

A primer on combined Fibroblast and Adipose Stem Cell Conditioned Media as a skincare ingredient.

Quick question for our BFT readers, especially those who have been keeping up with our series on cell culture derived bio-signals in skincare:

What would prompt a company to launch a product line combining the weak bio-signals produced by fibroblasts in culture with the highly pro-inflammatory ones produced by adipose (fat) derived stem cells?

That seems illogical to BFT and the literature - some of it recent - confirms that this is a bad idea.

For the record, BFT has no quarrel with anyone taking advantage of a legitimate and legal opportunity to make money. That's the American Dream. Your humble hosts, DrJohn and DrGeorge, have been busy these past few years doing the very same thing.

From day one, however, one of our missions has been to empower our readers with the knowledge necessary to make informed choices about how they invest their skincare dollars.

There are a number of cell culture-based products available. Before you open your wallet to buy products containing combined fibroblast and adipose derived stem cell conditioned media, you should take a few minutes to arm yourself with the science required to make an informed decision on whether or not this kind of product is for you.

A NEW GROWTH FACTOR "STORY": MULTIPLE CELL TYPE CULTURES

The April 2014 issue of The Journal of Drugs in Dermatology made it clear that dermatologists are lining up in agreement that topical bio-signals play an important role in skincare. In a feature article, Cytokines and Growth Factors were placed at the top of the Skin Health and Beauty Pyramid - above retinoids, above alpha hydroxyl acids, above sun blocks, above everything.

This is the major reason that new growth factor and cytokine products have multiplied in number over the past couple years.

Often, their stories lack important significant details about the underlying science. We feel this is one of those instances.



NEW MEANS BETTER? DON'T BELIEVE IT.

While "better" can be crafted into seductive-sounding prose that entices the non-scientist consumer to buy, BFT advises caution. The science of a fibroblast / fat stem cell culture combination doesn't confirm better, it confirms lack of understanding of the basic physiology of tissue healing and the negative role inflammation can and does play in that process.

That's a question we continue to ask, perhaps into the cone of silence, since no one has yet given us an answer.

Why would anyone want to apply daily skincare products that promote inflammation when it has been known for decades that inflammation actually promotes tissue aging? And what about the very well-known relationship between inflammation and the promotion of fibrosis (scarring) and hyperpigmentation?

And, fibroblasts? The bio-signals produced by them are so paltry that the first-generation product produced using fibroblast conditioned media contains more than 93% conditioned media, which because of the protein content gives TNS an odor that some people are not fond of. Smelly gym locker, anyone?

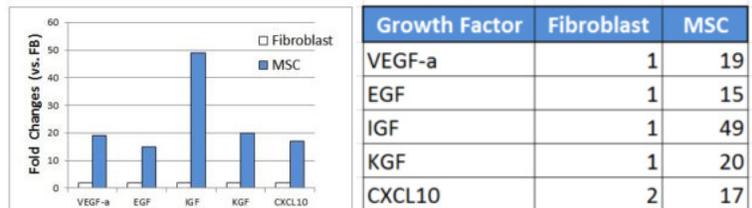
And if it takes that amount to get any oomph, there is no room in the formulation to add other recommended actives; that means buying numerous products and maintaining a complicated skincare routine.

Let's get to specifics.

FIBROBLASTS

Fibroblasts are nice enough cells and because our bodies contain enormous amounts of connective tissue, they are the second most abundant cell in the body, surpassed only by red blood cells. The job of fibroblasts is to produce collagen, elastin, reticular fibers and matrix. When it comes to producing bio-signals, they're weaklings; when it comes to providing structure and strength to tissues and organs, they're bodybuilders supreme.

Compared to the stem cell we champion, the bone marrow mesenchymal stem cell, fibroblasts are very puny, indeed. The images below show the comparative output of important biosignals by fibroblasts and bone marrow mesenchymal stem cells. In the graph, the small white bars indicate 1X of these biosignals, the amount produced by fibroblasts in culture. Below that is a chart that indicates how many fold increase is produced by bone marrow mesenchymal stem cells in culture.



But that's only part of the story. Several of the bio-signals produced by fibroblasts are pro-inflammatory e.g. TGFb1, IL-1b, IL-6, IL-33.

