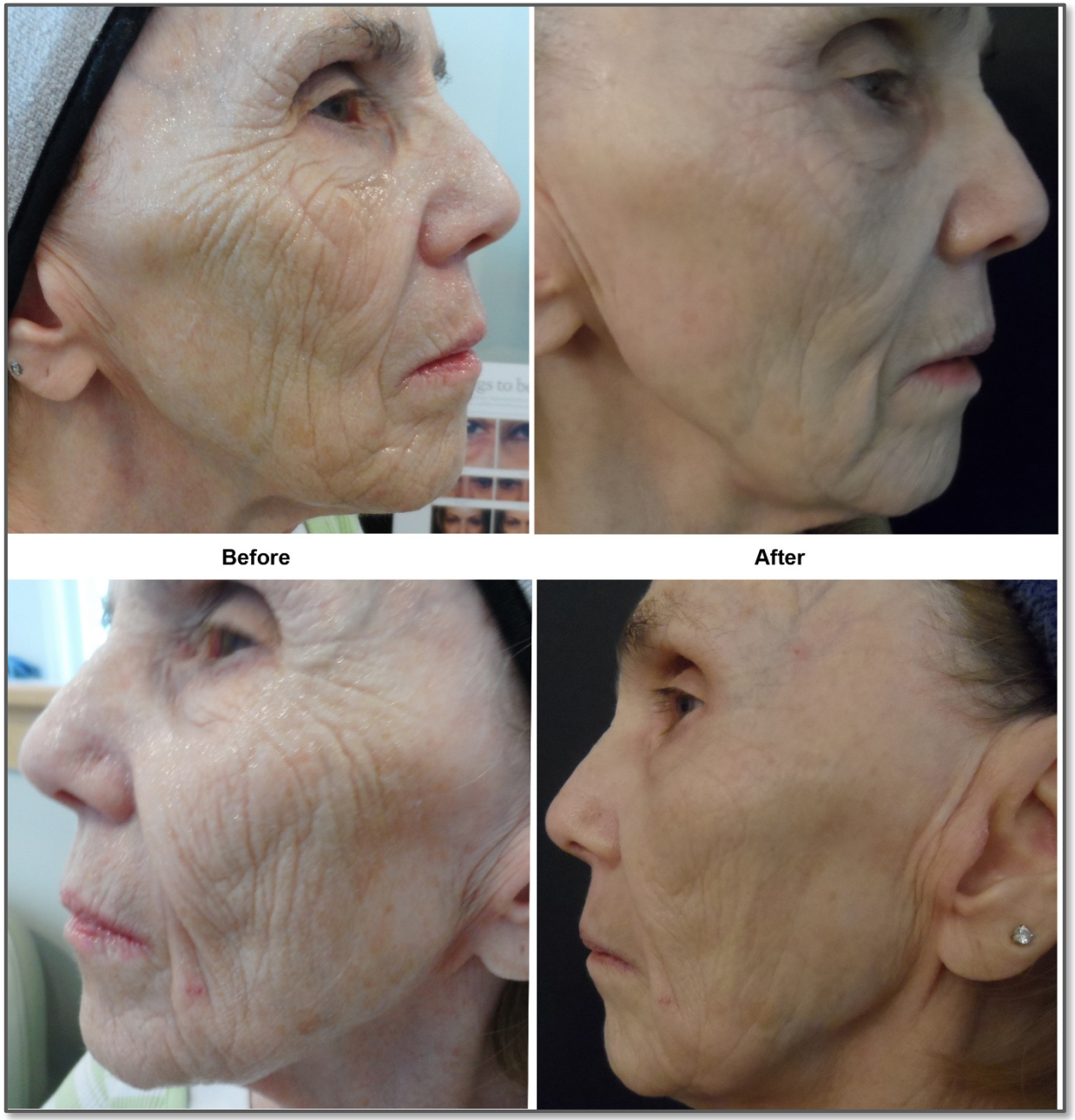
Day 3

Recovery after fractional CO_2 laser



Day 4

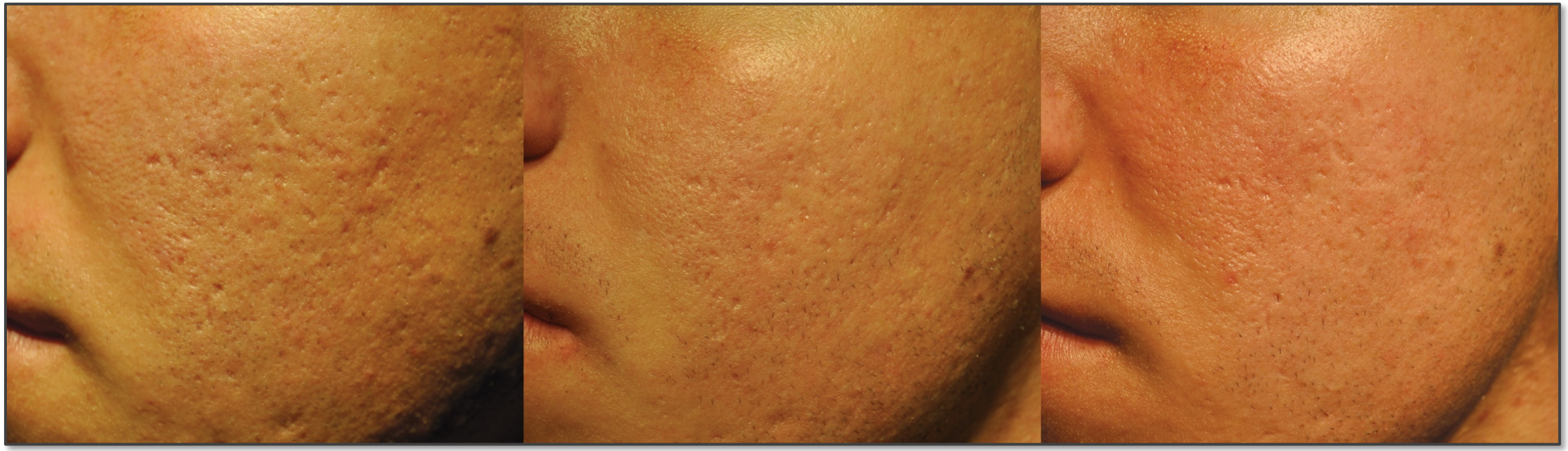
epionce
We Deliver the Beauty of Healthy Skin™



Dermal needling results in a 74 y.o. woman

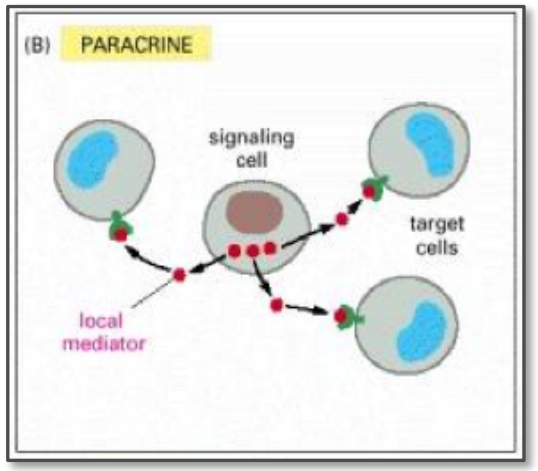
Four dermal needling treatments, each a month part using a BM-MSC cell culture derived topical at time of treatment, and another formulated for **twice daily anti-aging skin care**.

