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RATIONALE

SEFFIHAIR®

Regenerative Therapy through stromal vascular fraction (SVF) and adipose tissue derived stem cells (ADSCs)

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RATIONALE

Adipose derived stem cells (ADSCs) are among the most investigated and used cells in the field of regenerative medicine. ADSCs are found in the stromal vascular fraction (SVF) of the adipose tissue. The SVF contains large numbers of cells composing interrelated cell populations: ADSC progenitors, pericytes, endothelial progenitor cells, and transit amplifying cells.
In the last 15 years, a large body of work conducted on ADSCs reported their capability to differentiate into multiple cell types, including adipocytes, chondrocytes, myocytes, hepatocytes, endothelial cells – both in vitro and in vivo. Also, ADSCs display the ability to secrete bioactive molecules which stimulate angiogenesis and have antifibrotic, antiapoptotic and immune-modulatory properties. Moreover, SVF/ADSCs induce the secretion of cytokines and growth factors which promote angiogenesis and thus the revascularization of fat grafts.

S.E.F.F.I. AND MICROS.E.F.F.I. TISSUE GRAFT (Superficial Enhanced Fluid Fat Injection)

Since 2015 A. Gennai et al. have been publishing several studies (see references) about the new tissue graft techniques **S.E.F.F.I.** and **MicroS.E.F.F.I.**. These techniques aim to graft adipose tissue including the stromal vascular fraction (SVF) and Adipose Derived Stem Cells (ADSCs) contained therein, in order to achieve a skin enhancement and volume restoration of the face. The Authors proved that, using special cannula with very small side ports holes, the adipose tissue can be harvested so as to select small cellular clusters that don't need any kind of manipulation in order to fluidify the tissue.
SEFFI and MicroSEFFI are now among the most used techniques addressed to regenerate the skin and restore the volume for facial rejuvenation.
These techniques are considered as minimally invasive surgical procedures; hence they require surgical skills and surgical facilities.
In the light of this evidence the Regenerative Therapy has always been only in the hands of surgeons and not open to aesthetic physicians or dermatologists.
Dr. Gennai strongly believes that the Autologous Regenerative Therapy should be performed also by Doctors even without any liposuction skills. For this reason, he developed, standardized and patented* a special guide intended for harvesting the tissue in a safe, easy, effective way without any liposuction skill.
From this original idea SEFFILINE developed SEFFIHAIR®:
it's an all-in-one and disposable medical device to allow all doctors to perform the autologous regenerative hair loss treatment in their facility in a safe, easy, effective way.

Treatment with the SEFFIHAIR® medical device involves the autologous and homologous graft of the Vasculo Stromal component (SVF) of the adipose tissue selected with the SEFFI (Superficial Enhanced Fluid Fat Injection) technique. Numerous scientific papers have demonstrated the efficacy of regenerative therapy with SVF and ADSCs in the treatment of androgenetic alopecia; recent studies have also shown efficacy in alopecia areata.

*Italian patent

INDICATION

Treatment with the SEFFIHAIR® medical device is indicated in the following conditions:

- **androgenetic alopecia.**

Some international papers report the effectiveness of the SVF treatment also in:

- **alopecia areata**.

Therefore a careful diagnosis is essential before starting the treatment.

ANDROGENETIC ALOPECIA

It affects 70% of men and 40% of women at a certain stage of their life. Men typically show a recession of the hairline at the temples and hair loss at the vertex, while women normally show a widespread thinning over the whole upper part of the scalp.

Androgenetic hair loss in men begins above the temples and in the center of the skull. Usually the strip of hair on the sides and behind the head is maintained.

Androgenetic alopecia in women is colloquially referred to as *'female pattern baldness'*, although its characteristics may also occur in men. It usually causes widespread thinning without a hairline recession, and like the male counterpart it rarely leads to a complete hair loss.

