



AnteAGE®
with Stem Cytokines™

self-DEFENSE against
SKINflamMAGING

PARABEN
FRAGRANCE
CELL
CRUELTY
FREE

AnteAGE®

with Stem Cytokines™

MD

A Scientific Breakthrough From The Pioneers In Mesenchymal Stem Cell Cytokine Technology

- Post Laser
- Post Microdermabrasion
- Chemical Peels
- Micro-Needling
- Aging Skin
- Sun Damage
- Hyperpigmentation
- Rosacea
- Inflammation
- Wrinkles
- Laxity
- Erythema

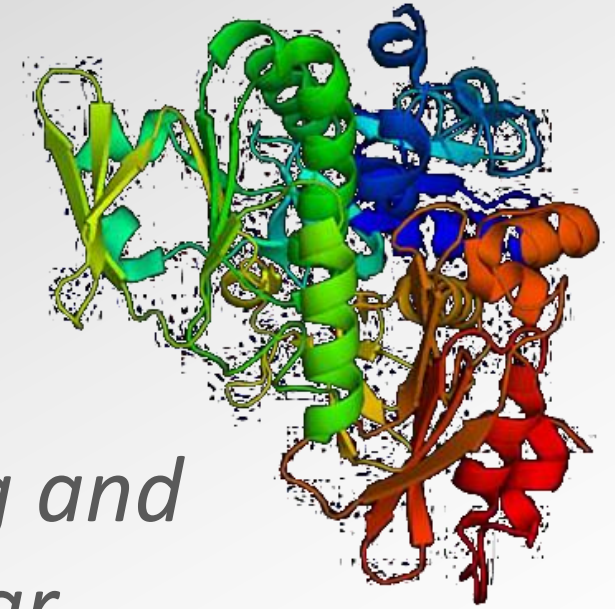
info@anteage.com | P 877-350-6350

www.anteAGE.com

Cytokine-Based Topical Adjuvants in Aesthetic Medical Practice

Cytokines: Molecular Bio-signals

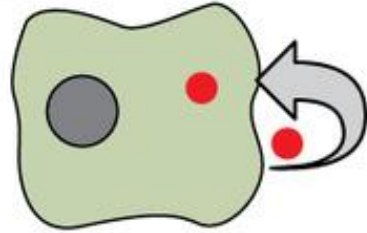
Embryogenesis, growth and development, wound healing and regeneration, and aging and senescence share a common set of molecular signaling mediators, collectively called “cytokines”. Included in the term are hundreds of proteins, peptides, and glyco-proteins divided into families of molecules: cytokines, chemokines, growth factors, interleukins, interferons, and others.



Forms of Chemical Signaling

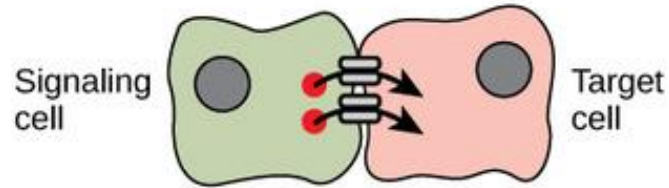
Autocrine

A cell targets itself.



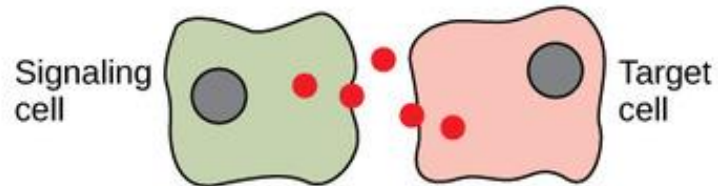
Signaling across gap junctions

A cell targets a cell connected by gap junctions.



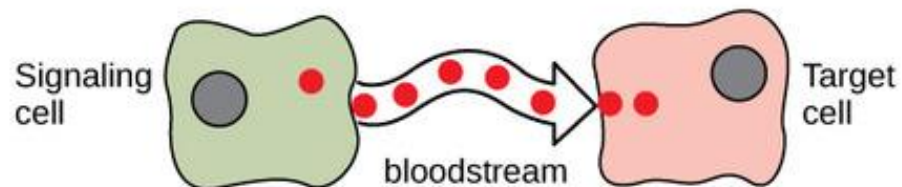
Paracrine

A cell targets a nearby cell.



Endocrine

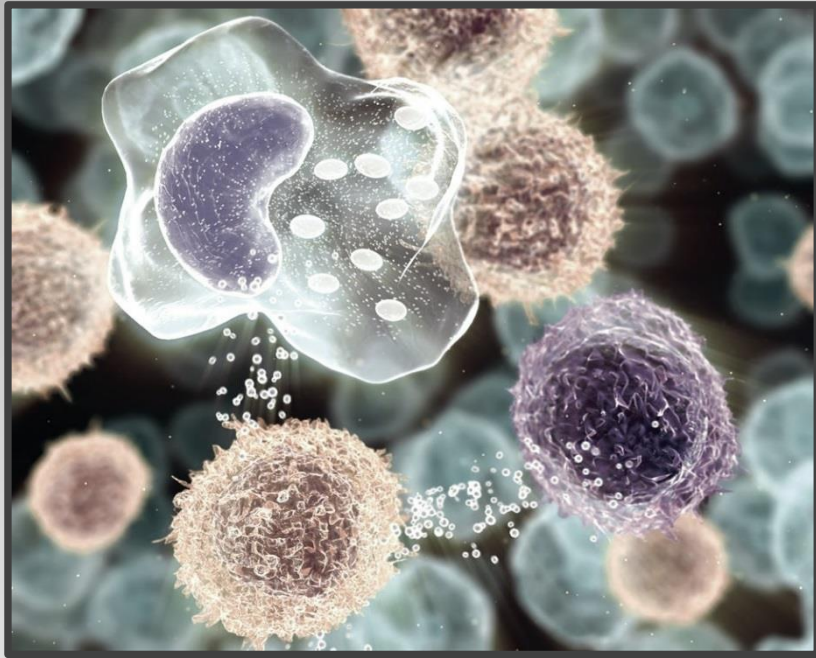
A cell targets a distant cell through the bloodstream.



Cells Communicate in 4 ways.

- Paracrine signaling - cytokines engaging in cell-to-cell communication.
- One cell targets another nearby cell, influencing its behavior and function.
- Topical cytokines mimic paracrine signaling.

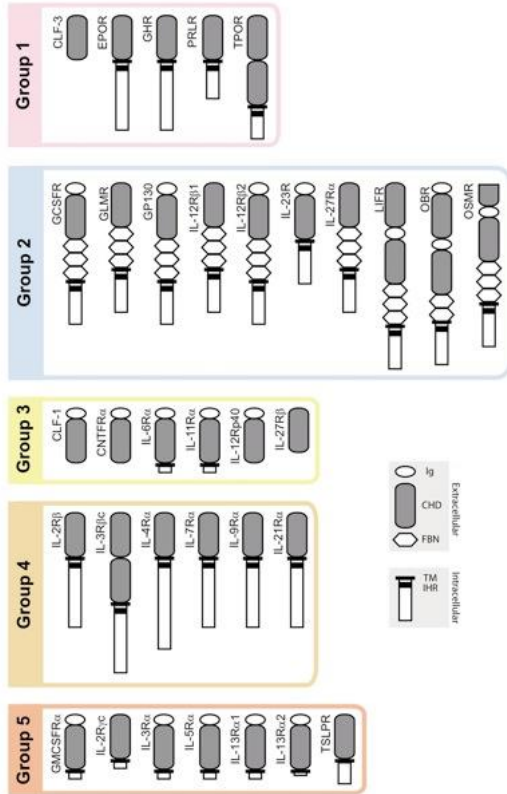
The Language of Cytokine Communication



- The human body contains over 200 individual cell types.
- Except for the red blood cell, all cells “speak” or “listen” or both in the language of cellular communication – the words in the language are *cytokines*.
- Certain cells have larger “vocabularies” and are more “vociferous.”
- **When it comes to healing, one type of stem cell is the most communicative of all, acting as command and control of the healing process.**

The Cytokine System is Highly Complex

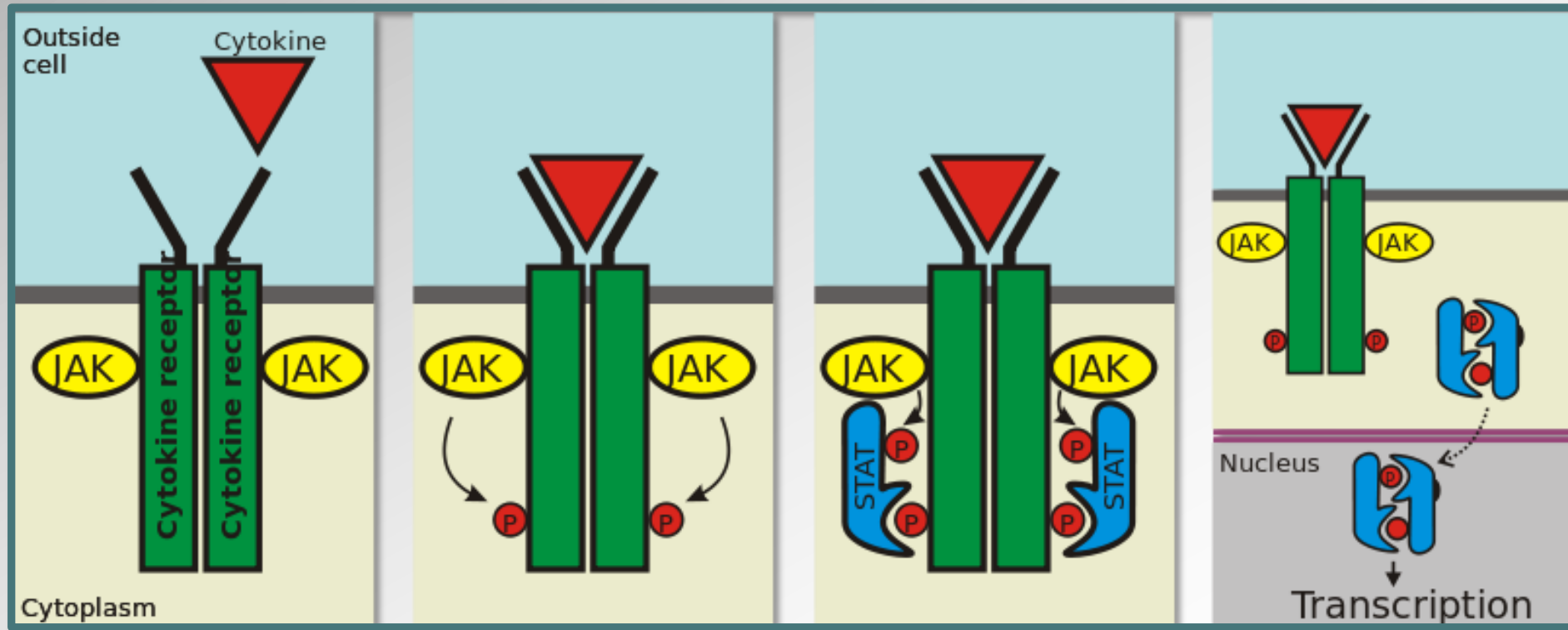
Cytokines type I receptors



| | Complex | Receptor Chain(s) | Type |
|---------------------------------|------------------|------------------------------------|---------------|
| Pollen Family Hormone Family | EPOR | EPOR | Homodimers |
| | TPOR | TPOR | |
| | GHR | GHR | |
| | PRLR | PRLR | |
| IL-6 Family | OBR | OBR | Heterocomplex |
| | GCSFR | GCSFR | |
| | IL-6R | IL-6R α | |
| | IL-11R | IL-11R α | |
| | IL-27R | IL-27R β IL-27R α | |
| | CNTF-2R | CLF-1 | |
| | CNTF-1R | CNTFR α GP130 | |
| | LIFR | LIFR | |
| | OSMR | OSMR | |
| | GLMR | GLMR | |
| | IL-12 Sub-family | IL-12R | |
| IL-23R | | IL-23R | |
| IL-4 Sub-family | IL-13R | IL-4R α IL-13R α 1 | Heterocomplex |
| | IL-13 Decoy | IL-13R α 2 | |
| IL-7 Sub-family | TSLPR | IL-7R α TSLPR | Heterocomplex |
| | IL-7R | | |
| IL-2 Family | IL-2R | IL-2R α IL-2R β | Heterocomplex |
| | IL-15R | IL-15R α | |
| | IL-4R Type I | IL-4R α IL-2R γ c | |
| | IL-9R | IL-9R α | |
| | IL-21R | IL-21R α | |
| | IL-3 Family | IL-3R | |
| | IL-5R | IL-3R β c IL-5R α | |
| | GMCSFR | GMCSFR α | |