Dermal needling results in a 21 y.o. man



Three dermal needling treatments, each a month part using a BM-MSC cell culture derived topical at time of treatment, and another formulated for **twice daily anti-aging skin care**.

The Close-range "Language" of Cells



- Cells communicate with neighboring cells in a highly **complex close-range conversation**.
- The **"words" they use are bio-signaling molecules** called cytokines and growth factors.
- Like people, **some kinds of cells have lots to say; others are much better "listeners."**
- **Stem cells have lots to say**.
- Some stem cells say things that **"calm and sooth"**, others say things that **"inflame and anger."**

What are cytokines?

- Signaling proteins
- Local and distant effects
- Peptides, proteins, glycoprotein,
- Picogram dose response curves
- Cellular communications
- Embryogenesis
- Immune function

Growth factors are one of the several classes of cytokines.

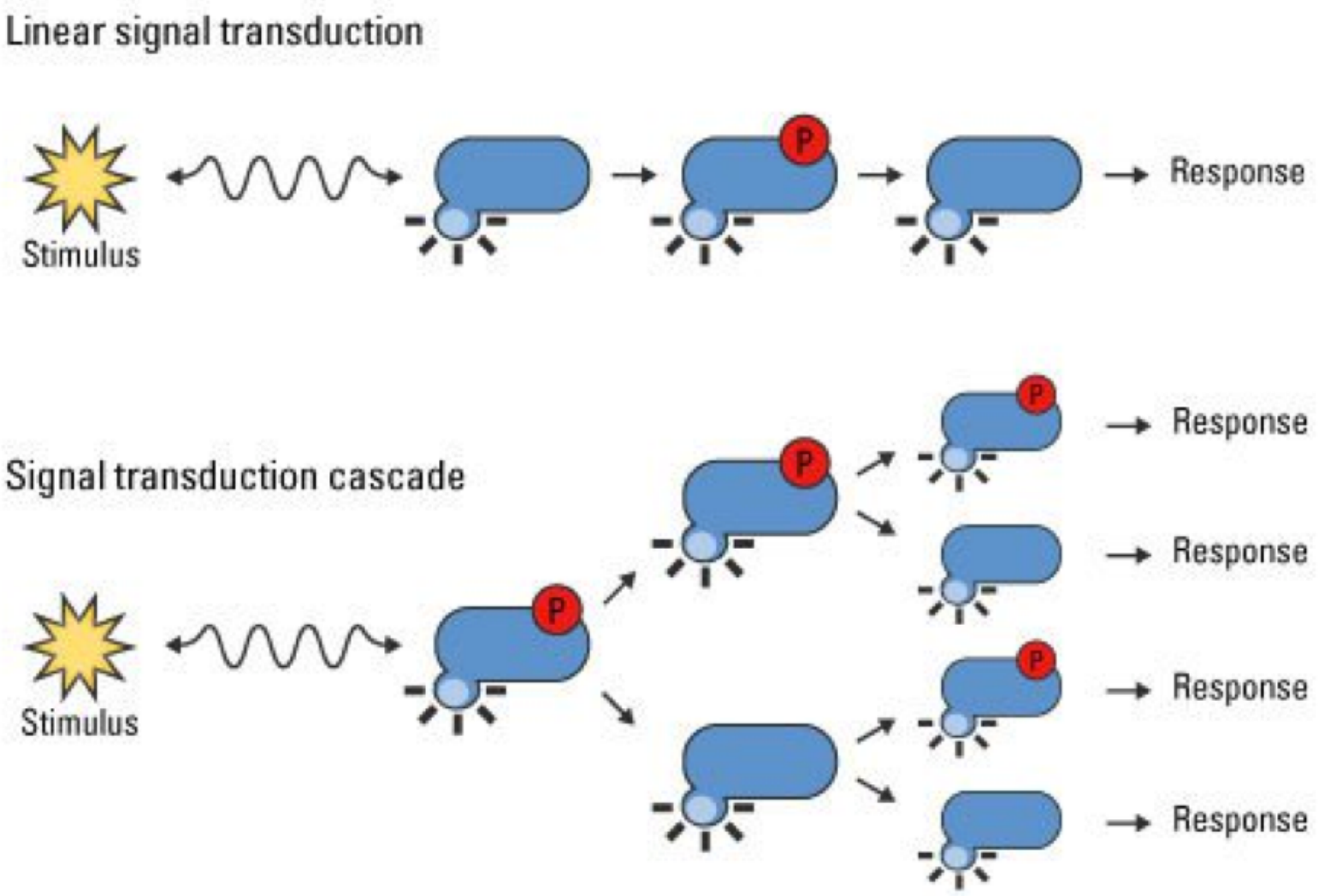
Some cytokines are pro-inflammatory.
Some cytokines are anti-inflammatory.

What are growth factors?

- Cell-to-cell signaling molecules
- Alter gene expression
- Promote cell division – proliferation
- May inhibit apoptosis
- Morphogenesis
- Angiogenesis
- Cell differentiation – maturation
- Tissue homeostasis
- Wound healing

Growth Factors	Source	Target Cells / Effect
Epidermal growth factor (EGF)	Macrophages, platelets, epithelium	Mitogenic for epithelial tissues, fibroblasts, endothelial cells
Fibroblast growth factor (FGF)	Fibroblasts, endothelial cells, bone cells, macrophages	Endothelial cells, fibroblasts
Transforming growth factor (TGF-alpha)	Macrophages, eosinophils, keratinocytes, epithelial cells, platelets	Similar to EGF, but more potent angiogenesis factor
Transforming growth factor (TGF-beta)	Macrophages, lymphocytes, fibroblasts, keratinocytes, platelets, bone	Inhibits replication of most cells in vitro.
Platelet derived growth factor (PDGF)	Endothelial cells, platelets, macrophages, fibroblasts	Mitogenic for vascular smooth muscles, fibroblasts, macrophages
Insulin-like growth factor (IGF-I)	plasma, liver, fibroblasts	Mitogenic for fibroblasts, endothelial cells, fibroblasts, fetal tissues