To classify the degrees of alopecia the Hamilton-Norwood Scale is used to measure the degree of baldness in men and the Ludwig Scale to measure the degree of baldness in women.

PATHOPHYSIOLOGY

In genetically predisposed subjects one of the causes of androgenetic alopecia is dihydrotestosterone (DHT), that derives from testosterone by the action of 5α-reductase. The miniaturization of the bulb occurs due to the transformation of testosterone into its most active metabolite, dihydrotestosterone (DHT). Such miniaturization can lead to the final death of the bulb and an irreversible hair loss. DHT promotes the growth of body hair and beard and can negatively affect the prostate and also the hair. There is still no absolute certainty about the genes causing androgenetic alopecia. Certainly the genes that control the 5α-reductase enzymes are responsible. Actually it has been shown that most of the genes involved reside on the X chromosome, that is the one that the mother transmits to her son, or that mother and father transmit to their daughter. Heredity towards a male child is greater according to the X chromosome that the mother inherited from her father, therefore the greater transmission occurs from the maternal grandfather to grandson and not from father to son. The fundamental pathological process consists in the acceleration, under androgenetic stimulation, of the mitotic phase of the hair cycle (*anagen I-V*) and in the consequent reduction of the differentiation phase, which is normally very long. Since the latter is necessarily incomplete, the stem that will derive from it will be thinner and shorter (*vellus*).

Generally in men we see a receding hairline, i.e. in the front part of the head the hair becomes thinner and thinner. Later the same happens in the vertex. Finally, baldness affects the entire

upper part of the head. At a later age, atrophic phenomena of the scalp - which becomes thin and shiny - overlap. At this stage the vellus disappears.
A second pathological process consists in the loss of the individuality of the papillary cycles (characteristic of the normal adult scalp) and therefore of their synchronization. This phenomenon is due to the reduction in the duration of the differentiation phase.
A third phenomenon is the increased *kenogen* phase. When the hair shaft comes off at the end of the *telogen*, the follicle is already occupied by another one in advanced *anagen* phase. An interval can occur between the fall of the hair in *telogen* and its replacement with the new in *anagen*: during this physiological interval (*kenogen*), the follicle remains empty.
In androgenetic baldness only the hair in the frontal region is lost because in this zone the 5α-reductase is more active, therefore a greater quantity of DHT concentrates there. In addition, also blood circulation comes into play. In fact, the frontal region is the most peripheral part of the scalp blood circulation, and therefore the one that is most subject to vessel atrophy. In any case, feeding the bulbs is a critical factor.
Another molecule favoring androgenetic alopecia in genetically predisposed subjects is prostaglandin D2 (PGD2), mediator of inflammation. Clearly also deficiencies of micronutrients and stress can favor androgenetic alopecia in genetically predisposed subjects. Diseases such as endocrinopathies (such as GH deficiency, hypothyroidism, menopause, polycystic ovaries and virilizing tumors) can cause baldness.

ACTION MECHANISM

Many studies have demonstrated the efficacy and safety of autologous tissue graft containing SVF and ADSCs:

- SVF and pre-adipocytes have demonstrated an important action by favoring the activation of follicle stem cells through the secretion of numerous and important Growth Factors, such as PDGF (dermal papillae growth factor), vascular endothelial growth factor (VEGF), insulin-like growth factors (binding protein IGFBP-1, and IGFBP-2).

  Adipocyte Lineage Cells Contribute to the Skin Stem Cell Niche to Drive Hair Cycling; DOI 10.1016/j.cell.2011.07.019 Eric Festa, Jackie Fretz, Ryan Berry, Barbara Schmidt, Matthew Rodeheffer, Mark Horowitz, and Valerie Horsley; Departments of Molecular, Cell, and Developmental Biology; Orthopædics and Rehabilitation Section of Comparative Medicine Yale Stem Cell Center; Molecular Cell Biology, Genetics, and Development Program Yale University, 219 Prospect St., New Haven, CT 06520, USA

  Eplasty. 2015; 15: e10. Published online 2015 Mar 26 's Hirotaro Fukuoka, MD, PhD and Hirotaka Suga, MD, PhD

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Stem Cell Res Ther. 2018; 9: 141 Published online 2018 May 15. doi: 10.1186/s13287-018-0889-y Cellular therapy with human autologous adipose-derived adult cells of stromal vascular fraction for alopecia areata. Rami Anderi, Nehman Makdissy, Albert Azar, Francine Rizk and Aline Hamade.

