Regenerative Therapies

Rewriting the Future of Medical Aesthetics

By Jeffrey Frentzen, Executive Editor

A revolution is taking hold in medical aesthetics. Increasingly, the use of stem cell-based therapies in advanced fat grafting and volumization technologies; platelet-rich plasma (PRP); platelet-rich fibrin (PRF) matrix; stromal vascular fraction (SVF); growth factors; and other tissue and cell-based techniques, are starting to replace the need for more invasive surgery, as well as drug or chemical-based treatments. These new approaches to anti-aging, which use the patient's own tissue and blood for repair and regeneration, are already in use within burn / wound care specialties and orthopedics, and are poised to revolutionize the entire medical industry, as technologies and techniques improve and gain regulatory approval.

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"Regenerative medicine is the future," stated Ryan Welter, M.D., Ph.D., CEO and medical director of Regeneris Medical (Attleboro, Mass.). "All of these therapies are starting to converge into one specialty of regenerative medicine that utilizes all facets of scientific technology to repair damaged tissue. If we can achieve this then anything is possible. This is where all of medicine will merge."

Regenerative medicine will also change the course of medical aesthetics, said Sydney Coleman, M.D., fat transfer innovator and plastic surgeon at Tribeca Plastic Surgery in New York City, N.Y. "The global importance of this is that the latest paradigm in surgery and medicine is the idea of healing yourself with your own blood and tissue, rather than with operations and drugs," he said.

Globally, the industry is moving towards an integration of biologics and medical devices, expressed Farhan Taghizadeh, M.D., a plastic surgeon in Phoenix, Ariz. "What we are beginning to see is a potent interplay among biologics, botanicals and other types of therapies. Most of the biologics being used in aesthetics today have their origins in the wound and burn literature."

In addition, when practitioners employ energy-based devices to stimulate collagen growth, "We are also creating controlled wounds," Dr. Taghizadeh added. "What we're seeing now is an augmentation of effects using traditional wound products in the aesthetic space. The opportunities are growing both domestically and internationally as people take traditional reconstructive products and apply them in cosmetic procedures."

This trend has been in play among pharmaceutical companies as well, stated Dr. Welter. "It is a whole different ball game. These companies are realizing that using biologics and cell-mediated treatments are generally more effective and safer than drugs, with fewer side effects."

Regenerative aesthetic procedures hold tremendous potential, noted Steven R. Cohen, M.D., F.A.C.S., medical director of FACES+ Plastic Surgery Skin and Laser Center in San Diego, Calif., and clinical professor of plastic surgery at the University of California, San Diego. "They represent a brand new philosophy, which is a more dynamic approach to management of facial aging and facial tissue degeneration, which is very exciting."

These biocellular therapies combine important biological materials, such as growth factors found in fat. "This fat tissue, modified with added PRP and/or SVF cells, assist with tissue repair, regeneration and replacement," Dr. Cohen continued. "A person's non-embryonic stem cells, which are usually derived from adipose tissues or bone marrow aspirates, are involved in that healing and regeneration. Stem cells act as a reservoir of replacement and repair cells that can be called upon to participate in the reparation needed to restore diseased or damaged tissue and functions."

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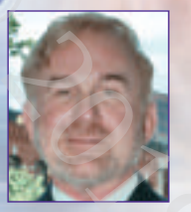

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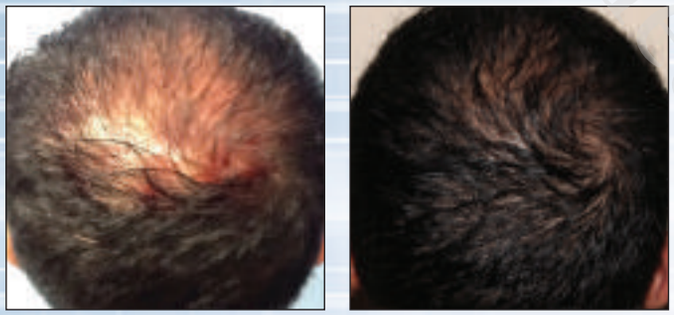
For instance, the latest developments in skincare products include biocellular approaches that indicate the regenerative potential of our own bodies, noted Dr. Taghizadeh. "Biocellular therapies can enhance the ability of the skin to rejuvenate itself. We know that fibroblast activity is heavily influenced by these biologics, and many of these products are potent anti-inflammatories. When you think of biocellular, it is biologic, but also botanical. We now understand that there is an interface between botanicals and these regenerative products. Developers are combining these to create better formulations that ultimately influence the outcomes."