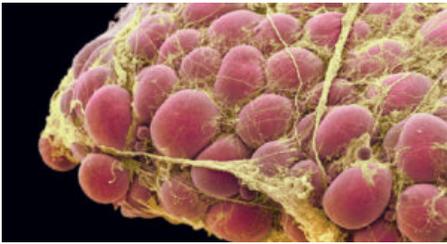
Furthermore, fibroblasts don't give orders, they take them. Their orders come from the migratory bone marrow mesenchymal stem cells that patrol our tissues via the vasculature. These cells arrive at sites of injury and produce the bio-signals that instruct neighboring cells, including fibroblasts, what to do and when to do it. In skin physiology and healing, fibroblasts are following orders, not giving them.

The two articles below cover this in some detail. Rodent wound models show significant healing with bone marrow stem cell conditioned media applied; fibroblast conditioned media did no better than media in which no cells whatsoever were grown. Puny producers of biosignals. Puny, indeed.

Mesenchymal stem cells induce dermal fibroblast responses to injury *Experimental Cell Research* Volume 316, Issue 1, 1 January 2010, Pages 48-54

Fibroblasts in fibrosis: novel roles and mediators *Front Pharmacol.* 2014;5:123

ADIPOSE (FAT) DERIVED STEM CELLS

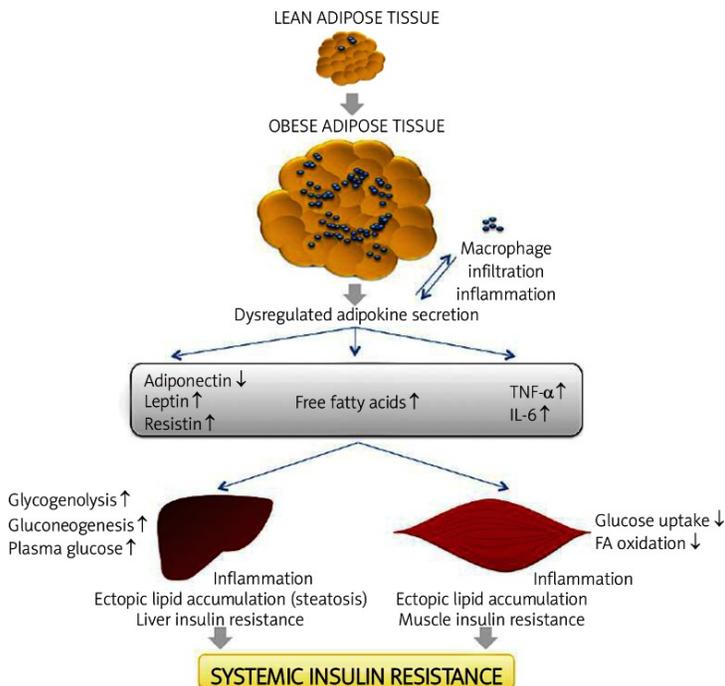


Fat has long been recognized as an endocrine organ, secreting a variety of bio-signals that can have negative physiologic consequences. As the amount of body fat increases, the negative effects are compounded.

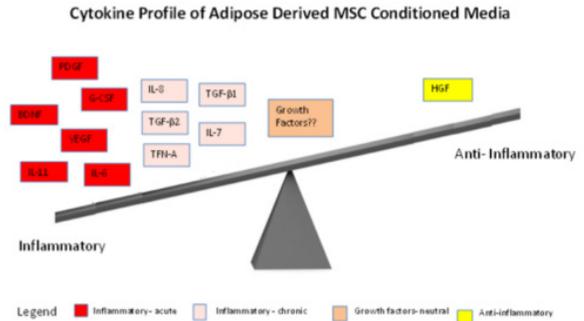
The quote below is from an article entitled: Biochemistry of adipose tissue: an endocrine organ *Arch Med Sci.* 2013 Apr 20; 9(2): 191-200.

"[...]As an endocrine organ, adipose tissue is responsible for the synthesis and secretion of several hormones. These are active in a range of processes, such as control of nutritional intake (leptin, angiotensin), control of sensitivity to insulin and inflammatory process mediators (tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), resistin, visfatin, adiponectin, among others) and pathways (plasminogen activator inhibitor 1 (PAI-1) and acylation stimulating protein (ASP) for example)."

The biologic effects of these bio-signals are numerous, as demonstrated in the accompanying diagram.