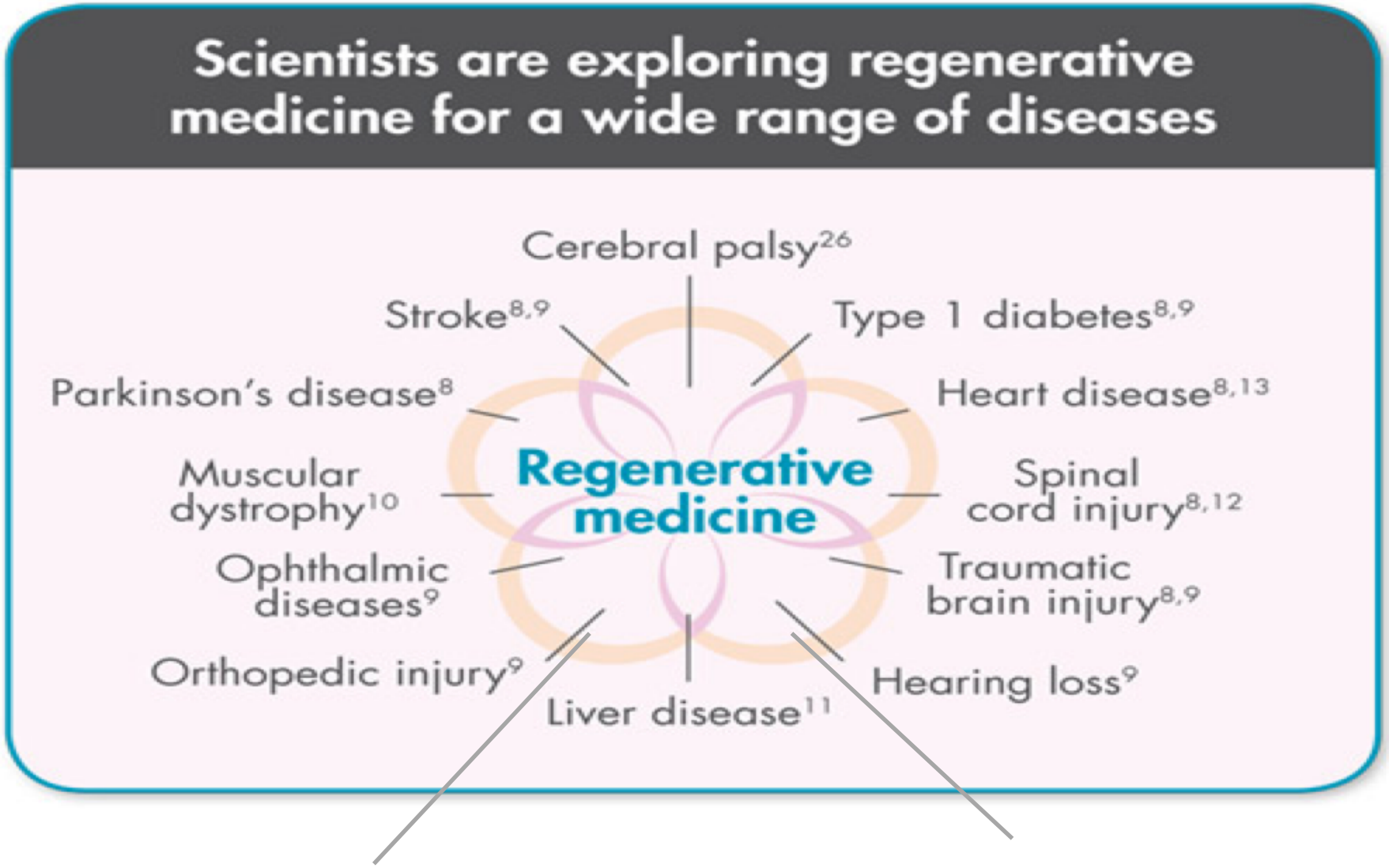
Paracrine amplification



One molecule - chain reaction – many cells

Don’t get with your botanical “actives”

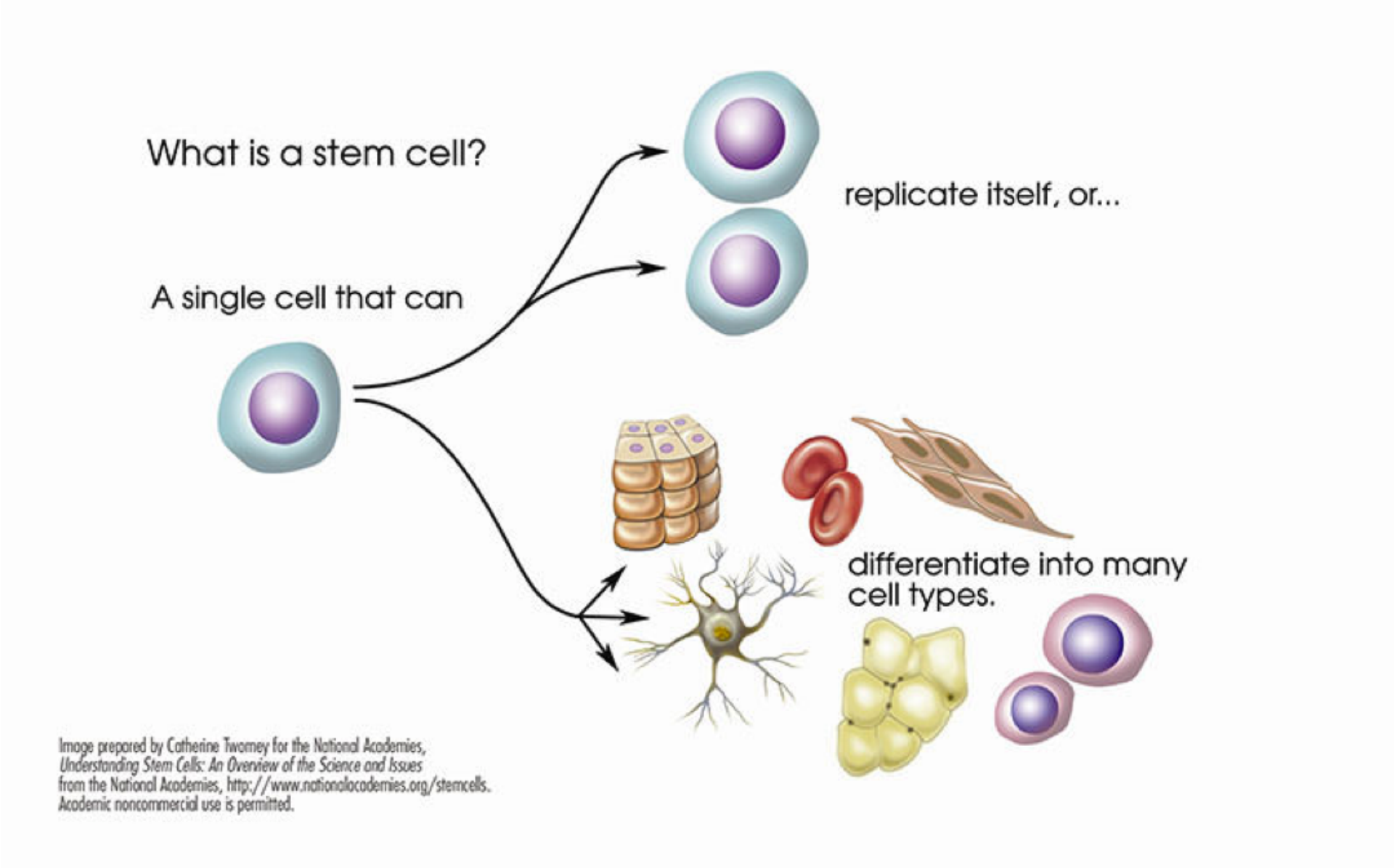
Dosing advantage for human !