Biomed Res. 2010 Feb;31(1):27-34 Hair growth stimulated by conditioned medium of adipose-derived stem cells is enhanced by hypoxia: evidence of increased growth factor secretion. Park BS[1], Kim WS, Choi JS, Kim HK, Won JH, Ohkubo F, Fukuoka H.

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Curr Stem Cell Res Ther. 2017;12(7):535-543. The Basic Mechanism of Hair Growth Stimulation by Adipose-derived Stem Cells and Their Secretory Factors. Won CH, Park GH, Wu X, Tran TN, Park KY, Park BS, Kim DY, Kwon O, Kim KH.

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J Dermatolog Treat. 2018 Aug;29(5):431-440 Stem cell therapy as a novel therapeutic intervention for resistant cases of alopecia areata and androgenetic alopecia Elmaadawi IH, Mohamed BM, Ibrahim ZAS, Abdou SM, El Attar YA, Youssef A, Shamloula MM, Taha A, Metwally HG, El Afandy MM, Salem ML

Adipocyte Lineage Cells Contribute to the Skin Stem Cell Niche to Drive Hair Cycling DOI 10.1016/j.cell.2011.07.019 Eric Festa,Jackie Fretz, Ryan Berry, Barbara Schmidt, Matthew Rodeheffer,Mark Horowitz, and Valerie Horsley; Departments of Molecular, Cell, and Developmental Biology; Orthopædics and Rehabilitation Section of Comparative Medicine Yale

Stem Cell Center; Molecular Cell Biology, Genetics, and Development Program Yale University, 219 Prospect St., New Haven, CT 06520, USA

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Facial Plast Surg Clin North Am. 2018 Nov;26(4):503-511 Mesenchymal Stem Cells and Stromal Vascular Fraction for Hair Loss: Current Status.Epstein GK1 Epstein JS.

- The association of stromal vascular component (SVF) platelet-rich plasma (PRP) has proved to be an effective protocol in the treatment of androgenetic alopecia.

Aesthet Surg J. 2018 Jul 13;38(8):811-822. Introducing Platelet-Rich Stroma: Platelet-Rich Plasma (PRP) and Stromal Vascular Fraction (SVF) Combined for the Treatment of Androgenetic Alopecia. Stevens HP, Donners S, de Bruijn J.

J Cosmet Dermatol. 2019 Sep 21. Stromal vascular fraction-enriched platelet-rich plasma therapy reverses the effects of androgenetic alopecia. Butt G1, Hussain I1, Ahmad FJ2, Choudhery MS

EXCLUSION FROM THE TREATMENT

- Ongoing infections in the area of tissue harvesting or grafting.
- Presence of malignancies in the area of tissue collection or grafting.
- Pregnancy or breastfeeding.
- Anticoagulant therapy or severe coagulation disorder.
- Allergy to the local anesthetic.
- Dysmorphophobia.
- Ongoing immunosuppressive therapies.
- Debilitated subjects.
- Chemotherapy.
- Compulsive hair traction (trichotillomania).