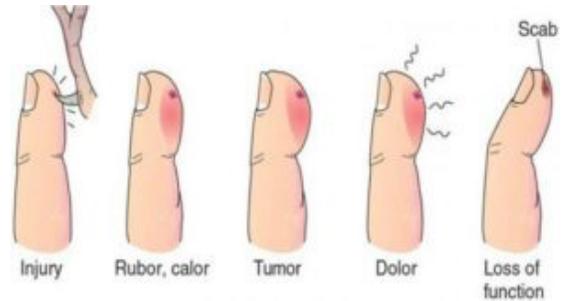


Not surprisingly, adipose (fat) derived stem cells also have a highly pro-inflammatory cytokine profile. Hence, these are the bio-signals contained within the conditioned media when fat stem cells are cultured in the laboratory. The balance beam graphic is highly pro-inflammatory.



What does that mean for products that contain fat stem cell conditioned media? It means that the net biologic effect on the skin will be to promote inflammation, and daily use will produce a chronic inflammatory stimulus which is not anti-aging at all, but the exact opposite. Not a good idea.

HOW INFLAMMATORY STIMULATION CAN PRODUCE POSITIVE CHANGES IN SKIN APPEARANCE – FOR A WHILE.



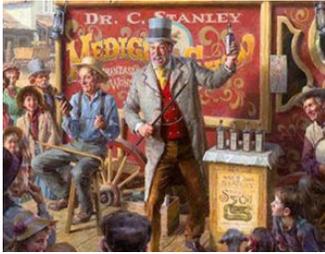
Inflammation can be "clinical", with all of the manifestations seen in this injured finger example. We are all familiar with that phenomenon. Inflammation can also be "subclinical", meaning that despite the fact that some of the classic signs are not evident, inflammation is present nonetheless. Chronic smoldering internal inflammation is present in many diseases and conditions of advanced age, most notably diabetes and atherosclerosis.

You can see from the finger example above that one of the hallmarks of inflammation is edema, or swelling, called tumor in Latin. It is BFT's strongly held conviction that the edema that is present, even with subclinical inflammation, is what gives the appearance of smoother, plumper skin with many products - the edema associated with inflammation can make fine lines disappear, for a while.

It is well proven that inflammation is pro-aging in all tissues. It is also well proved that inflammation contributes to fibrotic healing (scarring) and melanocyte stimulation, the reason that darker skin types are susceptible to post-inflammatory hyperpigmentation after any kind of injury to the skin. Does chronic subclinical inflammation of the skin sound like something desirable as an anti-aging strategy?

Not to us. Therefore the decision to produce a combination product containing conditioned media from fibroblasts and adipose derived stem cells is perplexing and irrational.

BEWARE WHAT STORIES YOU BELIEVE.



But, hey, no one ever said that skincare products have to make scientific sense; they just have to have a story that can be massaged into a marketing meme that can be parlayed into cash flow.

Perfect examples are plant “stem cell” products which have been around for years. To the unwary, it’s easy to pass off as plausible any number of stories. Here’s just three:

- A type of Swiss apple, grown preferentially during the 1800’s because of its ability to be cellared for long periods of time without shriveling and rotting, makes it the perfect stem cell “source” to help prevent and treat wrinkles in human skin.
- The Alpine edelweiss, which grows at high altitudes and thrives while being bombarded with increased UV exposure from the sun, is the perfect stem cell “source” for products that prevent and help repair the skin damage of sun exposure.
- Because date palms thrive in very arid and hot climates, they are the perfect “source” for stem cells that can help protect the skin from the effects of arid and hot conditions.

A bit of scientific reflection is all that is required to debunk these sales pitches as nonsense, but such products sell.

Now, admittedly, we are not talking such craziness here, fibroblast and fat stem cell culture-derived products have a much more plausible marketing story. In fact, “two-for-one” alone may entice purchasers to give it a try. But, just as two wrongs don’t make a right, two non-suitable cell types don’t make a superior skincare product.

It’s the details of the kinds of human bio-signals produced in culture that are important. Know and understand the details.

WHERE DO THE FIBROBLASTS AND FAT STEM CELLS COME FROM?