Dermatologic conditions

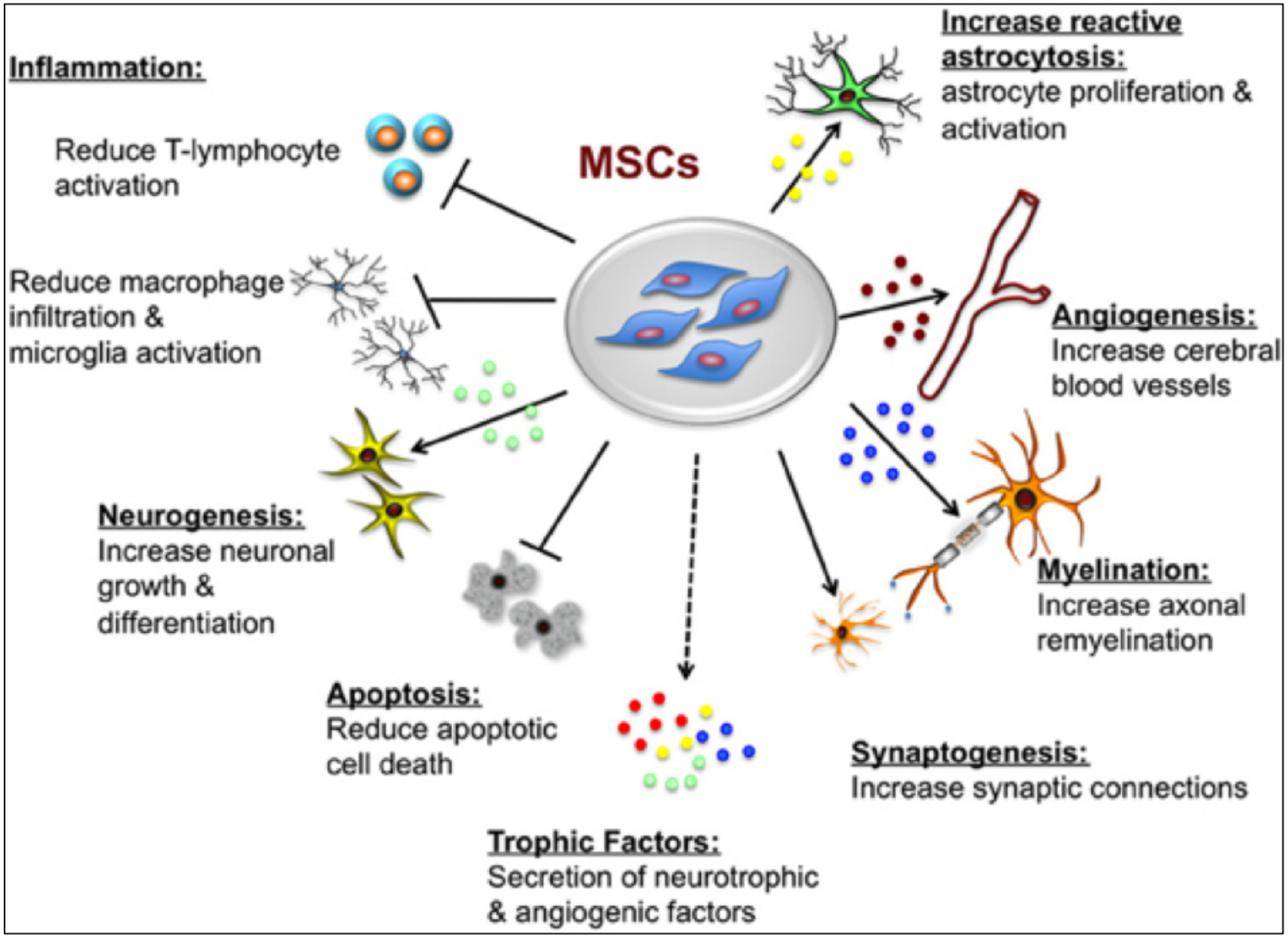
Rejuvenation / aesthetics

What are stem cells?

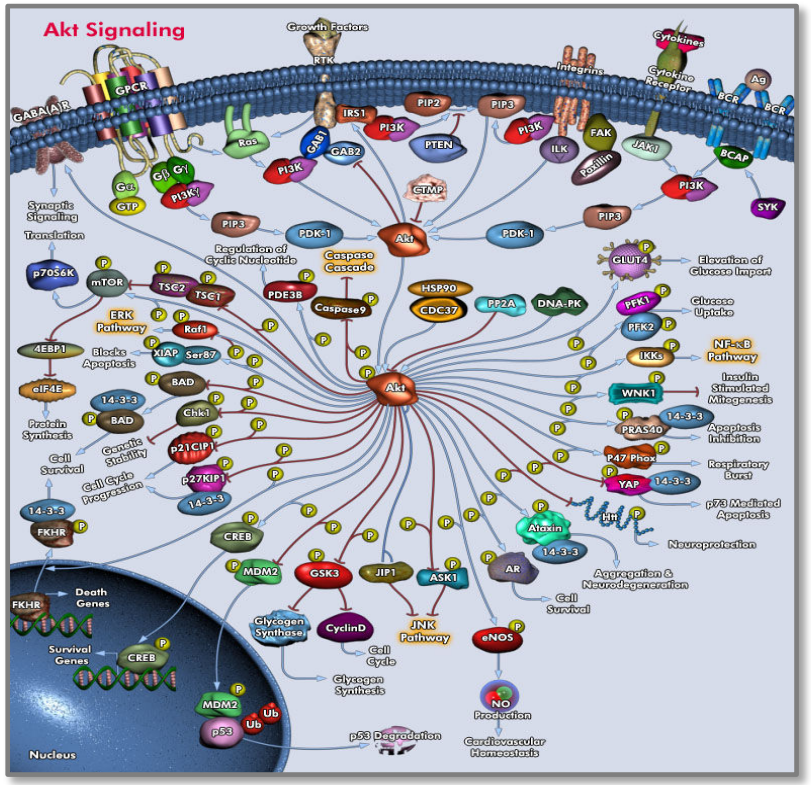


Stem cell therapy

- **95%** of the effect is due to paracrine chemical release
- **5%** is due to engraftment & differentiation into host tissue cell type
- **Conditioned medium of culture or stem cells →equivalent effects**