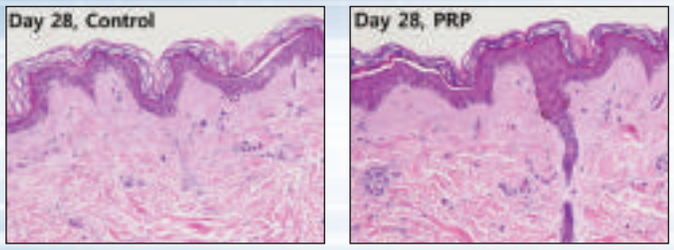
According to Nikolay Turovets, Ph.D., CEO of DefenAge/MediCell Technologies, a regenerative medicine company in Carlsbad, Calif., "We can directly activate specific molecular and gene-expression pathways with very fine tools, such as targeted molecules that mimic tissue damage without creating actual harm. A very specific single peptide can target an exact receptor on a dormant stem cell, thus activating it to repair tissue. For instance, there are stem cells in our skin that are responsible for repairing the basal layer and epidermis, and there are bulge stem cells accountable for hair growth. When rejuvenating the skin you do not want to activate bulge cells, because instead of skin rejuvenation you may get hair growth. Using the correct activator and the right target, in addition to accurate delivery of activator to that target is key."



30 year old male patient before and one month after 15 - 20 cc of ALMI fat transferred to the scalp and Eclipse PRP injections

Photos courtesy of Edward Zimmerman, M.D.

Some of the new products in development involve a raft of exotic technologies still in their infancy, noted Dr. Welter. "For instance, there will be autologous products that implement the use of your own cells in surgical products. Other products involve epithelial stem cells, amniotic cells and amniotic membranes taken from tissue banks or other sources. These might utilize amniotic fluid, epithelial growth factors and stem cell tissues, as well as adipose stromal connections, which provide scaffolding devoid of adipose cells and initiate proliferation of more adipose cells so you don't have to do liposuction to obtain the needed fat. Other sources include cord blood, bone marrow and stem cells for the heart."



Before and after ablative fractional CO_2 laser resurfacing combined with the application of autologous PRP. A thicker epidermis with a better-organized stratum corneum is seen in the PRP-treated side, together with thicker bundles of dermal collagen fibers (Right).

Courtesy of Jung-Im Na, M.D., Jee-Woong Choi, M.D., Hye-Ryung Choi, Ph.D., Jeong-Bok Jeong, M.Sc., Kyoung-Chan Park, M.D., Ph.D., Sang-Woong Youn, M.D., Ph.D., and Chang-Hun Huh, M.D., Ph.D.

At the practice level, regenerative approaches have already enhanced traditional fat transfer procedures, utilizing micronized fat, nanofat and amniotic stem cell therapies. New techniques allow for a higher chance of fat survival versus traditional methods.

"Biocellular procedures combine biologics and cellular therapy, such as harvesting some type of autologous component from patients, such as PRP and / or SVF from adipose tissue," said Tess Mauricio, M.D., a cosmetic dermatologist in Beverly Hills, Calif., who employs micronized fat that is carefully homogenized and then augmented with PRP to enhance the viability of stem cells contained within the adipose tissue. "By using both the biologics and cellular components from adipose tissue, the results have been amazing. We are really transferring a regenerative mix of pre-adipocytes that will turn into mature fat cells. By using PRP and micronized fat you

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are also cutting downtime, minimizing potential complications and decreasing inflammation in general."

An important distinction when performing these treatments is the difference between autologous versus homologous fat. "We define homologous use as utilizing fat cells the way they were originally designed," stated Edward M. Zimmerman, M.D., a cosmetic surgeon in Las Vegas, Nev. "If I take fat from the abdomen and place it into the breast or face, it is the same fat in terms of volume and its regenerative uses. But if I place fat that contains SVF, that would fall under what the FDA calls autologous, meaning that it ends up being different than it was before."

In order to comply with the latest FDA directives on fat transfer procedures, Dr. Mauricio injects the tissue-based SVF first and follows this with an injection of PRP. "A lot of data shows that we increase the viability of fat cells with PRP," she said. "At the point of service we don't alter the fat in any way, or add enzymes or anything else. We don't mix the two. They find each other *in vivo*."

Next-generation fat transfer also places more emphasis on growth factors, Dr. Coleman added. "We have sort of ignored the components of fat, but we're beginning to take notice," he said. "These include growth factors, which are the chemical messengers that control everything. We have paid a lot of attention to stem cells, but not growth factors. Conceivably, a regenerative stimulant could be placed into tissue or the blood stream. In addition, acellular matrix products hold a lot of potential, but still require fine tuning. It is my belief that we can use acellular matrix to find out how nanofat actually works."