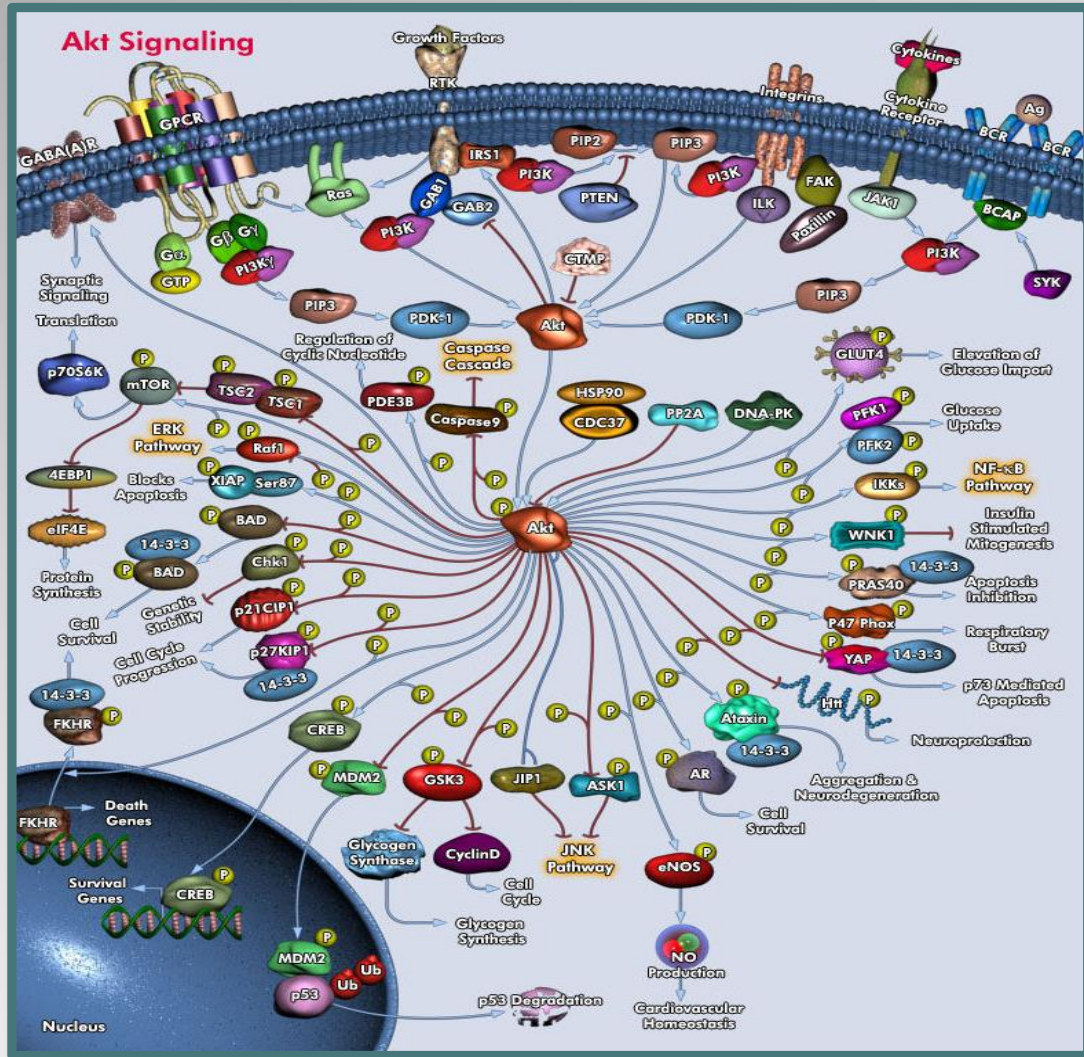
- Cytokines & receptors number in the Hundreds.
- This chart details only a small number of the cytokines identified thus far.
- Each cytokine and its receptor is highly specific.
- Some cells produce several types of cytokines and some target cells have more than one kind of receptor on their membrane. They can be stimulated by more than one kind of cytokine simultaneously.

Cytokines activate Cell Membrane Receptors



Each cytokine has a specific corresponding membrane receptor that it activates.

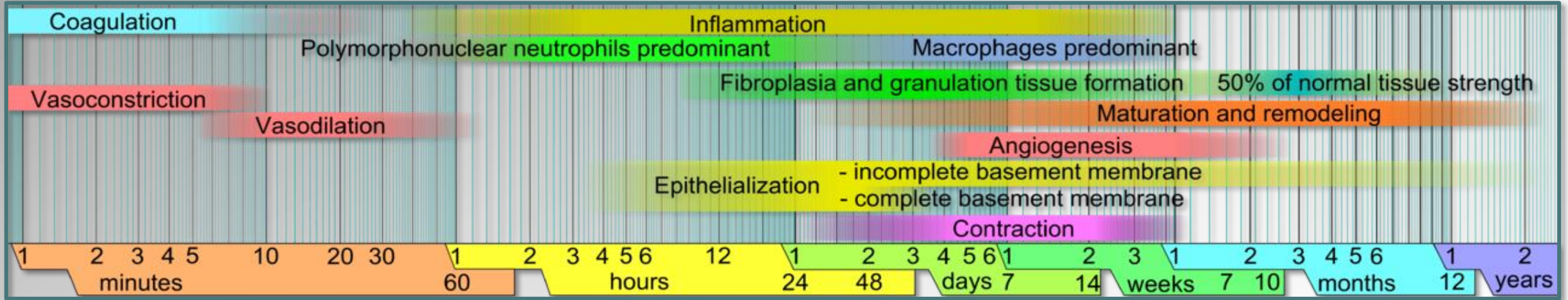
Activation initiates Cascades of Intracellular Events



- Cascades of intracellular signaling alter cell functions.
- Result in up and/or down regulation of genes and their transcription factors.
- Effect depends on cytokine, its abundance, and the presence and abundance of complementary or competing cytokines & receptors on the cell surface.
- Cytokines are characterized by considerable redundancy, in that many cytokines share similar functions.
- The net effect results from influences of competing and complementary cytokines.

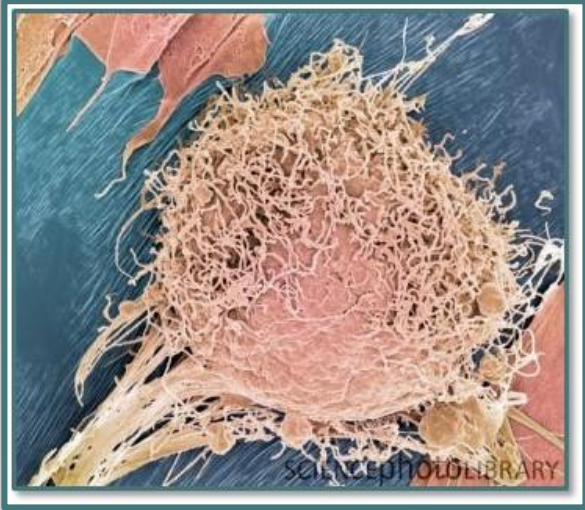
Skin Healing

Phases, Sequence & Timing of Skin Healing



- At time of injury, stopping blood loss is a priority.
- Platelets rapidly plug injured vessels.
- Pro-inflammatory cytokines are released from platelet alpha granules.
- Cytokines from platelets initiate early inflammation.

BM-MSCs: Skin's 911 Emergency Responders



- Originate in bone marrow and enter blood stream.
- Constantly “on patrol” for injury, and a major contributor to resident stem cell populations in multiple tissues.
- “Homes in” on injured tissues and acts as “command and control” of healing through secretion of cytokines (“mini-drugstore”).
- Suppresses inflammation and coordinates healing process.
- Some differentiate into tissues cells; some return to bone marrow.

- “There are a significant number of bone marrow cells that traffic through both wounded and non-wounded skin.” J Cell Physiol. 2003 Aug;196(2):245-50
- “The bone marrow contribution to normal skin and the healing cutaneous wound is substantially greater than the previously recognized.” Stem Cells. 2004;22(5):812-22.