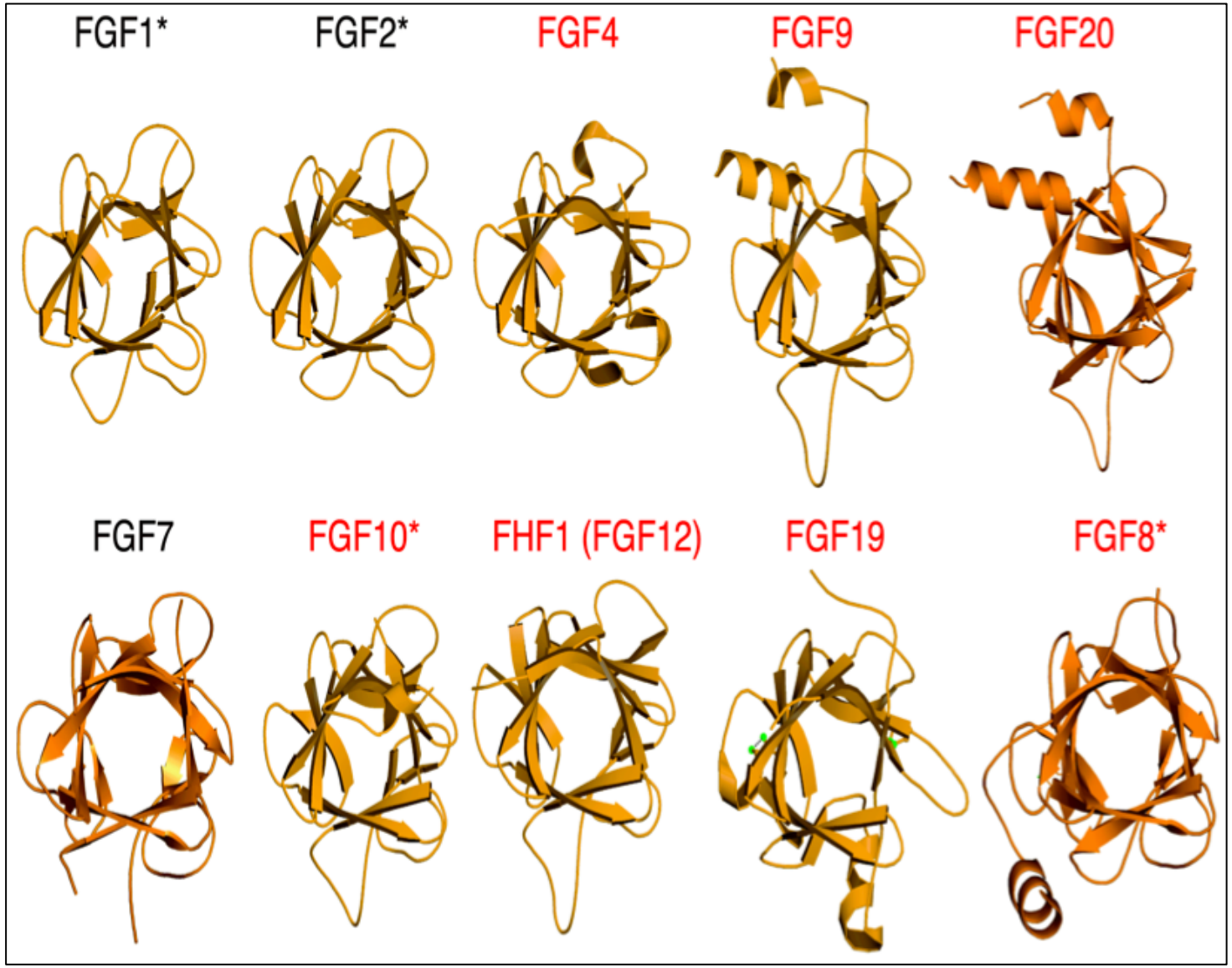


Activation triggers intracellular events



- Bio-signals are always part of a “pattern” of many bio-signals.
- Competing and complementary bio-signals produce a net effect.
- Gene activity in the nucleus of the cell is stimulated or inhibited.

Growth factor and cytokine arrays



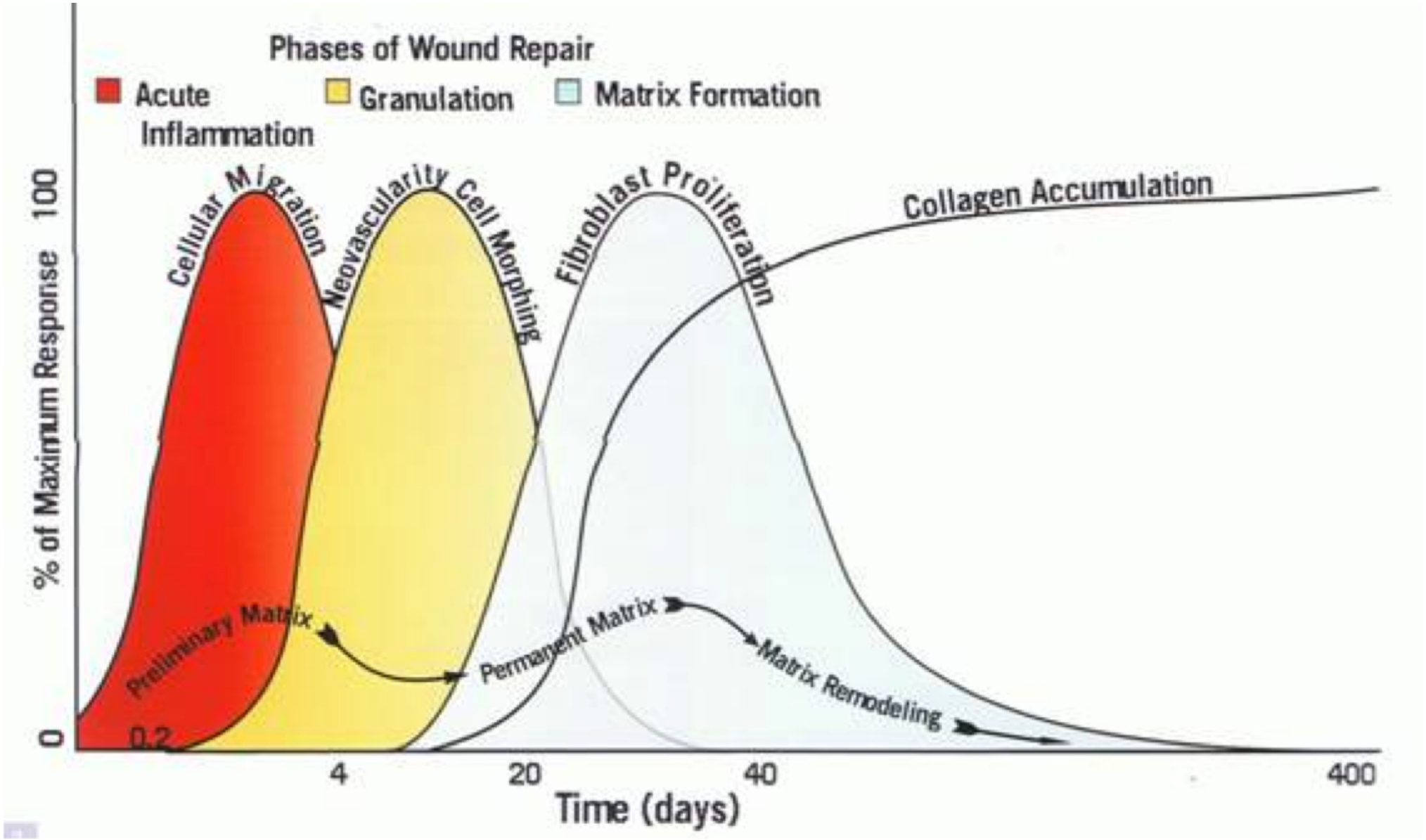
- Thousands of Cytokines
- Families of GF's
- Act in concert

- Single GF products are not physiologic.