When looking at regenerative approaches to facial rejuvenation, the whole nature of fat transfer is being reevaluated. "There are some new, specialized treatments we are doing with fat, such as Injectable Tissue Replacement (ITR), where we have developed a unique, anatomically specific dynamic approach to replacing deteriorating tissue related to aging," stated Dr. Cohen. "By replacing this loss with biologic tissue we are delaying tissue aging and deterioration. In addition we are restoring a blood supply. These concepts of precise anatomic tissue replacement are a radical departure from how we have managed facial aging and address the underlying aging process."

Fat resides in specific compartments of the face, Dr. Cohen added. "We grow and develop for 22 years and then degeneration begins. Symptoms of this deterioration include sun damage, volume loss (both bone and soft tissue) and laxity. In the deeper compartments the fat is more "pillowy" with less blood vessels; whereas, the superficial layer is tighter and more 'cobblestone-like.' This is important because some people just lose superficial fat while others lose deep fat, and most lose it in both layers. If we place fat in the proper compartments when it first becomes noticeable, then we are increasing the

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Before and after ALMI Tx

Photos courtesy of Tess Mauricio, M.D.

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A common denominator in regenerative aesthetics is PRP, which was originally FDA approved for orthopedic use, but has seeped into the medical aesthetic space. In addition to skin rejuvenation and body shaping it is used to address androgenetic alopecia and even vaginal and penile enhancement.

"Fat and PRP has been a great combination," noted Dr. Welter. "In hair restoration we are using a combination of PRP and extracellular matrix. We are just now on the frontier of these kinds of combination therapies and we don't really have a lot of compiled evidence to say one combination is absolutely better than another. However, in individual clinicians' hands we are seeing a lot of good results. As those outcomes are published we hone in on groupings of biologics that will have the best effect in any given treatment. The jury is no longer out on the effectiveness of PRP to stimulate tissue healing, it has been proven safe, easy and very effective."

Before and after facial rejuvenation treatments using stem cells with PRP injections
Photos courtesy of Ryan Welter, M.D., Ph.D.

For practitioners that are interested in choosing the best combination treatments and managing patient expectations around these approaches, Dr. Welter pointed out, "In general, now that we know these treatments are effective, we are trying to determine the best combination and overall treatment plan."

It then becomes important for aesthetic physicians to take a step back and look at the history of PRP, cell-based and fibroblast cultured media products, expressed Dr. Taghizadeh. "They all came from the wound and burn industry. It is not like these therapies were pulled out of the air. People have been testing these products on severely injured patients to create skin renewal programs that have ultimately converged into the aesthetic space."

Preparing a patient for successful cell-based regenerative procedures is different from getting them ready for cosmetic surgery. The patient should have good quality fat, tissue and blood to pull off these therapies.

Before and three weeks after 38 cc of ALMI fat transferred to the face, followed by Eclipse PRP injections to the temples, zygoma, anterior cheeks and jawline
Photos courtesy of Edward Zimmerman, M.D.

"If you don't have high-quality biologic material to start then cell therapy is bound to be less effective," stated Dr. Welter. "Physicians should educate their patients about healthy living and lifestyle choices, as well as nutritional habits that will continue the proliferation of the cell material. You are only as good as your cells, so you need to keep fit."

Aesthetic treatments will no longer revolve around just a single product or device, noted Dr. Taghizadeh. "It is the integration of lifestyle education in addition to these products and therapies that we already use. It is not unreasonable for advanced practitioners to provide educational programs leading up to these procedures."

For instance, in regenerative centers practitioners advise potential patients about the impact of high fatty acid, high peptide-based

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diets on platelet function. "One goal is to put people on a classic low peptide, low fatty acid diet to increase the opportunity of regeneration by decreasing the body's state of inflammation," Dr. Taghizadeh added. "It is all part of the same holistic model. The new world of regenerative medicine begins with diet, hormonal balancing and other functional aspects. This idea that aesthetics is separate from medicine is false. Patients are optimizing their ability to respond to the therapies we provide. In addition, many of these treatments tend to work better in people that have low states of inflammation."

It is not only the patients that must adjust. Physicians that want to enter the regenerative aesthetics field will have to become comfortable working with blood, fat and tissue, explained Dr. Welter. "We are not working with pre-filled syringe fillers. It requires experience and an understanding of how the body's own cells work to heal. Patients love it because they are attuned to not wanting foreign materials in their bodies. They are taking their cells and platelets and using those to heal. It is a phenomenally great advancement."