POSSIBLE THERAPEUTIC ASSOCIATIONS

- Minoxidil (vasodilator)
- Finasteride (5α-reductase inhibitor)
- Carboxitherapy

  J Cosmet Dermatol. 2018 Dec;17(6):1275-1285 Study of the efficacy of carboxytherapy in alopecia. Doghaim NN, El-Tatawy RA, Neinaa YME, Abd El-Samd MM
- Hair grafting

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As in all multifactorial pathologies, **therapeutic combination** is the one that achieves the best results. Regenerative therapy is indicated in all stages of androgenetic alopecia: certainly, in the advanced stages (Norwood Hamilton Scale V-VI-VII) it is indicated in association with hair transplantation. Regenerative therapy is recommended in **preparation** for surgery and post-intervention **maintenance**.

PROCEDURE

In order to reach the follicle, the implant must be performed with the following method:

- 4 ml luer lock syringe (included in the box)
- 27G 4 mm needle (included in the box)
- Injection perpendicular to the scalp at a distance of 1 cm
- Approximately 5 ml are grafted in about 10 spots
- After grafting the needle remains is kept in the scalp for about 2 sec.

POST-TREATMENT ADVICE

- Anti-inflammatory and / or antibiotic therapy is usually not prescribed;
- avoid showering for 24 hours;
- avoid sun exposure for 1 week;
- immediate work activity.

Results will be appreciable after 4-6 months.

CELLULARITY / DOSE

Our studies (object of forthcoming publication) show that the staminality obtained with the SEFFIHAIR® method is about 150,000 cells / ml. Therefore, considering the administration of 0.5 ml per inoculation point, about 75,000 stem cells are grafted in each inoculation spot. Considering that about 10 -15 ml of tissue are grafted on the whole, it can be stated that about 1,500,000 - 2,250,000 cells are grafted on a surface from 4x5 cm to 5x6 cm.

ALOPECIA AREATA

Alopecia areata is a disease in which the sudden fall of the hair, or body hair, typically occurs in hairless or aerial patches. Usually the first patches appear in the scalp and, in most cases, they resolve spontaneously, without showing signs of scarring. In about 1% of cases the pathology may extend to the entire scalp (total alopecia, TA) or to the whole body (universal alopecia, UA) with the total loss of all body hair.

PATHOPHYSIOLOGY

Alopecia areata has an immunopathological component (often due to the attack of IgE antibodies, those specific to allergies, or more generally of the antigens of second-class human leukocytes and T lymphocytes); in essence, an abnormal immune reaction is produced that temporarily and locally damages hair follicles. Moreover, it depends also on genetics, in fact this condition seems to affect people who have a genetic predisposition. Psychological stress is never the cause but, it is seen as an element that worsens the pathology.

ACTION MECHANISM

Clinical data show that patients with Alopecia Areata (AA) showed hair growth after ADSC grafting. Cytometry has shown the effect of ADSCs on Th2 cytokine regulation and in balancing Th1 / Th2 / Th3 cytokine production. Furthermore, immunohistochemical studies have shown the creation of a "ring of growth factor β1 (TGF-β1) formation" around the follicle, which seems to protect the follicle from the autoimmune attack.

> *BMC Med. 2015; 13: 87 Published online 2015 Apr 20. doi: 10.1186/s12916-015-0331-6 Hair regrowth in alopecia areata patients following Stem Cell Educator therapy, Yanjia Li, Baoyong Yan, Hepeng Wang, Heng Li, Quanhai Li, Dong Zhao, Yana Chen, Ye Zhang, Wenxia Li, Jun Zhang, Shanfeng Wang, Jie Shen, Yunxiang Li, Edward Guindi, and Yong Zhao*

> *Stem Cell Res Ther. 2018; 9: 141 Published online 2018 May 15. doi: 10.1186/s13287-018-0889-y Cellular therapy with human autologous adipose-derived adult cells of stromal vascular fraction for alopecia areata, Rami Anderi, Nehman Makdissy, Albert Azar, Francine Rizk and Aline Hamade*

Other studies have shown the importance of Treg cells (Regulatory T cells, a heterogeneous line of lymphocytes also present in adipose tissue) in stimulating the follicle through stimulation and proliferation of epithelial stem cells. Tregs stimulate the follicle (HF) by activating follicular stem cells (HFSC).

