Researchers Assess the Value of Regenerative Cells in Aesthetic Medicine

By Michael Moretti, Editor

Originating in the mid 1980s, fat transfer has acquired a moderate group of advocates. Early adopters, such as Sydney Coleman, M.D., a plastic surgeon in New York City, N.Y., Mel Bircoll, M.D., a cosmetic surgeon in Los Angeles, Calif. and James Carraway, M.D., director of the Plastic & Cosmetic Surgery Center of the Eastern Virginia Medical School (Norfolk, Va.) have amassed thousands of patient case studies with excellent results.

Practitioners utilize lipoaspirate to volumize and rejuvenate the face, breast, hands and buttocks, but for many clinicians, the variability of autologous fat transfer raises many questions including: How much fat is the right amount to transplant? What percent of the fat will "take"? How should touch ups be handled? What happens if too much fat gets injected?

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This variability limited early widespread acceptance of fat transfer. Furthermore, physician reluctance to adopting fat transfer was compounded by the introduction of hyaluronic acid (HA), calcium hydroxylapatite and injectable poly-L-lactic acid dermal fillers over the last two decades. These products provide precise dosing and improved reproducibility of results; however, in contrast to the longevity of successfully transferred autologous fat, the trade-off is diminished duration of effect. Additionally, HAs in particular provide the added ability to reverse complications via collagenase.

Two elements of clinical interest have pushed fat transfer back to the forefront of aesthetics. The first is the increased utilization of liposuction as a treatment option for body shaping, with a focus on methods that may preserve a better quality of fat for facial and body augmentation. These methods include ultrasound, vibration and water-assisted liposuction, as well as more automated systems for collection and separation of fat.

Second is an emerging interest in the field of regenerative medicine and the use of the patient's own cells (autologous cells, most commonly derived from adipose tissue) to influence the wound healing process. When combined with autologous fat transfer, regenerative cells hold the potential to improve fat graft survival and enhance cosmetic results.

The search for cellular regeneration began in St. Petersburg, Russia in the early twentieth century. Prior to this, German researchers had shown that the stammzelle was the reproductive engine in plants. At that time, the dominant theory of human hematopoietic cellular proliferation was that each type of cell, for example a red blood cell or platelet, was cloned from its like kind. In 1908, scientist Alexander Maximov, a professor at the St. Petersburg Military Academy proposed the Unitarian Theory of Hematopoiesis. Radical in concept, he argued that one core cell – the hematopoietic stem cell – could both self-renew, as well as transform itself into each of the blood elements. Professor Maximov vigorously defended his theory, which gradually gained universal acceptance over several decades.

Approximately 60 years later, A.J. Friedenstein, another researcher in Russia discovered a type of cell in the bone marrow. It appeared to be a type of stem cell, but Mr. Friedenstein quickly realized that it was not a hematopoietic stem cell, which was the only known stem cell type at the time. He was able to rapidly expand these cells in culture. Upon examination of his results, he realized that these newly grown cells were multipotent – able to differentiate into several distinct types of cells. In contrast to hematopoietic cells,

these new cells were responsible for forming connective tissue rather than blood cells.

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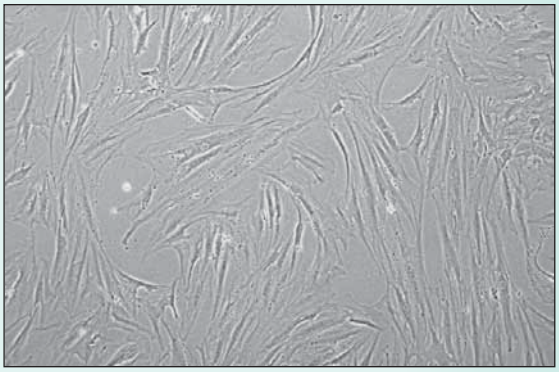
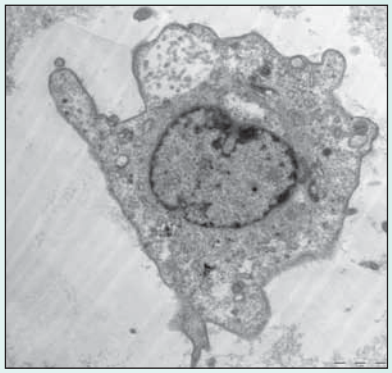
Mr. Friedenstein named his new cells Bone Marrow Stromal Cells (BMSC). Later, the cells would be called marrow stromal cells (MSC). As time progressed, the acronym MSC shifted, and now many scientists use the term MSC to mean mesenchymal stem cells. Mesenchymal stem cells are potent stem cells responsible for forming the connective tissue of the body. They can become chondrocytes and instigate collagen repair, or osteoblasts, the type of cell responsible for bone formation. Or they can form adipocytes, cells responsible for storing fat.

Later studies by Mr. Friedenstein and others revealed an additional ability; these cells could greatly aid in healing existing damaged tissue. More recent research has confirmed that the MSC action occurs through paracrine activity and the secretion of growth factors that modulate inflammation, promote angiogenesis and support wound healing.



