

Mesenchymal stem cells and regenerative medicine: how lipogems technology make them easy, safe and more effective to use

Abstract

Lipogems® was designed to harvest, process and inject aspirated fat tissue which is washed, emulsified and rinsed, while adipose cluster dimensions are gradually reduced in a completely closed device by only mechanical forces. Lipogems® tissue product represents a natural implantable bioreactor that incorporates the main elements for a perfect natural regenerative response: the Scaffold (the adipose tissue structure), the Cells (Pericytes/MSCs), and the Grow factors (secreted cytokines and chemokines).

The local injection of such a tissue is a living graft, which can work for long time enhancing the natural local healing potential. It has been used safely and effectively in thousands of patients, in human and veterinary medicine in many different clinical applications. The device has obtained general FDA clearance in 2014 and in 2016 for specific arthroscopic use. The purpose of this short review is to present the concepts of Lipogems® technology and an update in bibliography so that whoever is interested can easily search for more information. Figures and videos are easily available on google search so have not been added to this review.

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Adipose tissue as the Ideal Mscs source

MSCs are found as pericytes in all capillaries of all tissues of our body and the concept that fat tissue is an optimal source is now well established.¹⁻⁵ MSC of fat (ASCs) are very numerous compared to other tissues.⁴⁻⁸ Fat tissue is available in most patients and can be easily harvested with a minimally invasive surgical approach, using a blunt cannula and syringe vacuum, offering a highly viable ASC population with optimal differentiation potential that is maintained with aging.^{3,9-12} These cells can differentiate *in vitro* into several cell lineages, such as adipocytes, chondrocytes, osteoblasts, and myoblasts.^{2,5,13-19} In addition, they naturally secrete many bioactive molecules working as a sort of “mini-drugstore” that modulates the local immune response and creates an ideal regenerative environment.²⁰⁻²³ The use of ASCs, expanded or simply obtained by enzymatic treatment as SVF (Stromal Vascular Fraction), created a huge interest and both *in vitro* and *in vivo* studies clearly demonstrated their anti-inflammatory and regenerative potentials.²⁴ Nevertheless, the prolonged *ex vivo* expansion may induce cell senescence, thus leading to clinical results below expectations. In addition, the majority of the proposed techniques have complex regulatory issues.²⁵⁻²⁹ In the last few years, we have been facing a significant number of studies aimed at the improvement of the therapeutic effects provided by the traditional fat transfer and structural fat grafting techniques.³⁰⁻³³ In an effort to optimize this regenerative potential, MSC enrichment techniques, essentially based on enzymatic or mechanical devices, have been proposed.^{34,35} In our experience, a minimally manipulated fat tissue is preferable, not only from a regulatory prospective,^{28,29} but mainly because of the biological rationale. Indeed, mechanically derived MSC versus enzymatically isolated MSC have shown to have better differentiation potential^{9, 10}, wider secretome³⁶, and a large difference in exosomes contents.^{22,37,38} The Lipogems® technology guarantees all of the requirements in an easy, quick, disposable device and represents a very promising “natural” approach in different fields.^{9,39-51}

The Lipogems® system

The Lipogems® system incorporates a new technology to harvest, process and transfer adipose tissue. The technical part of the procedure is well described both in journal articles^{9,32,52} and in the web (https://www.youtube.com/results?search_query=Lipogems+system). The resulting product is composed of small intact adipose tissue clusters (250-650 microns) and contains pericytes retained within an intact stromal vascular niche. It is now well established that cells defined as MSCs exhibit perivascular location and pericyte identity *in vivo*⁵³⁻⁵⁵. Pericytes are structural cells embracing the external wall of the microvessels and capillaries of the stromal vascular fraction of fat tissue and, after an injury such as inflammation or a damage of the vascular wall, they detach from the capillaries and gradually convert into activated regenerative MSCs.^{21,53,54} Such pericyte-to-MSc activation entails the release (through exosomes) of regenerative factors and bioactive molecules which would make the transplanted Lipogems® product acting as a “personalized drugstore”⁵⁶. The exquisite balance between angiogenic, anti-inflammatory, immunomodulatory, anti-apoptotic, anti-microbial, mitotic, anti-scarring properties of MSCs allows a completely natural tissue repair and regeneration³⁶. The second main characteristic of Lipogems® is related to the time-advantage. Indeed, the gentle mechanical method allows obtaining a ready-to-use product in less than 20 minutes compared to the several hours, days or weeks required for the enzymatic digestion of the lipoaspirate and eventual *in vitro* cell expansion with substantial delay in the clinical application. In addition, Lipogems® is minimally manipulated according to the regulations set forth by the FDA. It received the FDA clearance as a class II medical device for processing autologous adipose tissue (510(k) first approval in US in December 2014 and new clearance in November 2016 for arthroscopic applications. The reduction of adipose cluster dimensions from 2-4, 5mm before processing to 0,3-0,7mm of the final product, maintaining a perfect structural integrity, improves its ease of handling and post-transplant engraftment, due

to the more effective and faster graft revascularization. Several new promising fields of application are reported every month as this technique is spreading all over the world and have already received regulatory approval in 23 countries (<http://www.lipogems.eu/index-eng.html>).