> *Cell 169, 1119–1129 June 1, 2017 Regulatory T Cells in Skin Facilitate Epithelial Stem Cell Differentiation Niwa Ali, Bahar Zirak,Robert Sanchez Rodriguez, ..., George Cotsarelis, Abul K. Abbas, Michael D. Rosenblum*

> PLoS One*. 2019; 14(7): e0210308.Published online 2019 Jul 5. doi:* 10.1371/journal.pone.0210308 *Alopecia areata patients show deficiency of FOXP3+CD39+ T regulatory cells and clonotypic restriction of Treg TCRβ-chain, which highlights the immunopathological aspect of the disease,* Fatma N. Hamed*,* Annika Åstrand*,* Marta Bertolini*,* Alfredo Rossi*, Investigation,* Afsaneh Maleki-Dizaji*,* Andrew G. Messenger*,*Andrew J. G. McDonagh*,* Rachid Tazi-Ahnini.

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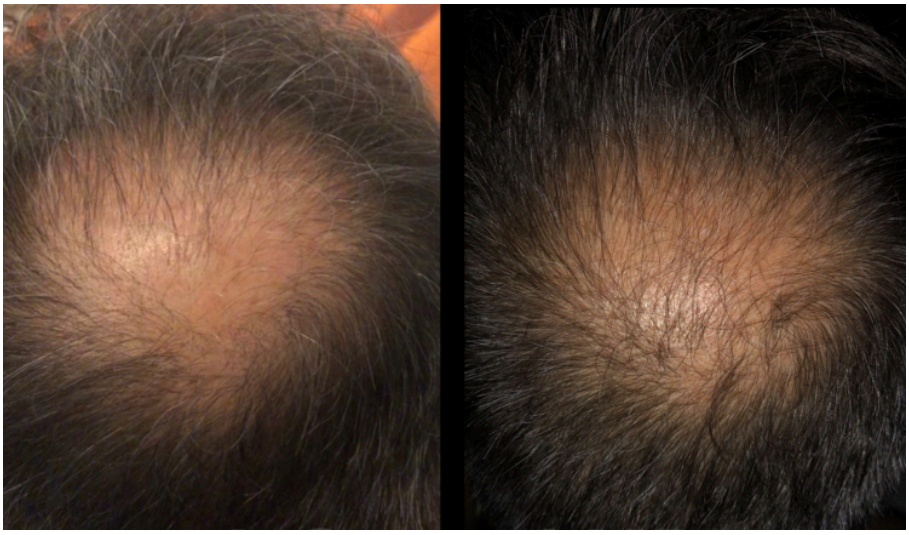
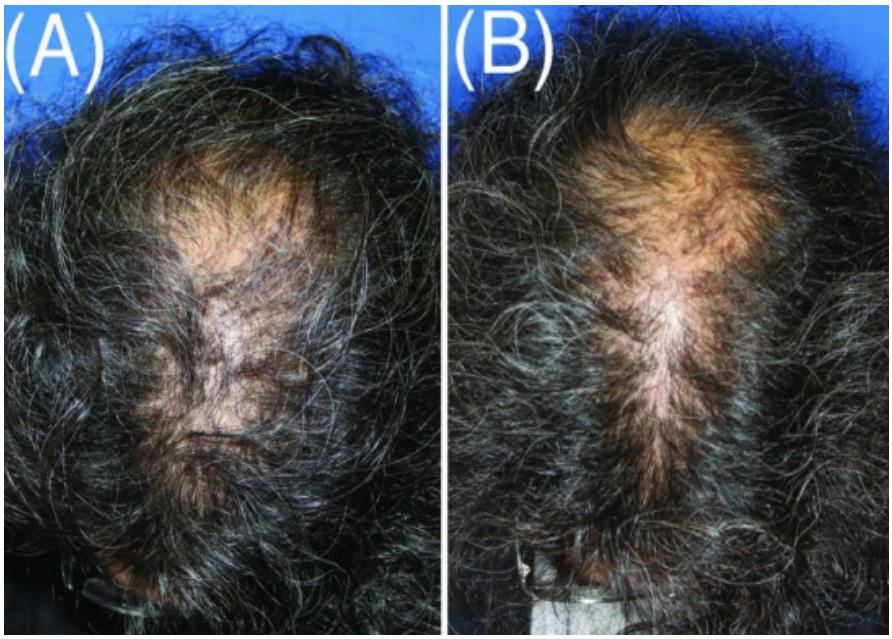
CASES from literature