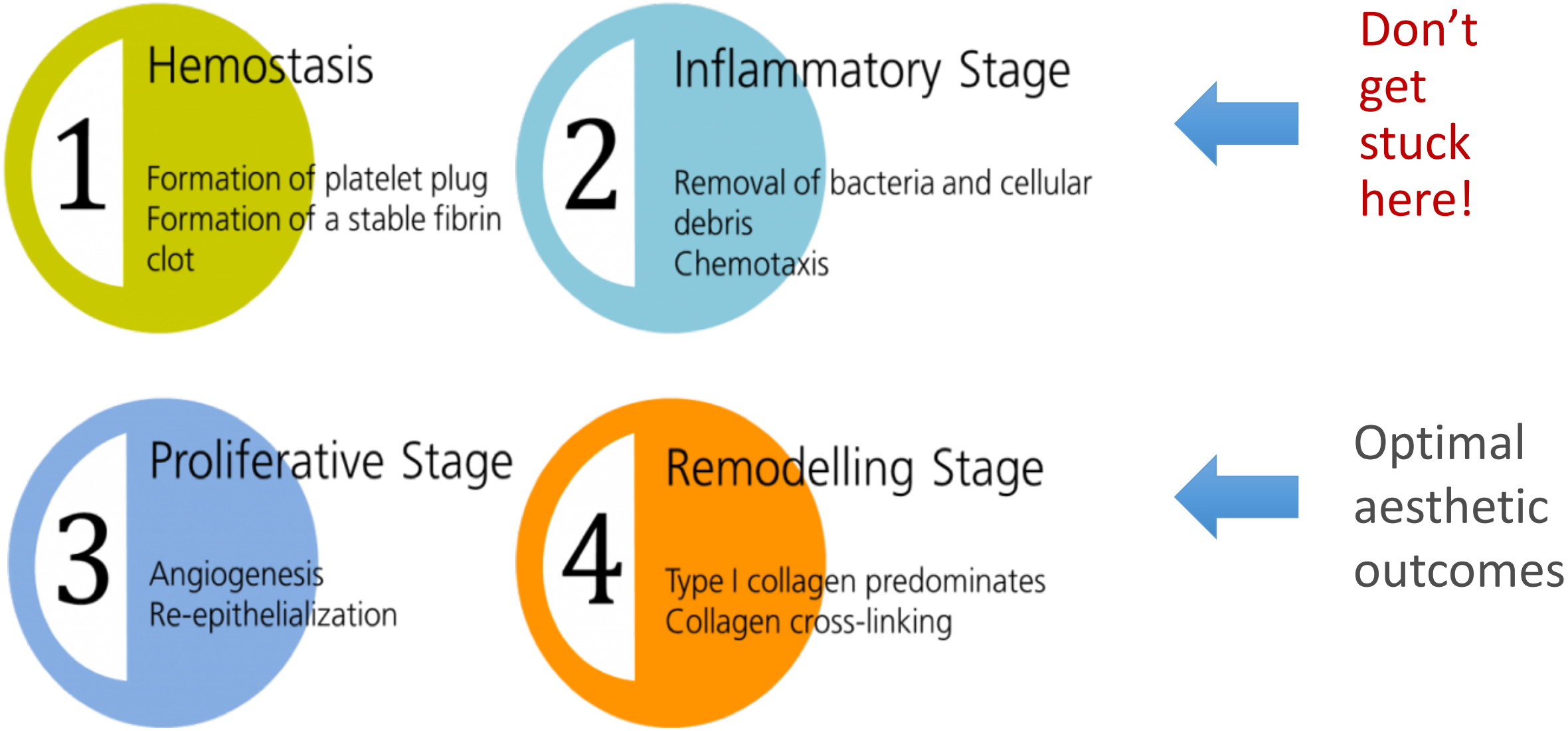
- GF's balance one another.