Clinical applications of lipogems

Lipogems has been shown to be safe and seems to work clinically much better than enzymatically iso-lated MSCs (both SVF or cultivated) as the preserved niche within a natural adipose scaffold works as the ideal “functional unit”.^{21,36} In general surgery, Lipogems® has been used as a valid approach for the treatment of fecal incontinence and anal fistulas, showing impressive long term real morphological regeneration of muscle and neurological function.^{41,43,49,57} In oncology, Lipogems® has been proved useful when injected in atrophied tissue after radiotherapy.⁵⁸ The regenerative potential in musculoskeletal diseases is impressive and more extended clinical trials are currently performed worldwide to confirm the first outstanding results.^{42,46,48,50} In orthopedic surgery, most patients with joint degenerative and inflammatory diseases may benefit of Lipogems® intra and peri-articular injection.^{59,60} After injection of a variable quantity of Lipogems® (2-12 ml depending from the joint), patients generally reported a brilliant immediate improvement of symptoms with long-term pain resolution. In many cases, patients previously candidate for surgery, no longer needed it because of the complete or substantial resolution of their symptoms. Preoperative and post-operative X-ray and MRI comparison showed a possible regeneration of the articular cartilage and a widening of the joint space 6 to 18 months after treatment. Moreover, the orthopedic use Lipogems® has also proved to be rewarding to foster repair in injured ligaments or tendons, in meniscal lesions, around surgical wounds, inside and around osteotomy gaps. These findings have been confirmed in Veterinary Medicine where Lipogems is becoming the leading regenerative therapy in polo horses and dogs.⁶¹

In plastic reconstructive surgery, Lipogems® helps the healing of chronic ulceration of the inferior legs and feet, above all in diabetic patients, with encouraging results. Only the vasculogenic properties of MSCs can explain these successes.^{62,63} The aesthetic surgery is a growing field of application. Lipogems® is used alone or in association with traditional surgical techniques such as facelift, blepharoplasty, breast augmentation and others. In the latter case, Lipogems® improves and accelerates wound healing and improves skin texture. Optimal results have been obtained in the periorbital area. After surgical intervention, the patients complain no pain, swelling or bruising, and are generally greatly satisfied. This treatment is often extended in a full-face bio-restoration aimed to define face contour, give it tone, new brightness and uniformity.⁶⁴ A recent publication describes the use of Lipogems® during orthognathic surgery in 120 patients who underwent a double jaw intervention. Lipogems® was injected in multiple tissue planes and tunnels where the soft tissue lack had to be restored (mid face and mandible contours, neck, lips, chin profile). Results were compared to a series of patients treated with a traditional lipofilling technique. All the patients, except for 2, showed better enhancement of face morphology and skin texture, and much less post-operative swelling with consequently faster recovery.⁴⁵

Lipogems and future horizons of regenerative medicine

Fat tissue transfer is a well established autologous method which has several clinical applications. The Lipogems® technology has been created to improve traditional grafting technique.⁹ The most important

and attractive feature of Lipogems® technology, and in general of MSCs, is the ability to naturally repair and regenerate certain types of tissue, such as joint cartilage, representing an ideal scaffold.⁴⁰ Recently, it has been demonstrated that exposure of Lipogems-derived MSCs to properly conveyed radio-electric fields was able to optimize stem cell expression of multipotency and lineage commitment at a remarkably higher degree than in enzymatically-dissociated MSCs obtained from the same donors.⁶⁵ This finding may significantly improve future cell therapy efforts.⁶⁶ Lipogems® technology fulfils the requirement to overcome the current limitations related to in vitro fat manipulation, making MSCs easily available within their natural 3D scaffold for immediate clinical use. It must be stressed that IFATS (International Federation for Adipose Therapeutics and Science) and ISCT (International Society for Cellular Therapy) recently established some clear definitions of Stromal Vascular Fraction and adipose-derived mesenchymal stem cells to better manage the future trials and to allow multicenter comparative studies.^{1,67,68} We strongly believe that many of these trials should be compared to Lipogems® safety and effectiveness.

Conclusion

Adipose tissue is the ideal source for extracting but above all for using MSCs since (i) it can be easily accessed and harvested via a minimally invasive surgical procedure, (ii) it can be found in sufficient quantities in most people and (iii) it guarantees an adequate amount of progenitor cells with a good viability and minimally age-related differentiating potential. The Lipogems® technology naturally optimizes fat tissue healing properties. Without using enzymes, additives or centrifugations, but relying upon the use of mild mechanical forces, the Lipogems® system yields a micro-fragmented product that rescue damaged tissues with a regenerative environment for a long time. A number of randomized and controlled studies are now ongoing to strengthen its critical analysis and further develop and accelerate innovative therapeutic strategies and clinical protocols.

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Conflict of interest

Carlo Tremolada is the president and founder of Lipogems company.

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