post 4 months, A. Gennai



post 4 months, Fokura

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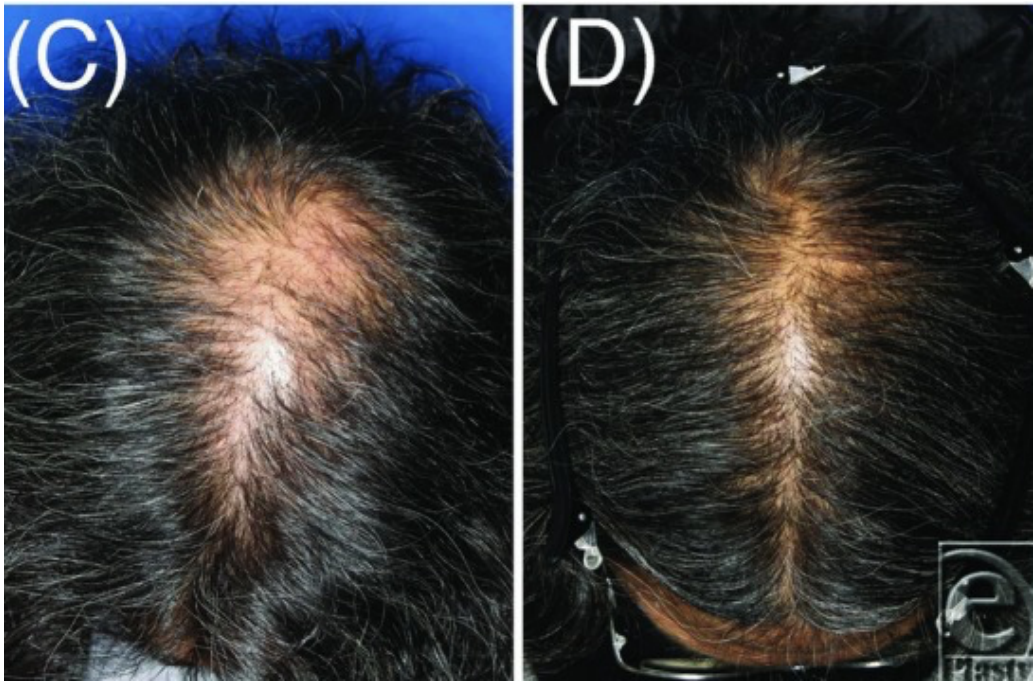
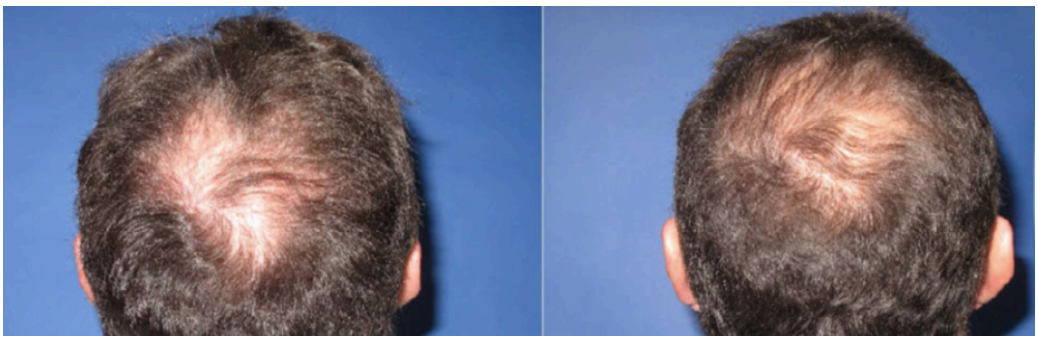