Early passage of MSCs
Photo courtesy of Stemedica Cell Technologies

Bone marrow is not the only source of MSCs. A more convenient, more concentrated and potentially more angiogenic source of stem cells is the stromal tissue derived from adipose tissue. In comparison to bone marrow-derived MSCs, adipose tissue-derived stromal cells (ADSCs) have less potential to differentiate into tissues of mesodermal origin. While it is possible to isolate a homogeneous population of MSCs from adipose tissue, in clinical practice, the most common route is to utilize the cells from the stromal vascular fraction. This heterogeneous population includes not only MSCs, but also endothelial cells, endothelial progenitor cells, leukocytes, and vascular smooth muscle cells.



Electron microscopy of ischemic tolerant MSC
Photo courtesy of Stemedica Cell Technologies

The stromal vascular fraction can be enzymatically separated from the fat cells, concentrated and then reinjected either alone or in conjunction with the autologous fat. Now the question that many are asking is: Does this enrichment of autologous fat transfer make any difference in clinical outcomes?

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Jeffrey Schafer, M.D., and William Chen, M.D., program co-directors of the Coronado International Adipose Stem Cell Aesthetic Workshop addressed this issue at this year's meeting, which took place August 19 – 21, 2011 in San Diego, Calif. Faculty included Dr. Bircoll, Kamran Khoobehi, M.D., F.A.C.S., a plastic surgeon from Louisiana, Steven R. Cohen, M.D., a plastic surgeon and clinical professor of plastic surgery at the University of California, San Diego in San Diego, and Kotaro Yoshimura, M.D., a plastic surgeon from the University of Tokyo Graduate School of Medicine (Tokyo, Japan). As with any gathering of clinicians, open debate generated both a divergence and convergence of opinion.

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All faculty members agreed on the importance of patient selection and an appropriate fat grafting technique – a viable blood supply to the grafted tissue is essential for the new fat to survive. To this end, Dr. Yoshimura noted that he often spends up to three hours placing grafted fat tissue into breasts in order to enhance tissue survival. He uses micro-aliquots of 5 cc of fat, injected into a particular vector plane. For Dr. Yoshimura an ideal patient is one who is younger, extremely thin, has excellent existing vascularity in the breasts and is accepting of a moderate enhancement in volume.

Faculty also pointed out a positive relationship between a physician's experience with fat injections into the breast and potentially decreased microcalcifications. Dr. Yoshimura's work suggested that there may also be fewer microcalcifications with cell enriched adipose tissue.

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In general, the faculty was less certain as to the value of cellular enrichment for fat grafting. As with other areas of aesthetics, this is a promising field with great potential. Yet claims made by marketing oriented physicians and a hungry media tend to overshadow the fact that, at this point, there is little validated evidence that clinicians can reference that scientifically proves the value of stem cell enriched fat.

According to Dr. Cohen, "There is a body of preclinical work that shows that enriching fat will increase graft survival and capillary density, which has suggestions of regenerative properties. However, at this time, we have no prospective clinical studies in aesthetics that show any outcome data to substantiate the preclinical information."

Dr. Cohen noted that while adipocyte derived regenerative cells are obtained when performing conventional fat transfer; the questions that need to be answered are, "How do we know whether patients have a high or low quantity and quality of cells? What is the right dosing for enrichments? Are the adipose derived regenerative cells affected by age? If anywhere from 30% to 60% of transplanted breast fat survives, will cellular enrichment improve this outcome?" Dr. Cohen emphasized the need for studies in well-designed trials to show that cell enrichment makes a difference.

Recently, a small study by Aris Sterodimas, M.D., M.Sc., a plastic surgeon in Brazil, retrospectively compared autologous fat transplantation to ADSC enriched lipografts (*Aesthetic Surgery Journal*, August 2011 vol 31 no 6 682-693.). A group of 20 patients with congenital or acquired facial tissue defects were randomized into two groups. The ten patients in treatment group A received traditional fat grafts (155 mL per session), while the other ten patients in treatment group B received cell enriched lipografts (165 mL per session). Three of the ten patients in treatment group A obtained cosmetically acceptable results with a single treatment; seven required additional sessions. Conversely, all ten patients in the cell enriched treatment group B only required one treatment. Patient satisfaction ratings for the first six months were more favorable for treatment group B; however, at 18 months, there was no statistical difference between the two groups.

Despite the relative lack of research, physicians such as Dr. Cohen remain hopeful. "We know from the emerging studies that the most promising applications of cellular therapy are related to wound healing, radiation injuries, cardiac disease and possibly renal and liver conditions. These are medical disease states marked by ischemia and inflammation," Dr. Cohen advised. "Is aging or photodamaged skin an ischemic or inflamed condition that may benefit from cell enrichment? My gut says this may be true, and I am looking forward to contributing to the body of evidence that substantiates this."

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Given the intense interest in this field, as well as newer harvesting techniques that promote growth factor viability, the accelerated rate of investigator initiated clinical studies and anticipation of additional pre-clinical and clinical trials, there is a great likelihood that cell enrichment of fat will soon be part of the routine aesthetic armamentarium. Many aesthetic physicians are anticipating a time when the proof meets the promise for patients seeking a more natural, autologous cosmetic enhancement. ■