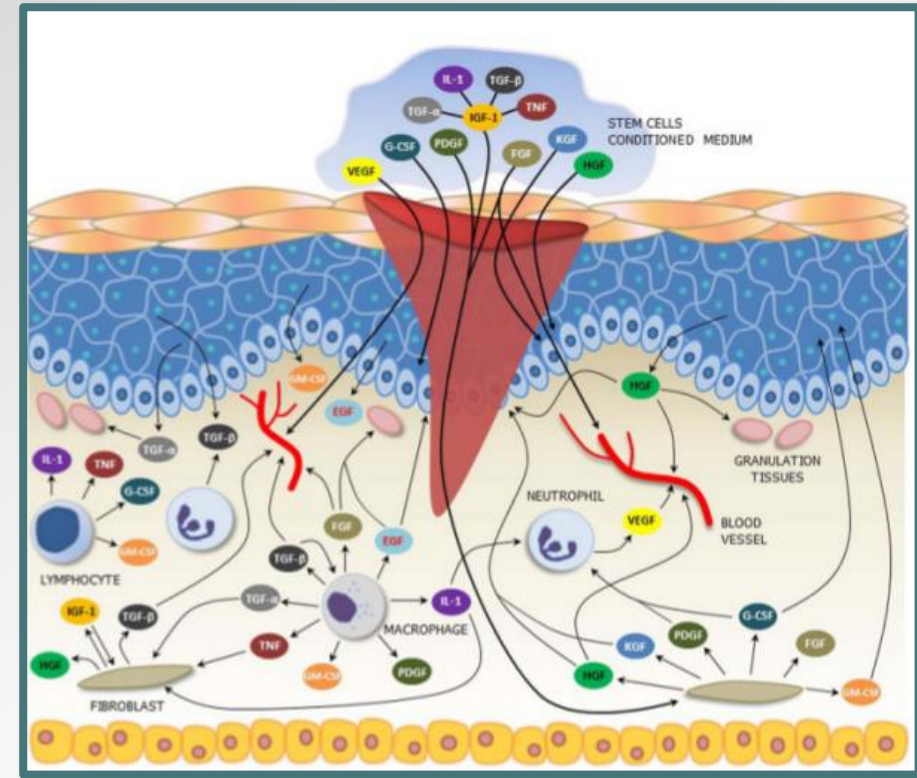
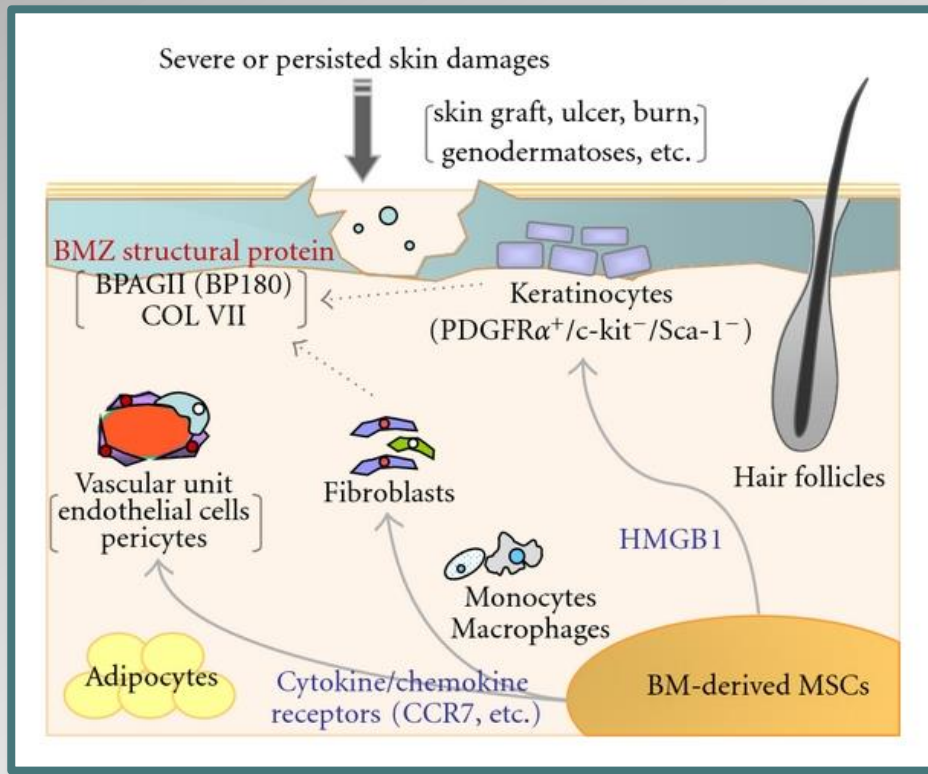
- “Bone marrow (BM)-derived stem/progenitor cells may also be attracted at distant extramedullary peripheral sites after intense injuries and participate to the tissue repair through remodeling and regeneration of damaged areas.” Stem Cell Rev. 2008 Spring
- “BM-MSC-treated wounds showed more rapid closure and increased collagen synthesis, cellular proliferation and angiogenesis. BM-MSC-treated wounds showed decreased expression of pro-inflammatory cytokines.” Tissue Eng. 2007 Jun;13(6)
- “Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds.” Tissue Eng. 2007 Jun; 13(6)



↓ Key point ↓

“...evidence shows that administration of BMSC-derived conditioned media (BMSC-CM) can recapitulate the beneficial effects observed after stem cell therapy. Bone Marrow Research Vol. 2011, Article ID 207326


Cytokines Effective from Cells or Conditioned Media



Cytokines derived from cell culture produce beneficial effects when topically applied to injured skin tissue. Cell Biology International 9999 (2013) 1–7

What Stem Cell Research Colleagues are Discovering

Conditioned Medium from Bone Marrow-Derived Mesenchymal Stem Cells Improves Recovery after Spinal Cord Injury in Rats: An Original Strategy to Avoid Cell Transplantation

Dorothee Cantinieaux, Renaud Quertainmont, Silvia Blacher, Loïc Rossi, Thomas Wanet, Agnès Noël, Gary Brook, Jean Schoenen, Rachelle Franzen 

- It's no longer about engraftment, targeted differentiation, and whole cell replacement alone.
- BM-MSC's are smart drug stores, intelligently secreting the right cytokines at the right time to effect rescue and regeneration of damaged tissues.



Stem Cell Research

Volume 6, Issue 3, May 2011, Pages 206–214

ELSEVIER

Human mesenchymal stem cell-conditioned medium improves cardiac function following myocardial infarction



ELSEVIER

Stem Cell Research

Volume 1, Issue 2, June 2008, Pages 129–137



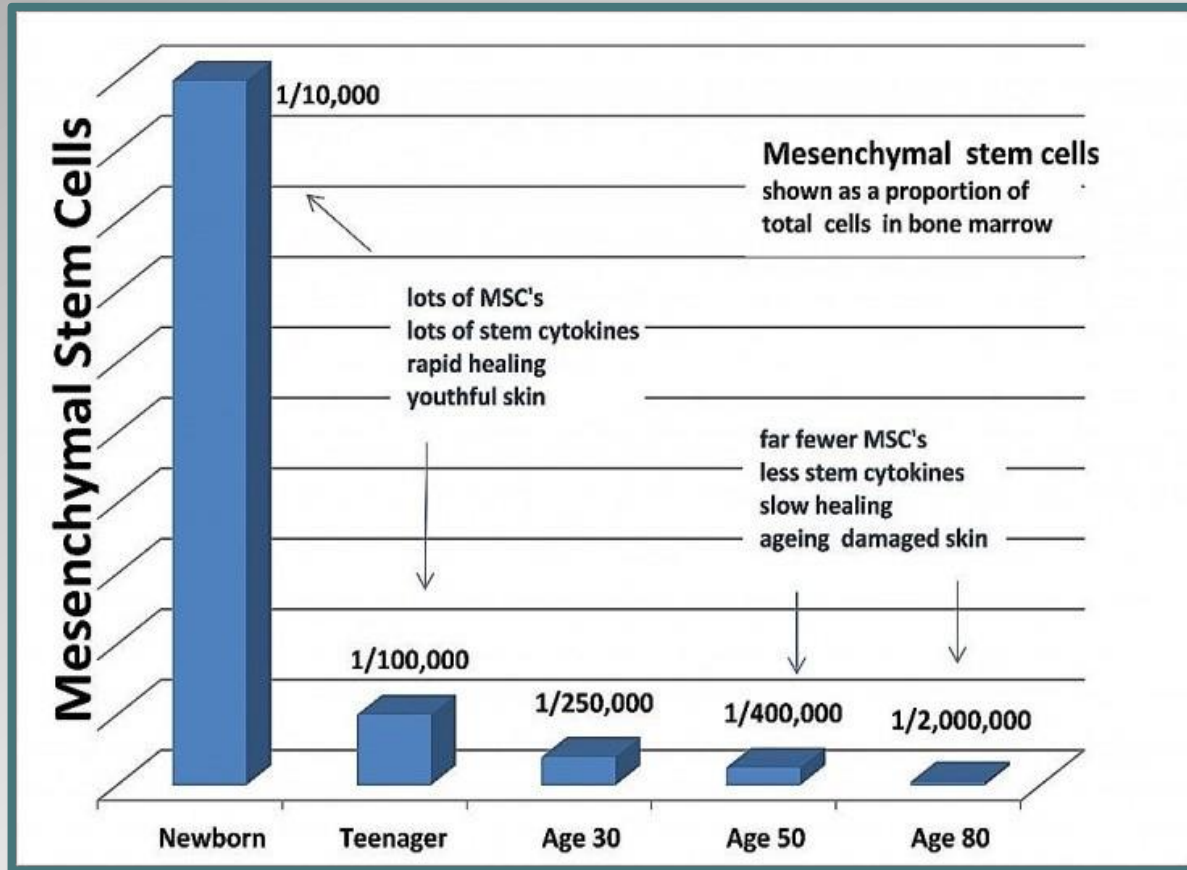
Reduction of myocardial infarct size by human mesenchymal stem cell conditioned medium

Studies confirm Skin Benefits of Topical Cytokines



- “Growth factors and cytokines, in addition to their role in cutaneous wound healing, are beneficial for skin rejuvenation...promoting skin cell proliferation and stimulating collagen formation.” [J Drugs Dermatol. 2007](#)
- “The role of growth factors and cytokines in cutaneous wound healing is well described [...]the application reduced periorbital and perioral wrinkles and improved skin texture...which confirms the beneficial use of growth factors and cytokines for skin rejuvenation.” [J Drugs Dermatol. 2007](#)
- “...demonstrate positive cosmetic and clinical outcomes of topical application of growth factors for the treatment of photodamaged skin.” [Dermatol Surg. 2005 Jul;31](#)
- “Clinical studies have shown that topical application of products containing high concentrations of a physiologically balanced mixture of cytokines appears to reverse the signs of skin aging.” [J Drugs Dermatol. 2009 May](#)
- “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 Cosmet Laser Ther. 2003 Apr](#)

Is Impaired Healing with Age related to Fewer BM-MSCs?



- The relative population of bone marrow mesenchymal stem cells declines dramatically with age.
- At age 30, there is only 4% of the relative number present at birth.
- By age 50, that number drops to only 2.5%.
- Aging skin results from decades of accumulated damage from micro-injuries, while at the same time, the cells tasked with repair decline in #.
- Fewer cells means reduced pro-healing anti-inflammatory cytokines at sites of skin injury.