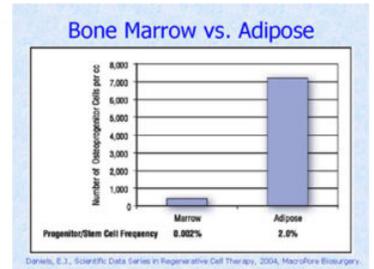
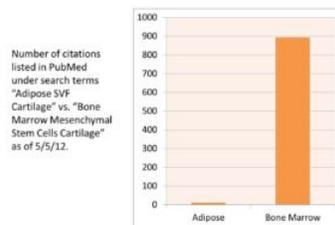
Were it not for their use in cell culture, the tissues sources for fibroblasts and fat stem cells would be incinerated as medical waste. Fibroblasts are typically sourced from the discarded foreskins of circumcised male infants, and fat stem cells from the fat removed from middle-age women during liposuction. Fibroblasts and fat stem cells are therefore plentiful, easy to obtain and inexpensive.

INTERESTING COMPARISONS OF FAT STEM CELLS TO BONE MARROW STEM CELLS

Stem cells have been investigated in medical research and practice for well over two decades. Recently the global number of research articles that examined the basic physiology, characteristics and clinical used of stem cells surpassed 300,000! All types and sources of stem cells have been studied, with nearly 2/3 of them focusing on bone marrow stem cells which have proved superior to all other types in many ways. One major use of stem cells in clinical practice has been in orthopedics to aid in regeneration and treatment of cartilage disorders. The graph below shows that bone marrow stem cells have received the greatest scrutiny.

Of particular interest is the fact that adipose stem cells are so much more plentiful and easier to obtain, yet bone marrow stem cells continue to be the “go to” cell in regenerative and therapeutic medical applications. This should not be surprising since this is their physiologic role throughout life - repair and regeneration of damaged tissue. The physiologic role of fat stem cells? Make more fat; nothing more.

The published data on adipose SVF vs. bone marrow stem cells (MSCs) for cartilage repair?



Despite being relatively much less plentiful within their tissue “niche”, which makes them more difficult to obtain, bone marrow stem cells continue to be the preferred stem cell type for medical research and therapies.

ADDITIONAL THINGS TO PONDER ABOUT FAT STEM CELLS

Procoagulant activity of human mesenchymal stem cells

J Trauma Acute Care Surg. 2017 Jul;83(1 Suppl 1):S164-S169.

[.....] All MSC populations are not equivalent; care should be taken to select cells for clinical use that minimize potential safety problems and maximize chance of patient benefit. Adipose-derived MSCs seem more consistently pro-coagulant than BM-MSCs, presenting a potential safety concern...

A Proinflammatory Secretome Mediates the Impaired Immunopotency of Human Mesenchymal Stromal Cells in Elderly Patients with Atherosclerosis

Stem Cells Translational Medicine 2017.6:1132-1140

[.....] Elderly adipose MSCs exhibited a pro-inflammatory secretome with increased levels of IL-6, IL-8, CXCL8, and MCP-1/CCL2. (BFT note: the summary is that the older the source of the fat stem cell, the more inflammatory will be its secreted biosignals. Fat stem cells in skin products are sourced from liposuction waste. The average liposuction patient in the U.S. is an overweight female in her early fifties.)

Review Article: Advances in Adipose-Derived Stem Cells Isolation, Characterization, and Application in Regenerative Tissue Engineering.

Stem Cells International, Vol 2016, article ID 3206807

[.....] ADSCs may exert unintended paracrine and endocrine effects on peripheral tissues (through) secretion of metabolically active hormones such as leptin and cytokines such as TNF- α and IL-6...Obese derived ADSCs induce a pro-inflammatory response... (BFT note: patients undergoing liposuction, the source of ADSCs commercially, are not lean but significantly overweight.)

Platelet-Derived Growth Factor BB Enhances Osteogenesis of Adipose-Derived but Not Bone Marrow-Derived Mesenchymal Stromal/Stem Cells.

Stem Cells 2015 Sep;33(9):2773-84

BM-MSCs and ASCs cultured under identical osteogenic (bone forming) conditions responded differently with ASCs producing more calcium per cell.

Comparison of autologous bone marrow and adipose tissue derived mesenchymal stem cells, and platelet rich plasma, for treating surgically induced lesions of the equine superficial digital flexor tendon. Vet J. 2017 Jun;224:76-84.

[.....] BM-MSCs resulted in a better outcome than PRP and AT-MSCs.