post 1 months and 2 years, Fokura



post 6 months, Perez - Meza

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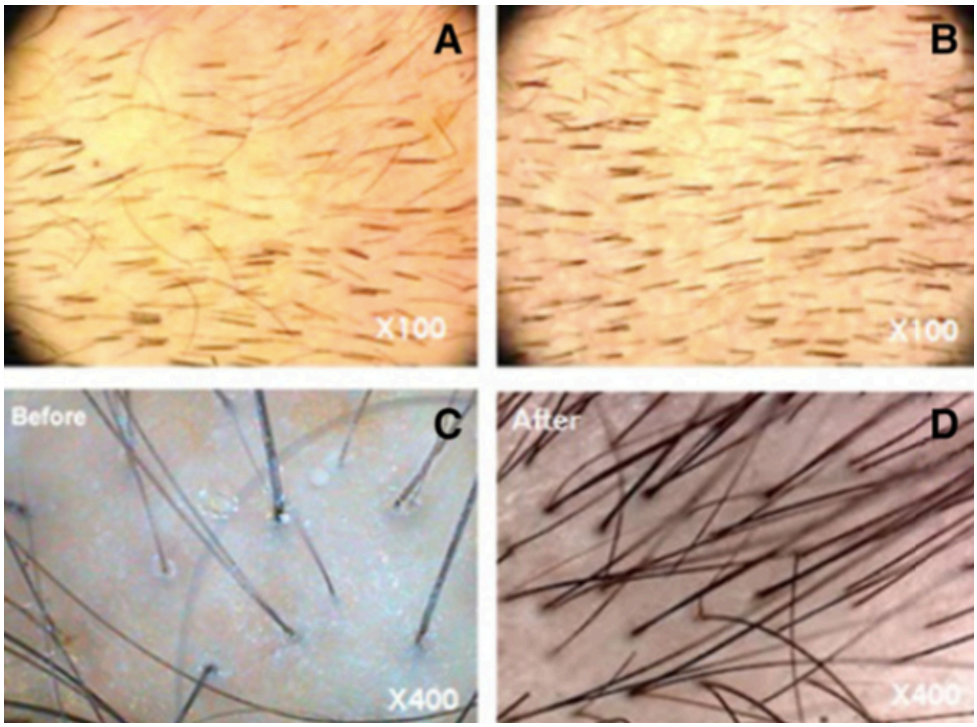

post 6 months, Rami Anderi

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Review focused on the effect of ADSCs and their secretory factors on the stimulation of hair growth in vitro, ex vivo and in vivo.
The conditioned media of ADSCs (ADSC-CM) increases the proliferation rate of human follicular cells. ADSCs-derived proteins improve hair growth and protect human dermal papilla cells against cytotoxic injury caused by androgen and reactive oxygen species.
ADSC-CM induces the anagen phase and promotes hair growth in mice, and enhances the elongation of hair shafts in ex vivo human hair organ cultures.

9. Shin H, Won CH, Chung WK, Park BS; Up-to-date Clinical Trials of Hair Regeneration Using Conditioned Media of Adipose-Derived Stem Cells in Male and Female Pattern Hair Loss; Curr Stem Cell Res Ther. 2017;12(7):524-530.
Review on the use of adipose-derived stem cells (ADSCs) on hair regeneration. Besides replacing degenerated cells in affected organs, ADSCs exhibit their beneficial effects through the paracrine actions of various cytokines and growth factors.
Several laboratory experiments and animal studies have shown that ADSC-related proteins can stimulate hair growth. In addition, we introduce our clinical pilot studies using conditioned media of ADSCs for pattern hair loss in men and women, which shown to be a promising alternative therapeutic strategy for hair loss.