Inflammation & Related Issues

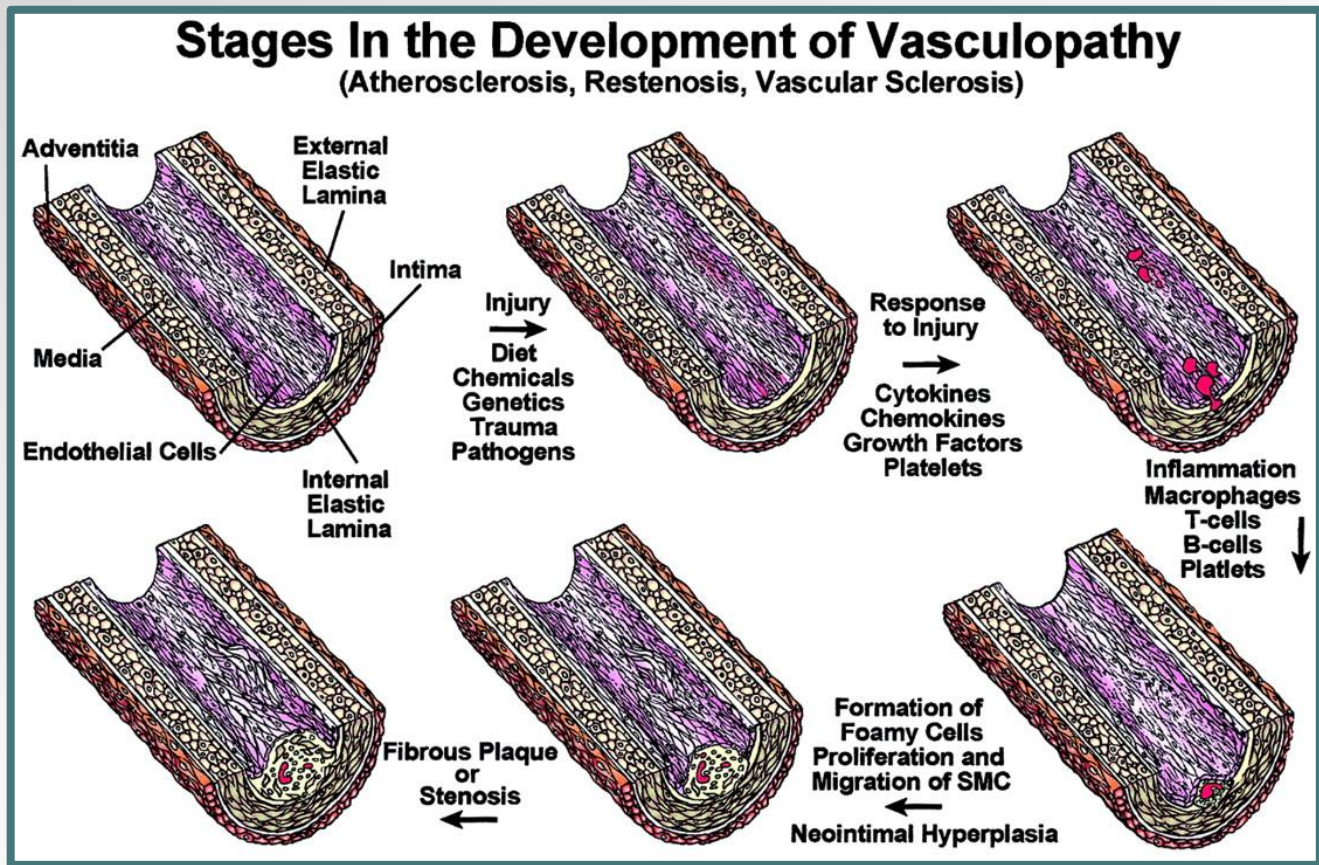
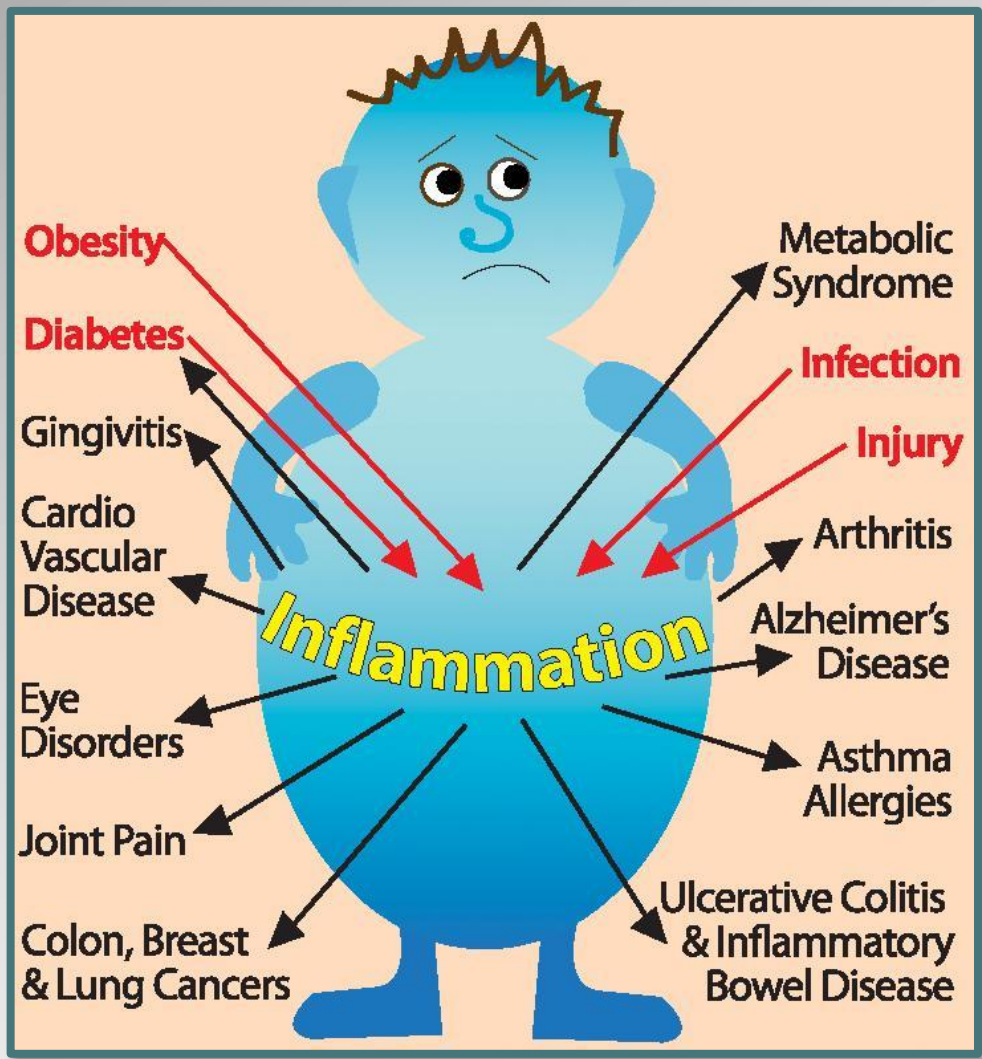
Inflammation: ~~Not Necessarily a Good Thing~~



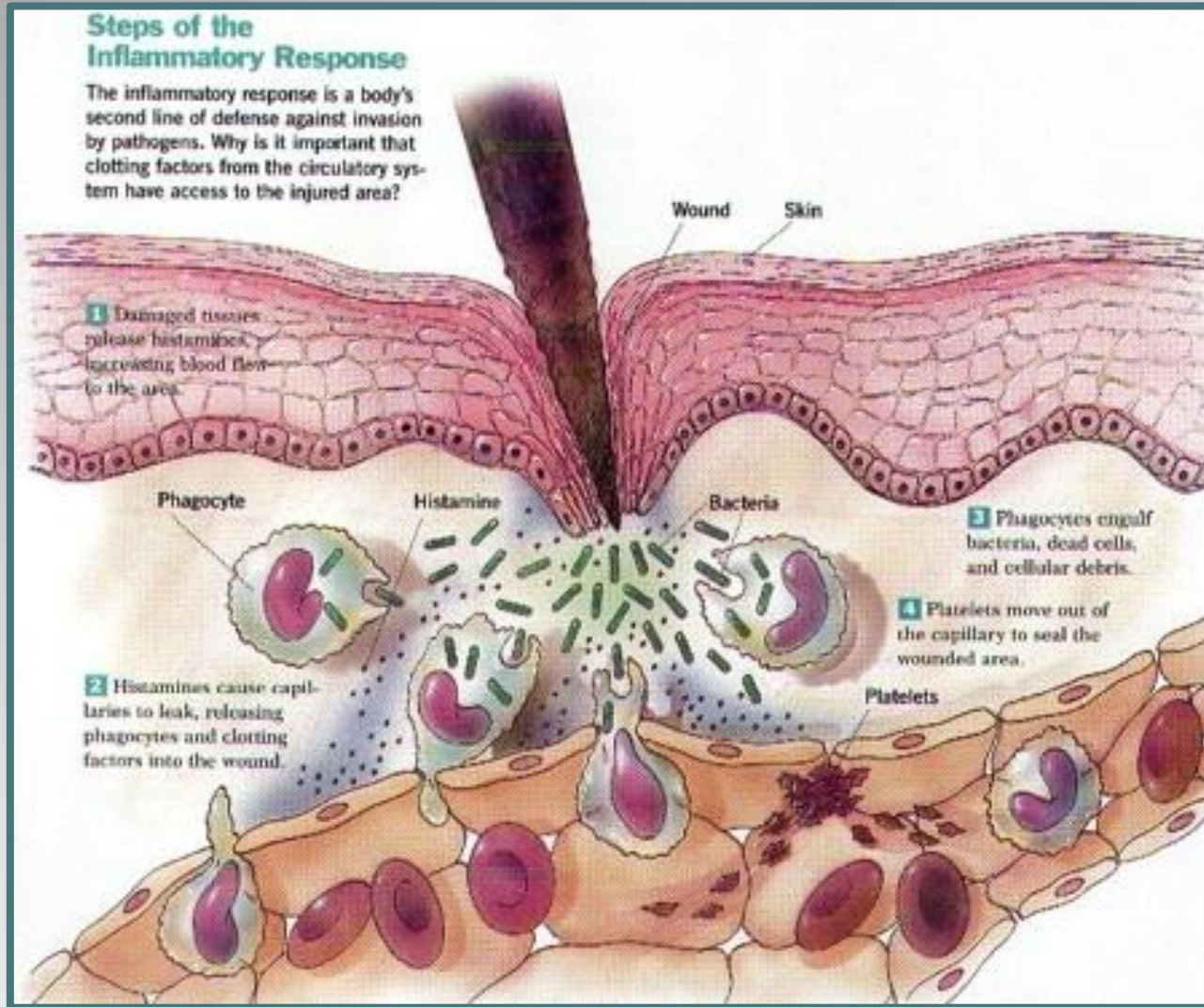
Correction, make that

Definitely Not a Good Thing !

Chronic Inflammation is Bad & Sometimes Deadly



The Evolutionary Burden of Inflammation



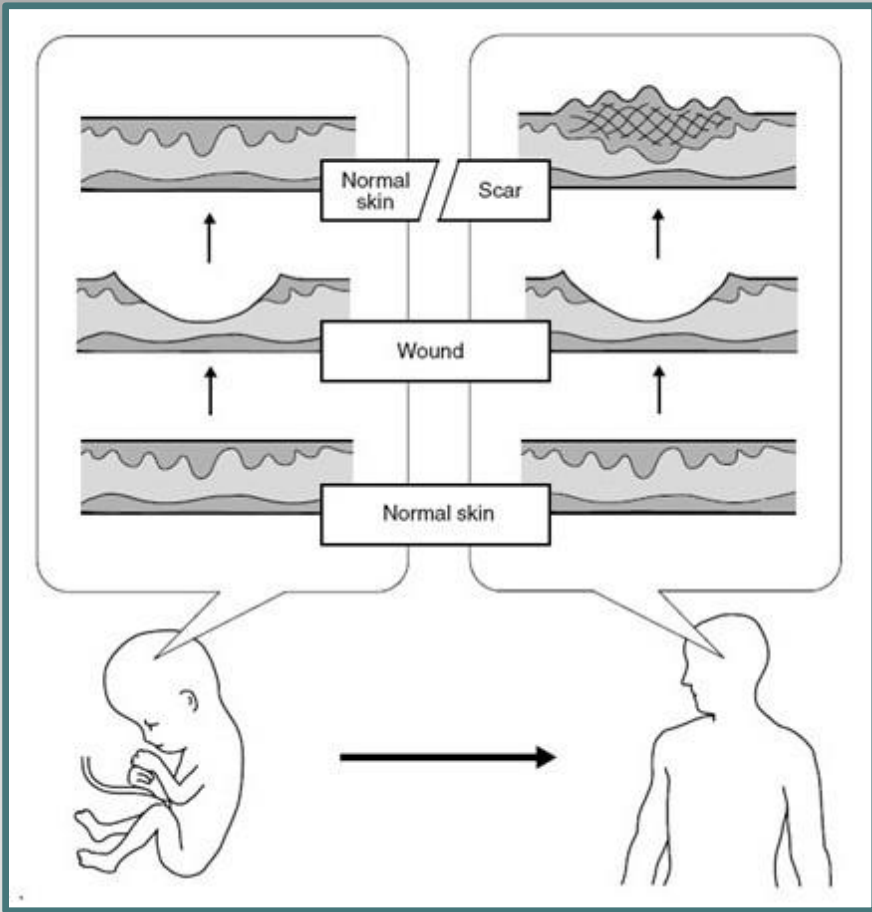
- For most of human history, the primary causes of death have included infection...it is thus not surprising that large portions of the human genome are dedicated to 2 interrelated problems: innate immunity and the inflammatory response (how to ward off infection and survive trauma) [....]
- While of obvious value with injuries from dirty rocks, sticks, and animal claws, it is often counterproductive in an era of sterile surgical incisions and modern hygiene.