Patients have to be able to afford these new procedures, as well, noted Dr. Mauricio. "That will be the limiting factor. If they have the means, then it makes sense for people with very busy lives. They have almost no downtime and the results are tremendous."

In addition, comprehensive research should always be done before offering new methods of treatment, warned Dr. Turovets. "Regenerative medicine contains powerful tools to rejuvenate and repair tissues and organs, but we need to remember that stimulation of regeneration in old or aged tissues can be dangerous because it may, potentially, trigger tumor growth. With the introduction of new therapies, techniques, ingredients or devices, patient safety should be a top priority," he said.

In the near future, count on significant guidance from the FDA on how and where regenerative therapies and devices can be used, as well as products that gain a better biologic response. For instance, fat transfer procedures of the future may not necessarily require the use of your own fat.

"Exploring the idea of off the shelf fat, which comes from acellular matrix, is becoming an important option and I think it will soon be a reality," expressed Dr. Coleman. "Off the shelf fat has the potential to replace a lot of fillers and become an integral part of wound healing. Some pioneers in the field have engineered fat to successfully treat burns and damaged lower extremities."

Also on the horizon is the continued development of combining robotics and aesthetics, noted Dr. Taghizadeh. "If one could realize a singularity between what is happening in the robotics space and the biocellular space, then it all comes together. Currently, the role of pathology is advancing towards automation.

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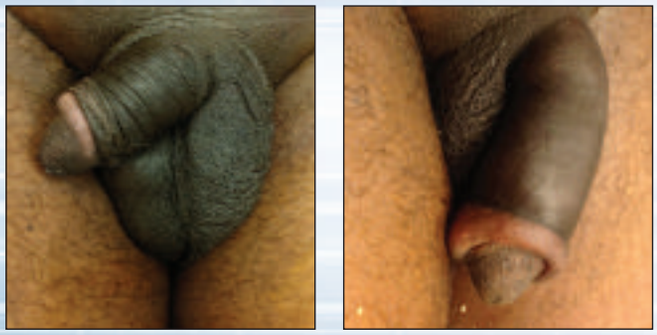

Before and after penile enhancement with fat transfer using PRP
Photos courtesy of Edward Zimmerman, M.D.

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It is the interface between automation and biocellular therapies that will encompass the future. You cannot divorce biocellular therapies from what ultimately occurs as we completely automate all of our aesthetic systems."

Still on the fringes, though, are tissue banking, genetics-based therapies and the expansive use of botanicals, especially anti-inflammatory botanicals, but the evidence suggests that this fringe will soon move closer to the mainstream.

"People are still trying to bank tissue successfully in order to harvest and maintain these cell-based products," noted Dr. Coleman. "It is still not clear if or how that is going to work. The current process for banking tissue is very rigorous, too, in terms of how donors are selected. Does this person carry any disease? How old is this person? The process used today is a lot like the one used for organ transplants." There is however, already evidence that tissue banking will become a practical aspect of regenerative aesthetics.

Jawline before and one month after ALMI Tx
Photos courtesy of Edward Zimmerman, M.D.

As Dr. Welter expressed, "There are some niche studies about the decline of cellular activity as you age, and there are also some promising, exciting studies of young patients donating cells to older patients. It sounds very sensible. Of course, there are issues that would have to be addressed, such as infections, but the science is very interesting. It is the idea that younger cells can stimulate older cells and tissues to regenerate. Thus, the natural progression of that thought process is to bank your tissue early in life so that you have your own young cells to use later in life. It is something that should be made cost-effective, so young people can take advantage of these lifesaving technologies somewhere down the road. I'm sure that within 15 or 20 years we will have very strong anti-aging technologies that take advantage of our own cells."

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Ultimately, people will be able to take their younger cells and store them for a rainy day, Dr. Zimmerman concurred. "They should be able to take cells and reprogram them. Notably, it goes far deeper than just dealing with aesthetics or superficial therapies. For instance, we could reprogram the pancreas to produce the right amount of insulin, or reprogram peripheral cells so that people could be at their optimal body weight."

Medical aesthetics is poised to drive some of these developments. "It is sort of a Star Trek-ish view of the world at this point, but the implications are just amazing," added Dr. Zimmerman. "We won't be able to cheat death. Eventually, we will not be able to repair the genetic transitions that occur as part of the aging process, but we will be able to push the clock back a bit and reverse or just altogether avoid those disease states. And hopefully be in a healthier condition when we die."

As stated by Dr. Mauricio, "Regenerative medicine is unleashing our body's natural ability to heal and regenerate. If you believe in the fountain of youth, it resides inside us." ■