- We routinely measure 80 key GF's from our cells

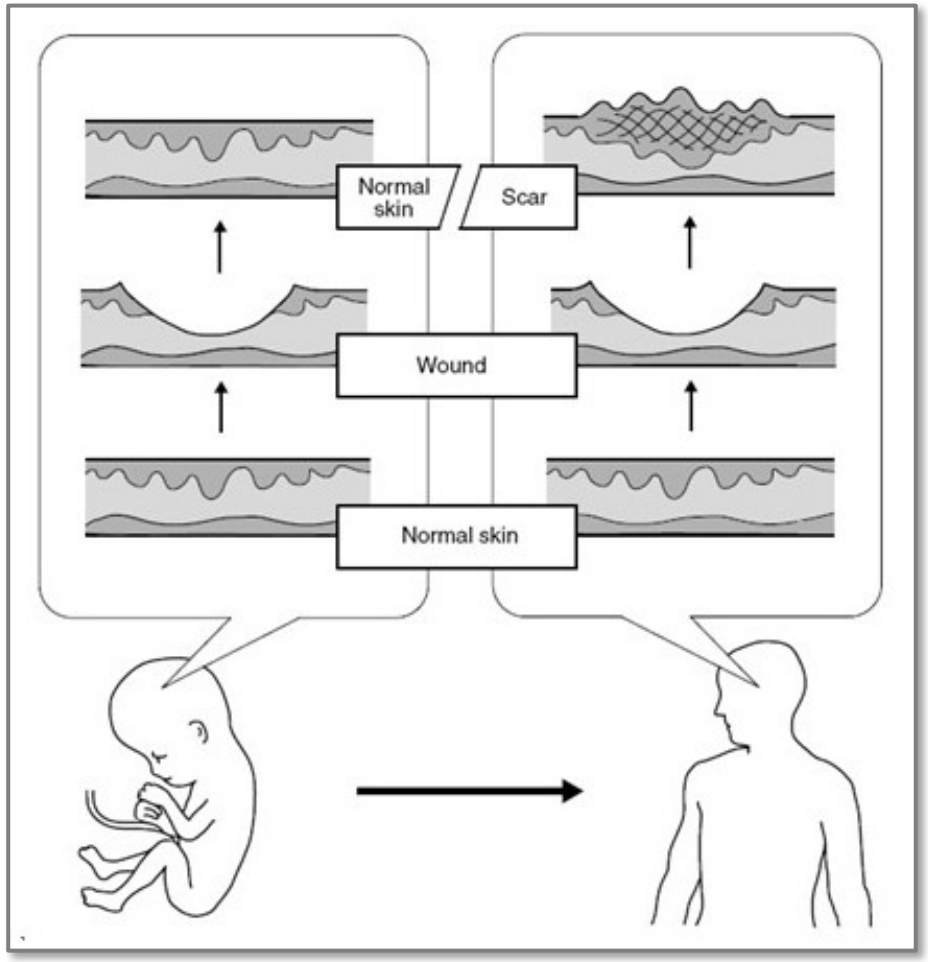
Collagenesis during wound healing



Stages of Wound Healing

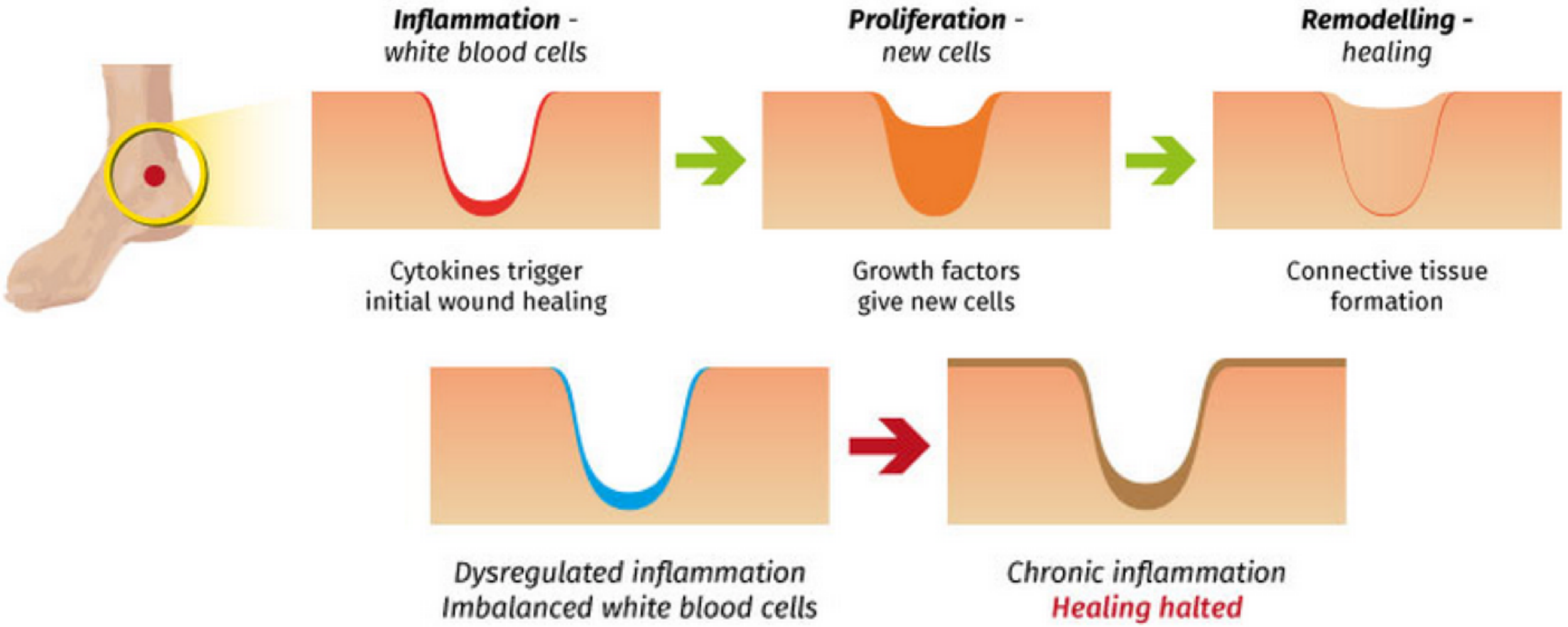


Fetal skin heals scar free.



- During first and second trimesters, **fetal skin heals rapidly without scars.**
- Inflammation is **absent or extremely brief.**
- **Anti-inflammatory cytokines are abundant**.
- During the third trimester, **cutaneous wounds heal more slowly, with adult-like inflammation**.
- **Results in scars** with over-production of densely packed, disorganized collagen.

Cytokines, growth factors, and healing

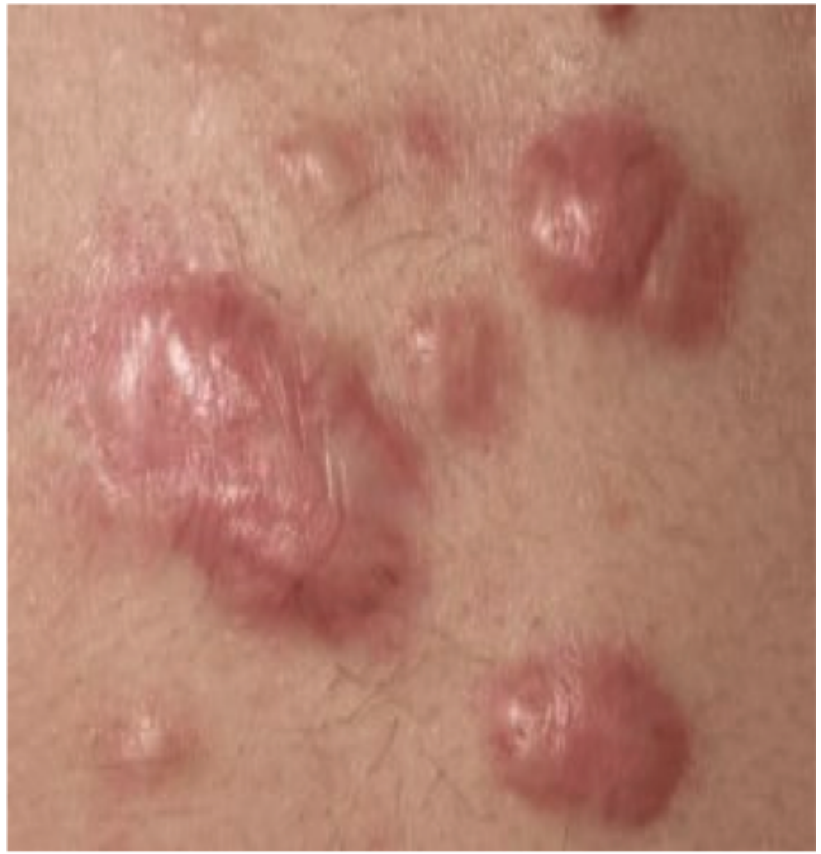


Inflammation:
the primary culprit in poor aesthetic results

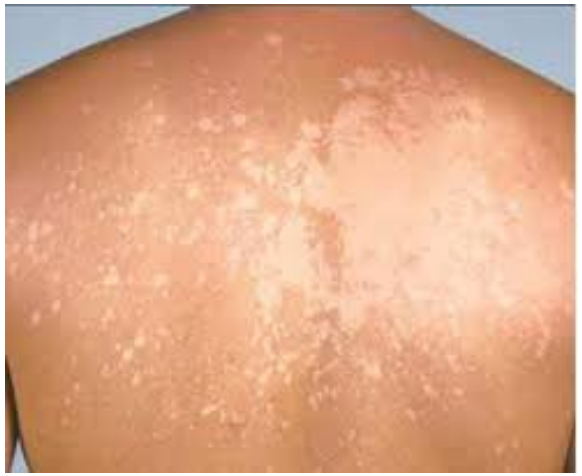
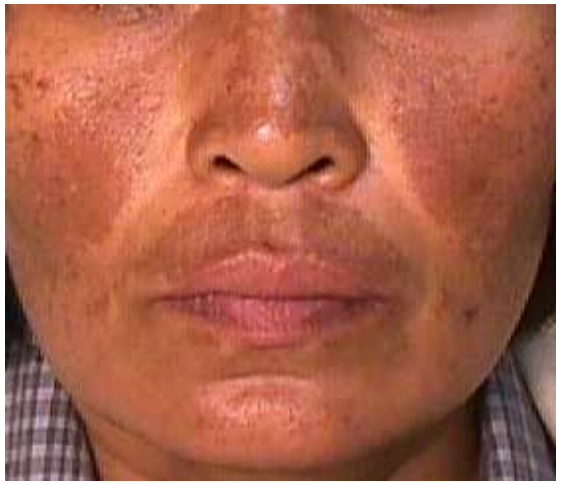
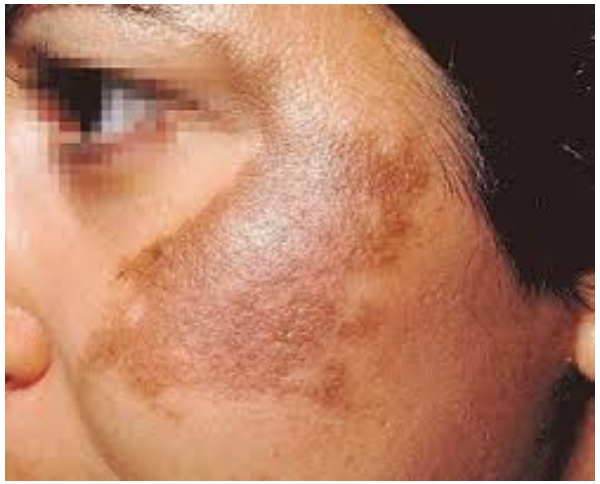
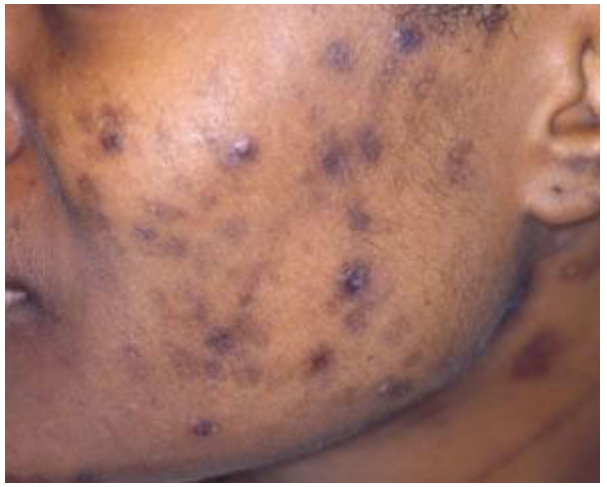
Major contributor to **skin aging** &
most skin maladies