“SKINflammAGING”

- Prolonged presence of ROS (reactive oxygen species) from sun exposure, toxins, and metabolic functions, produces chronic low-grade inflammation.
- Chronic skin inflammation is closely linked to aging of the skin and cancers.
- Collagen undergoes abnormal crosslinking, becoming stiff and inelastic.
- Chronic skin inflammation can lead to fibrosis, and hyper & hypopigmentation.



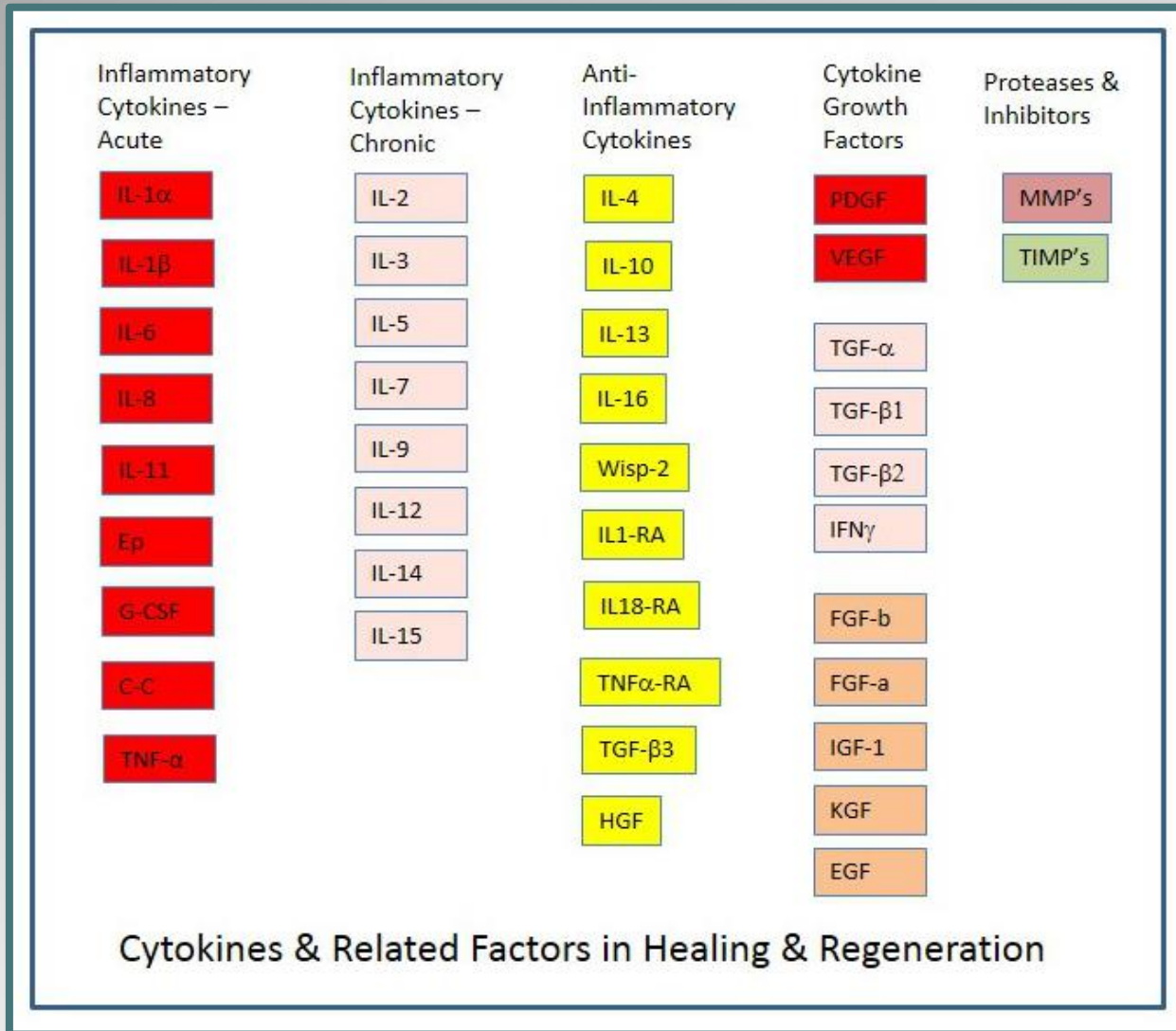
Fetal Wound Healing is Scar-free



- During the first and second trimesters, fetal skin heals rapidly and without scarring.
- **Inflammation is absent or extremely brief.**
- **Abundant anti-inflammatory cytokines e.g. TGF- β 3**
- During the third trimester, cutaneous wounds heal more slowly and with adult-like inflammation.
- Late gestation healing results in scars with over-production of densely packed, disorganized collagen.

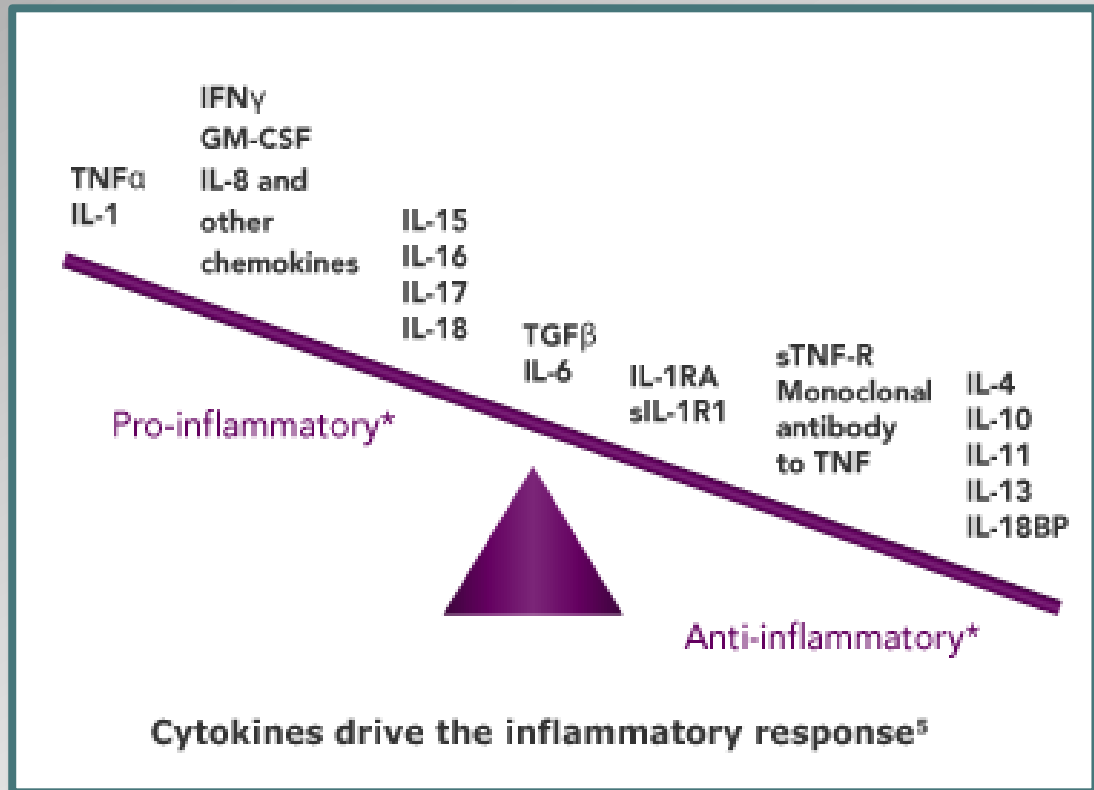
The Role of Cytokines in Inflammation

Cytokines have Pro, Anti, or Neutral Inflammatory Effect



- Cytokines do not exist in solitary isolation.
- Illustrated are the “pro” (acute and chronic), “anti”, and “neutral” major cytokines involved in skin healing.
- Different types of cells secrete different patterns of cytokines - in vivo and during laboratory culture.
- Recall that cytokines released from platelet alpha granules are pro-inflammatory.

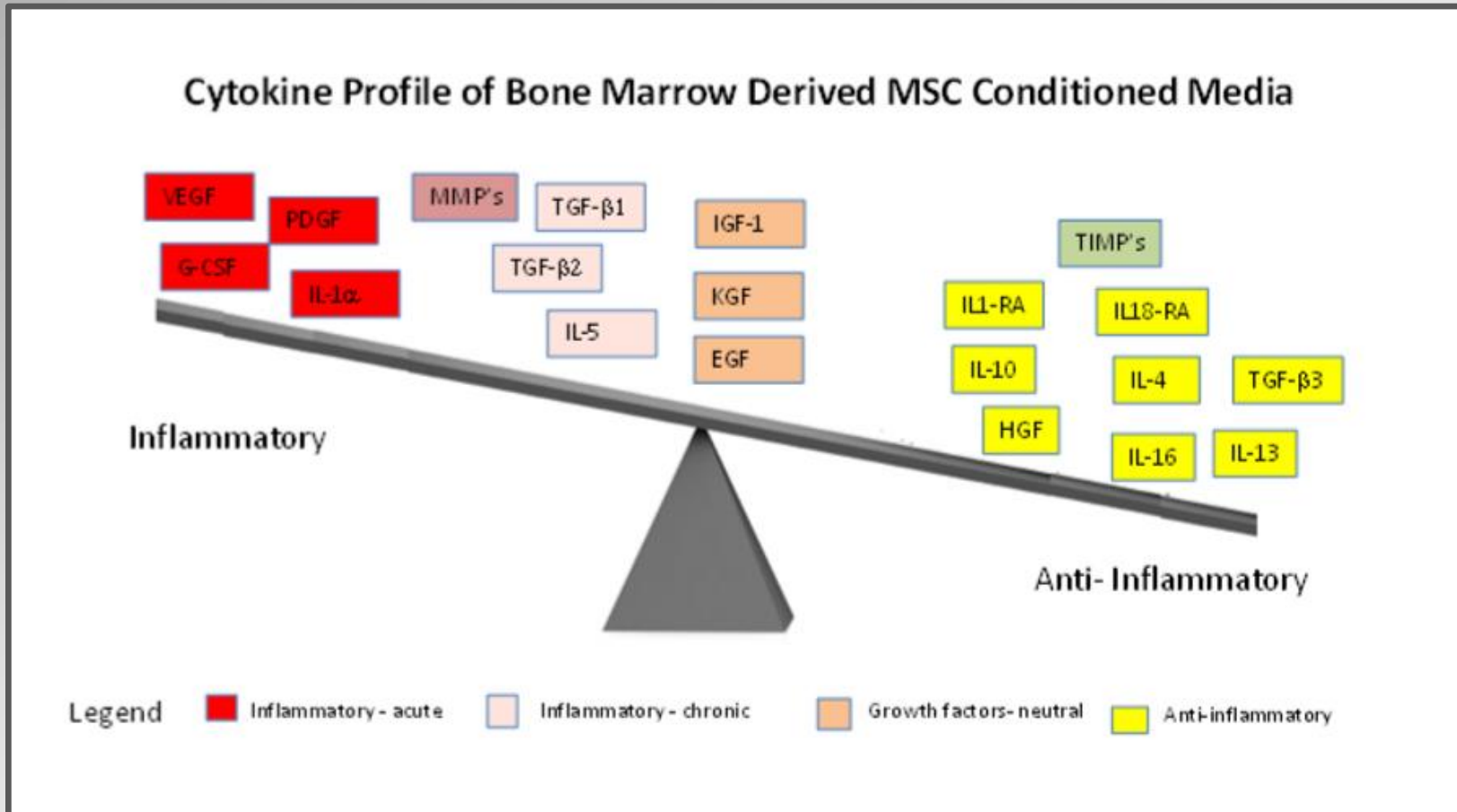
Cytokine “Net Pattern” determines Inflammatory Response



- Cytokines determine onset, duration, and severity of the inflammatory phase of healing.
- No cytokine works in isolation; it is the “net pattern” of their collective complementary and competing effects that determines the inflammatory response.
- If a more fetal-like healing response is desired (less fibrosis and dyschromia), net cytokine pattern must be anti-inflammatory.
- **Hypothesis:** providing supplemental anti-inflammatory cytokines to skin will tend to reduce deleterious effects of inflammation.