Often **responsible for suboptimal outcomes** in skin rejuvenation and energy based skin treatments

Positive aesthetic outcomes can be enhanced/engineered
by controlling inflammation.

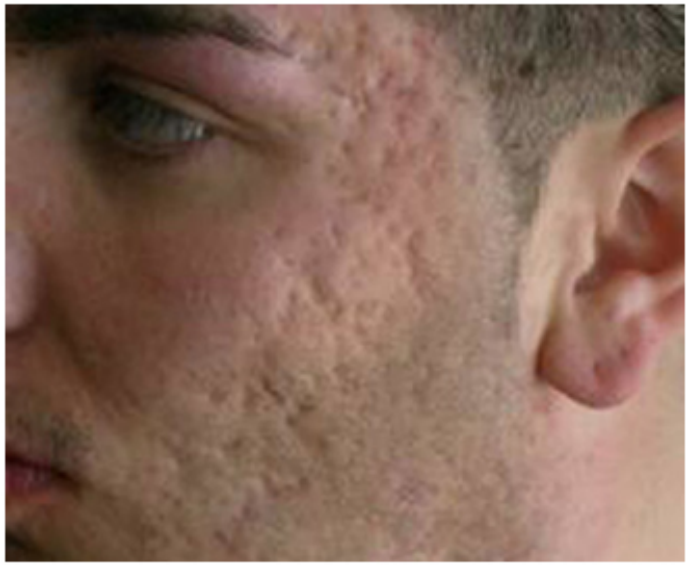


Inflammation and Pigmentation

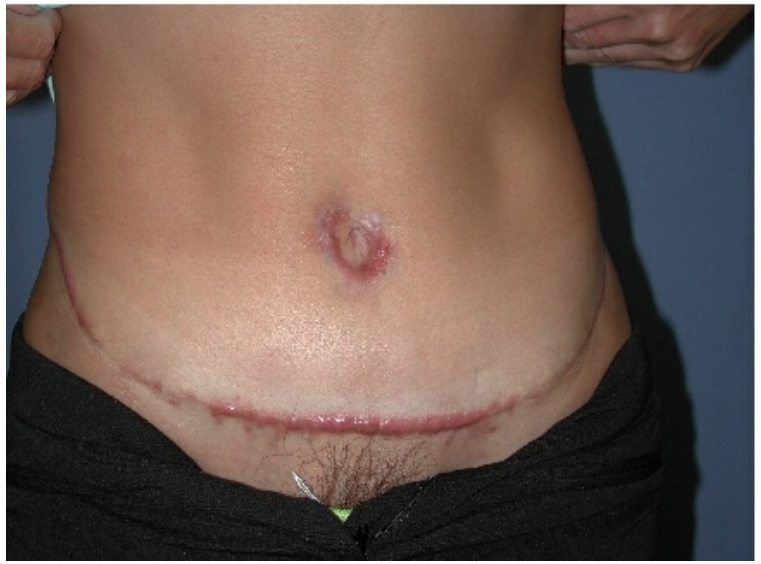





Inflammation is *the* major contributory factor in *hyper*pigmentation and *hypopigmentation*.

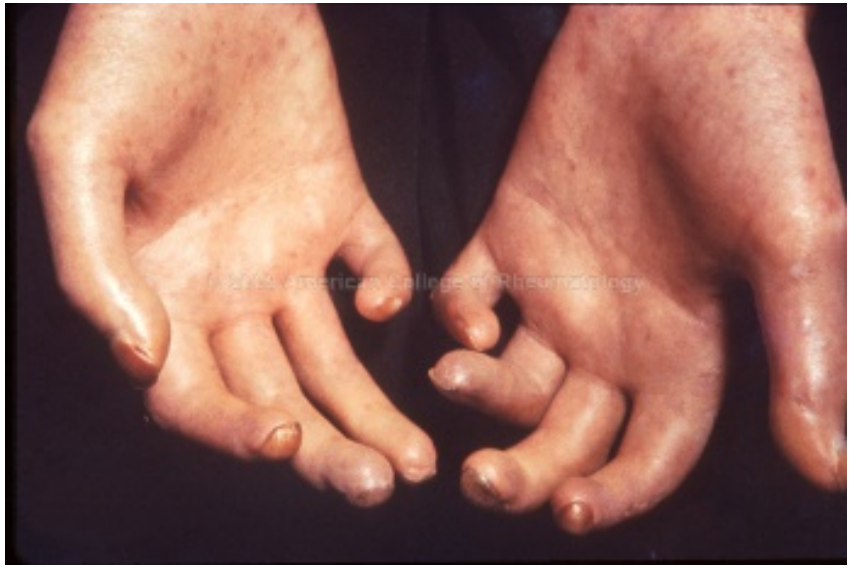
Collagenesis: *desired* Fibrosis: *definitely not*



Fibrotic acne scarring



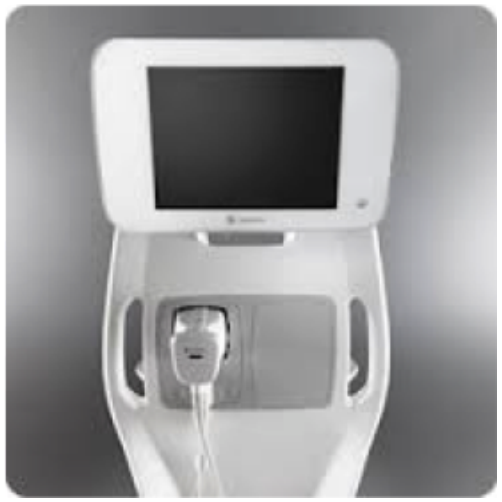
Hypertrophic Scars



Scleroderma

Inflammation is *the* major contributory factor in fibrosis.

Devices create controlled wounds



Nature heals them

…in an orderly fashion

(But not always)