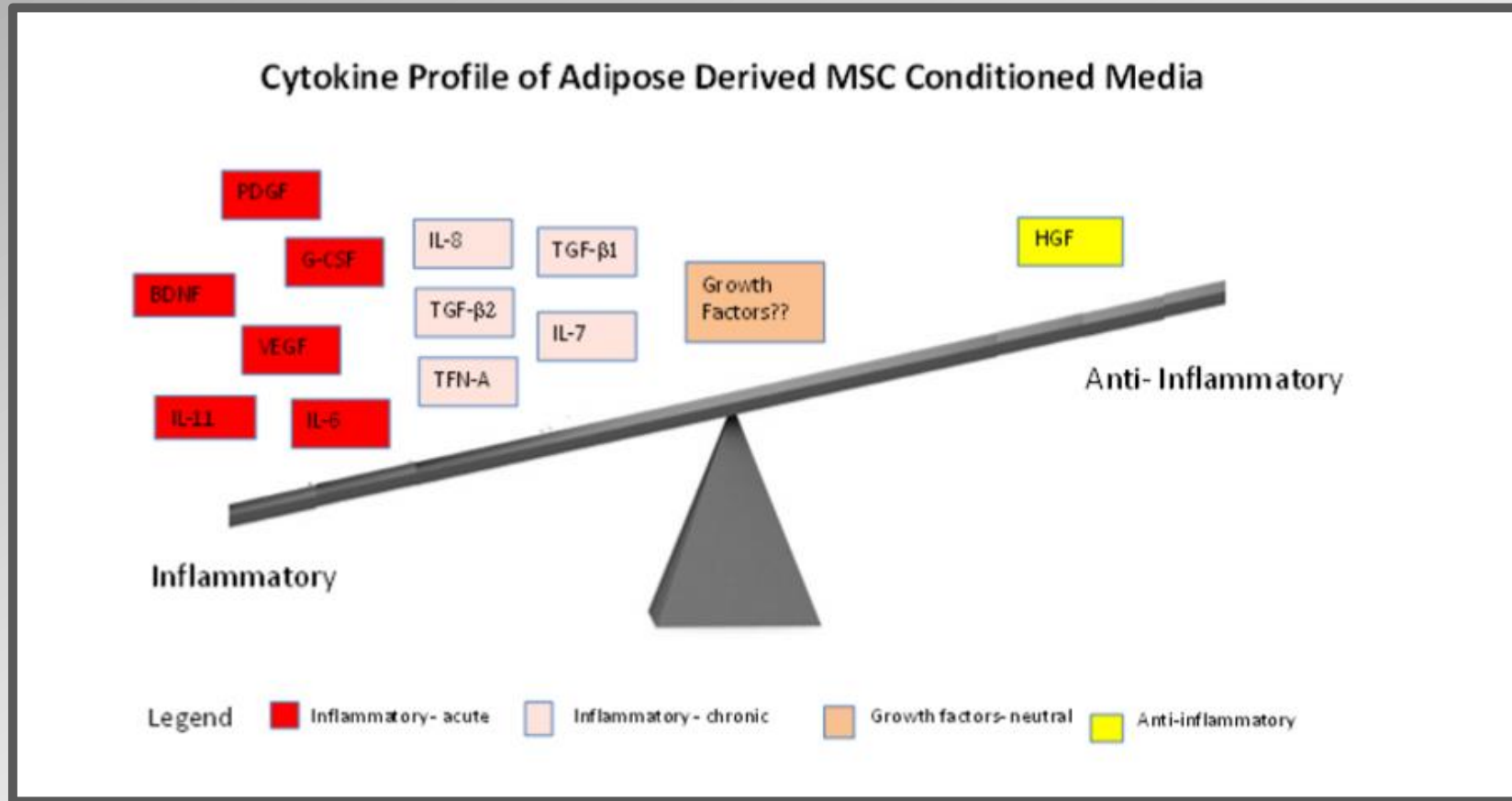
Cytokine Patterns are Origin Specific

Bone Marrow Derived Mesenchymal Stem Cell Culture



- Highly anti-inflammatory cytokine pattern.
- Cell source is volunteer donors, typically male and average age 22 years.
- Younger stem cells are more metabolically active, replicate at a more rapid rate, and produce greater quantities of cytokines and growth factors in culture.
- BM-MSC appear to have distinct advantages over other cytokine sources.

Adipose Derived Mesenchymal Stem Cell Culture



- Highly inflammatory cytokine pattern.
- Consistent with pro-inflammatory “endocrine” function of fat.
- Cell source typically liposuction waste, primarily from females, average age 53 years old.
- Obese women have higher breast cancer and recurrence rates.

New Findings: Adipose Mesenchymal Stem Cells

WJSC World Journal of Stem Cells


Online Submissions: <http://www.wjgnet.com/1948-0210office>
wjsc@wjgnet.com
doi:10.4252/wjsc.v2.i5.103

World J Stem Cells 2010 October 26; 2(5): 103-113
ISSN 1948-0210 (online)
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EDITORIAL

Adipose tissue-derived progenitor cells and cancer

Elman et al. *Journal of Inflammation* 2014, 11:1
<http://www.journal-inflammation.com/content/11/1/1>

 JOURNAL OF INFLAMMATION

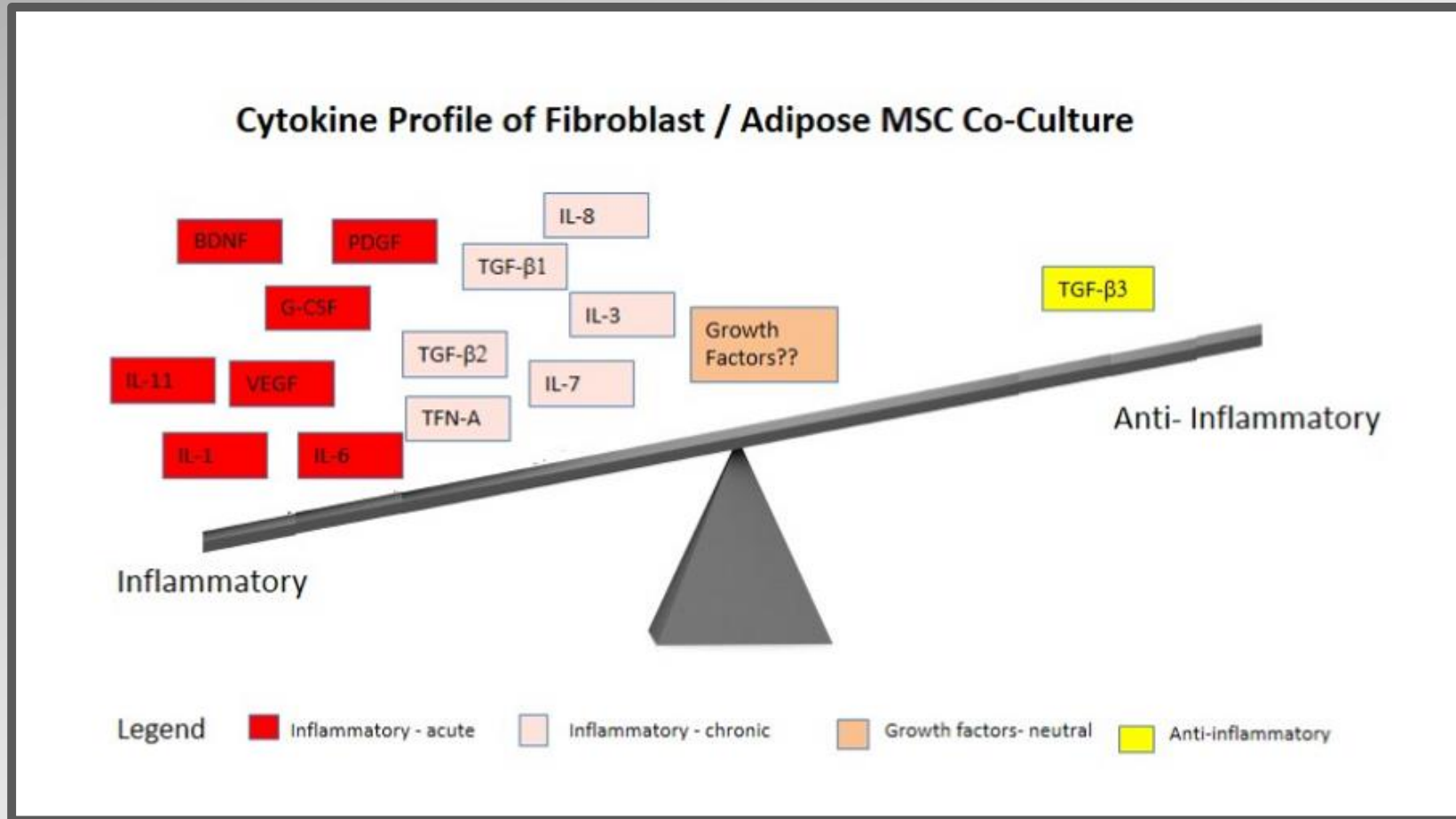
SHORT REPORT **Open Access**

A comparison of adipose and bone marrow-derived mesenchymal stromal cell secreted factors in the treatment of systemic inflammation

Jessica S Elman¹, Matthew Li², Fangjing Wang¹, Jeffrey M Gimble³ and Biju Parekkadan^{1,4*}

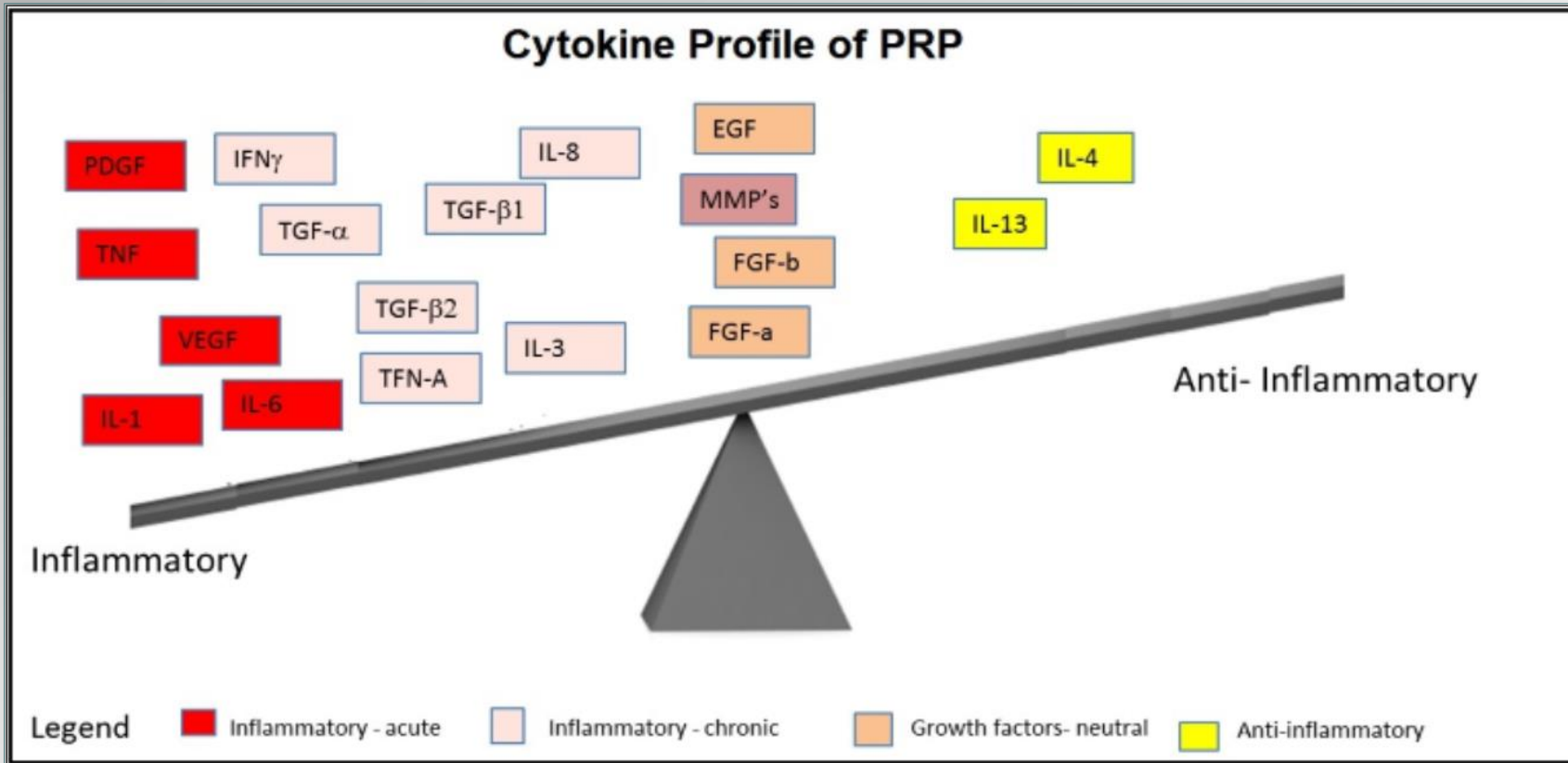
- Cytokine secretory patterns are quite “niche specific”
- Adipose-derived mesenchymal stem cells tend to produce adipokines in culture (inflammatory cytokines and hormones).
- BM-MSC secreted cytokines superior in treating systemic inflammatory conditions e.g. endotoxic shock

Co-culture - Adipose Derived MSC / Fibroblasts



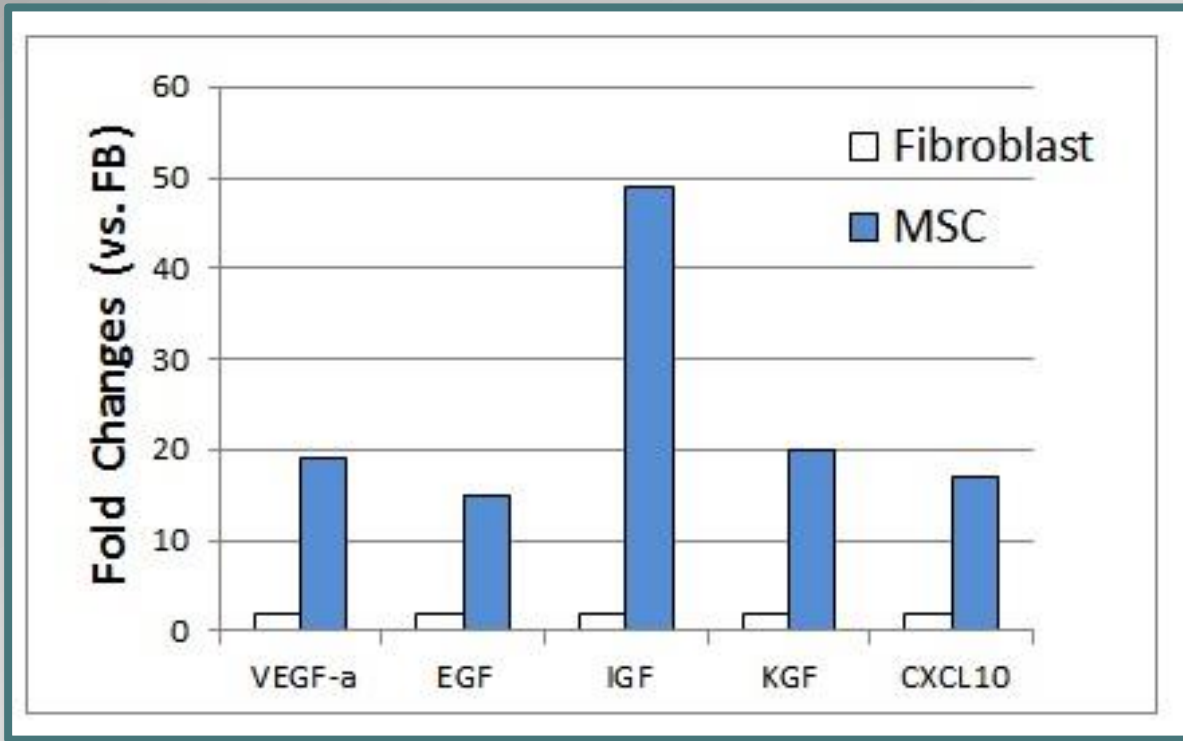
- Highly inflammatory cytokine pattern.
- Again, consistent with pro-inflammatory “endocrine” function of fat.
- Fibroblasts yield only modest amounts of cytokines and growth factors.

Platelet Rich Plasma is Pro-Inflammatory



- Autologous Platelet Rich Plasma (PRP) pattern is highly inflammatory.
- Consistent with its action at time of injury and the role of platelets in triggering inflammation.

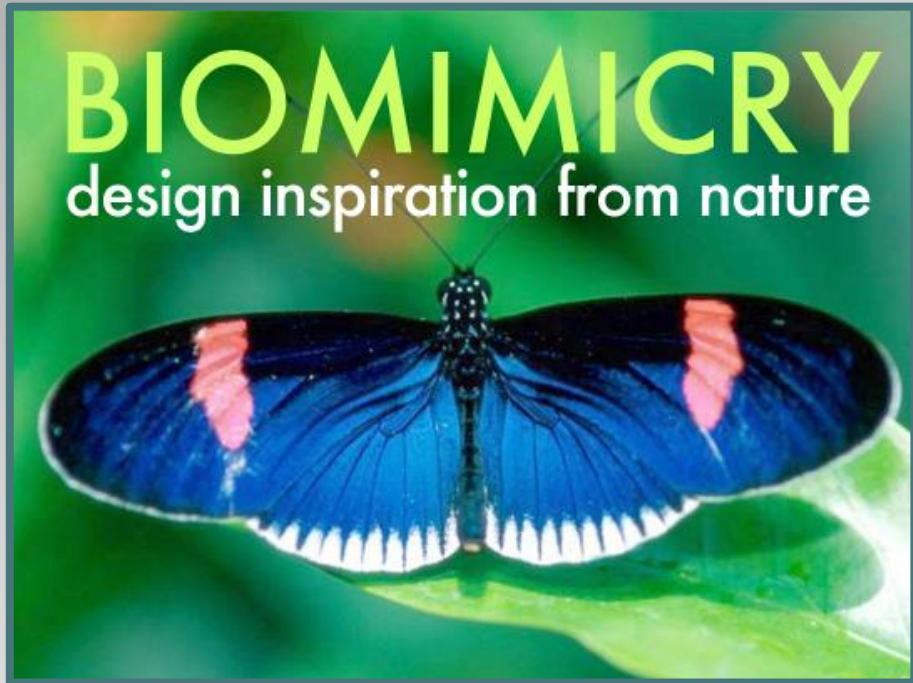
Cytokine Composition: Fibroblast vs BM-MSC Conditioned Media



- Study compared cytokines released by BM-MSCs vs. dermal fibroblasts and impact on wound healing. [PLOS ONE](#) April 02, 2008
- “Fibroblasts released high levels of IL6, a potent pro-inflammatory cytokine.”
- “BM-MSC conditioned medium enhanced migration and proliferation of keratinocytes and endothelial cells.”
- “BM-MSCs release high levels of growth factors beneficial to normal wound healing.”

The first cytokine product marketed for application to skin (13+ years) contains fibroblast conditioned media. A decade of subsequent research suggests that the preferred cell to culture for cytokine application to skin is BM-MSC.

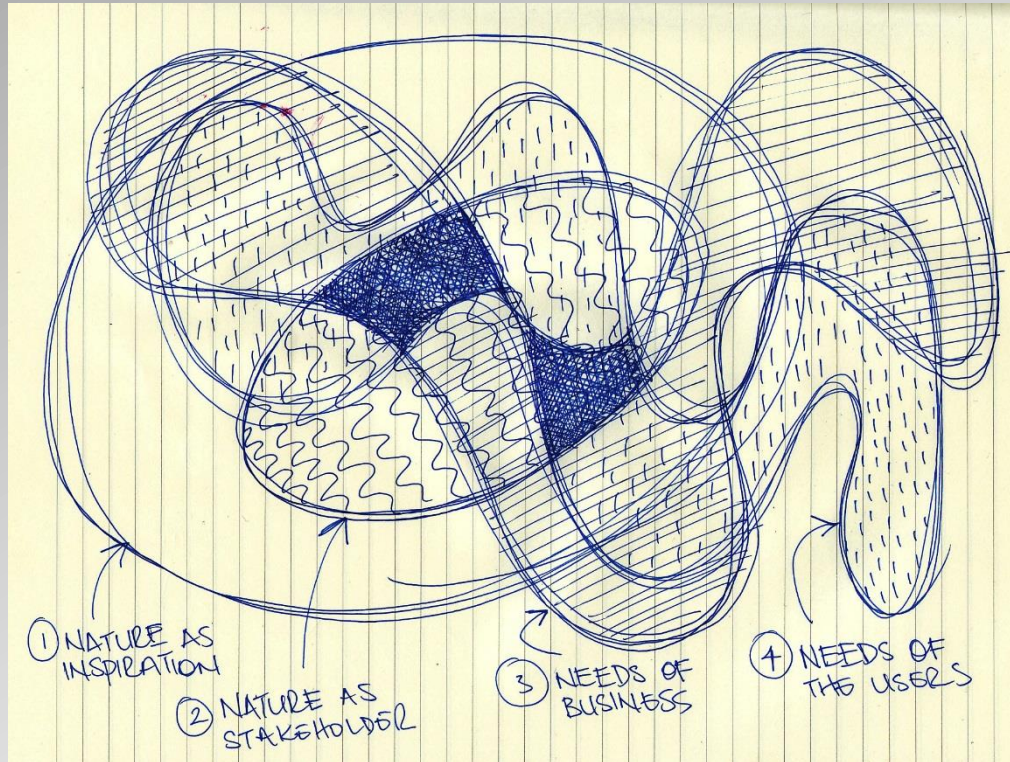
Replicating Natural Healing in the Laboratory



- Hypothesis: The secretome of BM-MSC's in laboratory cultures is not a constant, but depends on numerous variables. BM-MSC's by nature are dynamically "responsive".
- Examination of the secretory patterns of BM-MSC's (cytokines, growth factors, etc.) responses to various stimuli leads to a knowledge base of BM-MSC proteonomics.
- A proprietary platform for optimizing BM-MSC "cocktails" has emerged.

We deploy BM-MSC's not as classical "cell therapies" but as ex vivo factories for the creation of cytokine / growth factor admixtures whose net composition is based on natural mechanisms of growth, repair, and regeneration.

Taking a Page from Nature's Playbook

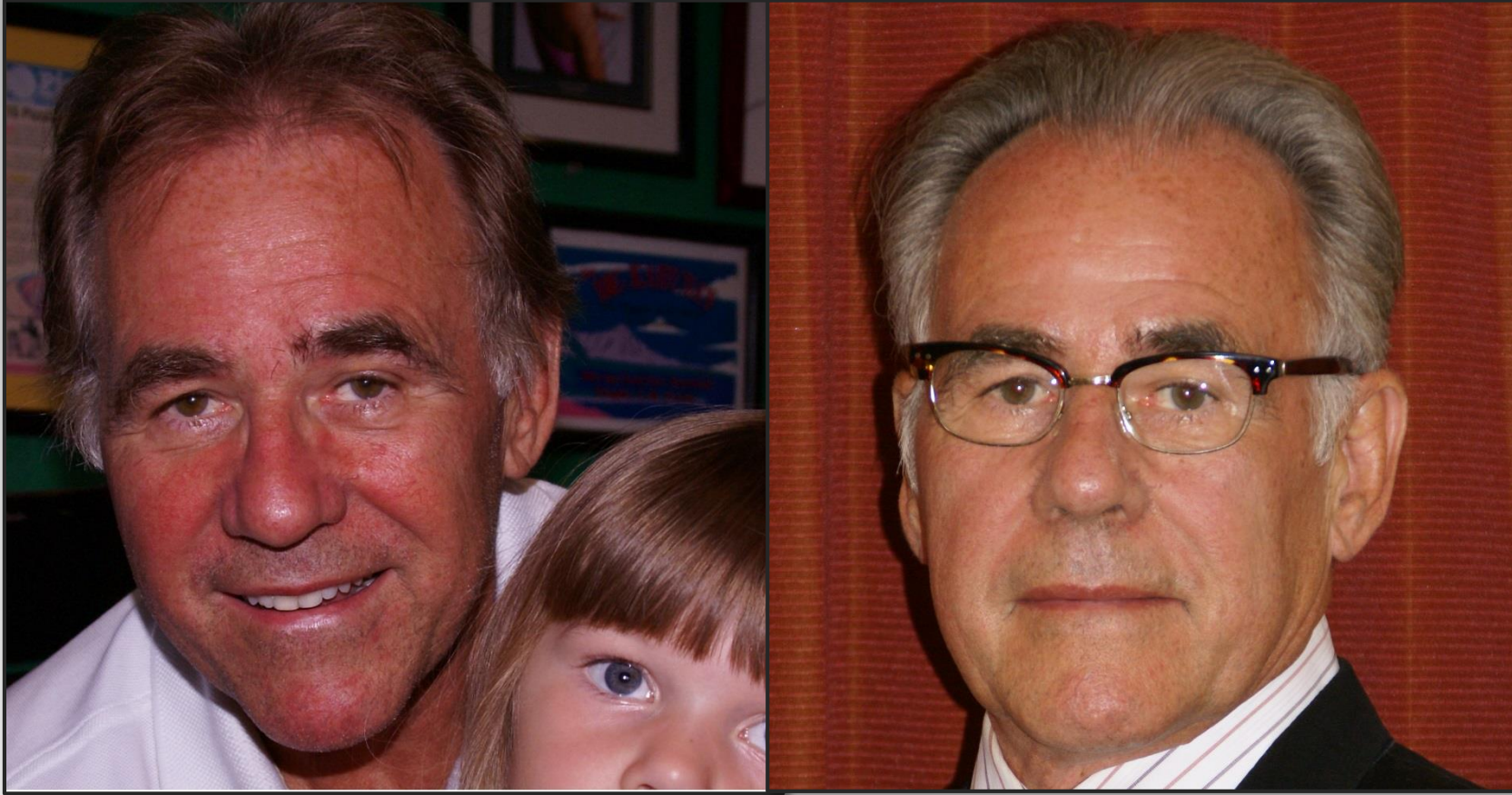


- **Hypothesis:** Topical application of BM-MSC conditioned media can mimic the effect of having a larger population of BM-MSCs secreting cytokines at sites of skin injury.
- The result is reduced inflammation and improved healing after injury, less post-inflammatory fibrosis, and reduced incidence of hyper & hypo pigmentation.
- Daily application provides an anti-aging benefit by restoring skin behavior to a “younger” state.

Topical application of BM-MSC conditioned media following medical aesthetic procedures provides anti-inflammatory and pro-healing cytokines that can result in reduced “downtime” and improved cosmetic outcomes.

Observed Clinical Benefits

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.

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
- Photos and testimonials sent unsolicited to Cellese
- Continues to use AnteAGE daily

Benefits on Acne & PIH

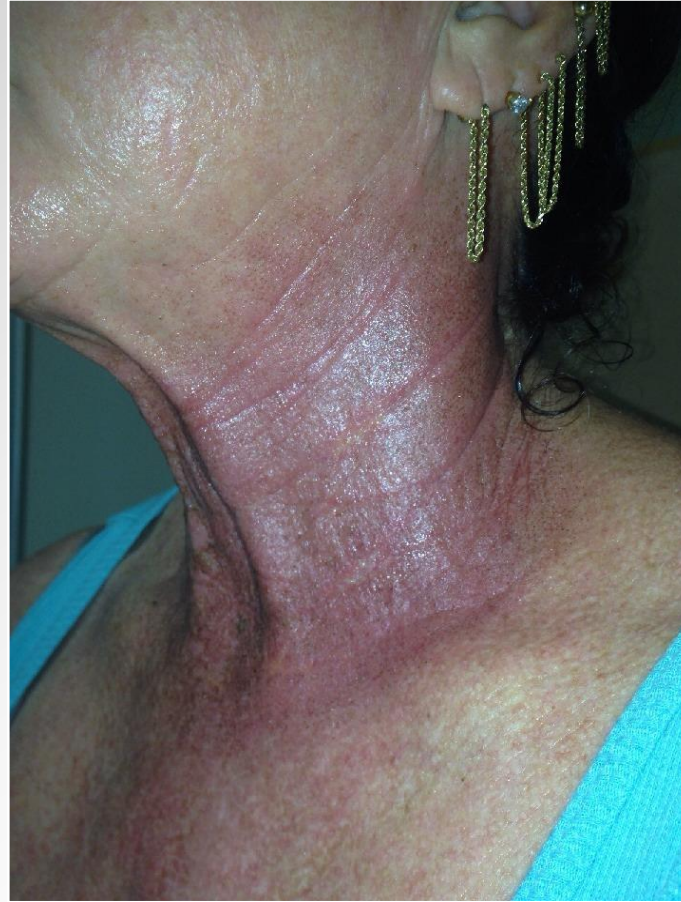


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Recovery after Fractional CO₂ Laser

AnteAGE[®]
with Stem Cytokines™
MD

“Less pain, less redness, less swelling, more peeling”



epionce
We Deliver the Beauty of Healthy Skin™

“More pain, more redness, more swelling, less peeling”

Day 3

Recovery after Fractional CO₂ Laser



AnteAGE[®]
with Stem Cytokines™
MD

Day 4

epionce.
We Deliver the Beauty of Healthy Skin™

AnteAGE® MD Shortens Recovery Time in Fractional CO2 Laser Test

Lasering USA recently evaluated AnteAGE MD Serum & Accelerator for use as a topical adjuvant to aid in recovery following fractional CO2 laser resurfacing. The President of Lasering USA tested the product on himself. His result speaks for itself.

Lasering USA has been evaluating post-laser topical products for over 5 years. We wanted a product that would shorten the down time, reduce edema, reduce erythema, and reduce the incidence of PIH (post-inflammatory hyperpigmentation) after fractional CO2 skin resurfacing. We never found such a product until now. The product is a two stage cytokine-based topical called AnteAGE MD produced by Cellese, Inc.

I was so intrigued by the science, I decided to personally test the product on myself. I was treated with our MiXto Micro Fractional CO2 laser. The treatment was rather aggressive using both the 180 micron and 300micron spot scanner with multiple passes. I wanted to put AnteAGE MD to a real test. This was the first time that this product had been used as a post-laser treatment topical.

What I found was that the edema and erythema went away on day 3 post-op and my down time ended at the beginning of day 4 post-op. Typically, post-laser down time is 6 days or more. To date (one month post-op), I have no incidence of PIH and am very pleased with the outcome. We now include AnteAGE MD as an important part of our recommended post-laser treatment protocol.

Allen R Howes
President, Lasering USA



Also Suitable for Non-Ablative Skin Treatments



Benefits using topically applied products containing BM-MSC conditioned media has been observed during recovery from non-ablative skin treatment involving varying degrees of invasiveness.

- ✓ Esthetic and medical micro-needling
- ✓ Dermarolling
- ✓ Mild and Moderate chemical peels

Daily Anti-aging Skincare Regimen Second to None



22 month experience with
consumer version of AnteAGE

- Extremely high user satisfaction scores
- Extremely high online re-order rate
- Estheticians report nearly 100% re-sale rate to existing customers.
- Refunds nearly non-existent (<0.1%)

Cellese Product Pipeline

Cellese continues to pursue discovery leading to innovative products utilizing the stem cytokine platform.



Areas of intense interest include:

- Rosacea & other inflammatory dermatoses
- Regeneration / activation of hair follicles
- Restoration of melanogenesis (hair color)
- Wound healing (minor cuts, abrasions, burns)
- Fibrosis & scarring prevention
- Improved results from aesthetic procedures
 - CO2 lasers, dermabrasion, hydrafacial
 - Plastic surgery, microneedling
 - Adjuvants to fillers & implants

Celесе Product Pipeline

Celесе is also exploring elements high on the periodic table
As bases for dermatologic therapeutics

A hand-drawn periodic table with two elements circled in red: Hydrogen (H) and Boron (B). The table is color-coded by groups: Group 1 (H, Li, Na, K, Rb, Cs) is pink; Group 2 (Be, Mg, Ca, Sr, Ba) is light pink; Groups 3-10 (Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn) are light green; Group 11 (Ag, Au) is yellow; Group 12 (Cd, Hg) is light blue; Group 13 (B, Al, Ga, In, Tl) is light yellow; Group 14 (C, Si, Ge, Sn, Pb) is light green; Group 15 (N, P, As, Sb, Bi) is light pink; Group 16 (O, S, Se, Te, Po) is light blue; Group 17 (F, Cl, Br, I, At) is light yellow; Group 18 (He, Ne, Ar, Kr, Xe, Rn) is light blue. The elements H and B are circled in red.

| | | | | | | | | | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| H | | | | | | | | | | | | | | | | | He |
| Li | Be | | | | | | | | | | | B | C | N | O | F | Ne |
| Na | Mg | | | | | | | | | | | Al | Si | P | S | Cl | Ar |
| K | Ca | Sc | Ti | V | Cr | Mn | Fe | Co | Ni | Cu | Zn | Ga | Ge | As | Se | Br | Kr |
| Rb | Sr | Y | Zr | Nb | Mo | Tc | Ru | Rh | Pd | Ag | Cd | In | Sn | Sb | Te | I | Xe |
| Cs | Ba | La | Hf | Ta | W | Re | Os | Ir | Pt | Au | Hg | Tl | Pb | Bi | Po | At | Rn |

- **Hydrogen** – superior free radical quencher
- **Boron** – non toxic superior anti-inflammatory, antibacterial, antifungal