10. Shin H, Ryu HH, Kwon O, Park BS, Jo SJ; Clinical use of conditioned media of adipose tissue-derived stem cells in female pattern hair loss: a retrospective case series study; Int J Dermatol. 2015 Jun;54(6):730-5.
Adipose tissue-derived stem cells (ADSCs) and conditioned media of ADSCs (ADSC-CM) are reported to promote hair growth in vitro.
This study evaluates our clinical experience in the use of ADSC-CM for the treatment of FPHL. A retrospective, observational study of outcomes in 27 patients with FPHL treated with ADSC-CM
The application of ADSC-CM showed efficacy in treating FPHL after 12 weeks of therapy. Hair density increased from 105.4 to 122.7 hairs/cm (2) ($P < 0.001$). Hair thickness increased from 57.5 µm to 64.0 µm ($P < 0.001$). None of the patients reported severe adverse reactions.

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This review describes the significant advantages of adipose-derived stem cells and fibroblasts in terms of safety and efficacy and compares them to relatively risky platelets and bone marrow stem cells.

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Abstract
BACKGROUND: Since antiquity, humans have been trying to devise remedies to cure androgenetic alopecia (AGA). These efforts include use of oral and topical concoctions and hair transplant strategies. As AGA affects people of all colors and creed, there has been a continuous effort to find a magic bullet against AGA. Unfortunately, to date, all the strategies to negate AGA effects have limitations and thus require new treatment options.
AIM: To evaluate the efficacy of use of stromal vascular fraction (SVF) in androgenetic alopecia patients.
METHODS: Stromal vascular fraction was obtained by enzymatic digestion of autologous adipose tissue. The patients were divided into two groups, that is, platelet-rich plasma (PRP) group and SVF-PRP group. In PRP group, only PRP was injected, while in SVF-PRP group a mixture of PRP and SVF was injected in affected scalp areas. After two sessions (4 weeks apart), the patients in both groups were assessed and analyzed using various parameters.
RESULTS: Mean hair density in PRP group was increased from 52.44 hair/cm2 to 63.72 hair/cm2 (21.51% increase); while in SVF-PRP group, it was 37.66 hair/cm2 before treatment and 57.11 hair/cm2 after SVF-PRP therapy (51.64% increase). Percentage reduction in pull test was more significant in SVF-PRP group (80.78 ± 5.84) as compared to PRP group (34.01 ± 22.44). The physician and patient assessment scores also indicated a significant improvement in SVF-PRP group.
CONCLUSION: A combined SVF-PRP therapy reversed effects of AGA more efficiently as compared to PRP therapy alone.

16. Epstein GK, Epstein JS; Mesenchymal Stem Cells and Stromal Vascular Fraction for Hair Loss: Current Status; Facial Plast Surg Clin North Am. 2018 Nov;26(4):503-511. doi: 10.1016/j.fsc.2018.06.010. Epub 2018 Aug 16.
Abstract
The current state of the applicability of cell therapy for the treatment of various conditions of hair loss reveals a promising and potentially effective role. Further research, based on published work to date, is indicated to further explore the potential roles of autologous fat grafting, mesenchymal stem cells, and stromal vascular fraction therapy. The authors' evolving experience matches these promising scientific findings.

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Abstract
BACKGROUND: Androgenetic alopecia (AGA) is characterized by miniaturization of the hair follicles gradually causing conversion of terminal hairs into vellus hairs, leading to progressive reduction of the density of hair on the scalp. Approved therapeutic options are limited and show side effects.

OBJECTIVES: To evaluate injections of stromal vascular fraction (SVF), which is rich in adipose-derived stromal cells (ASCs) in combination with platelet-rich plasma (PRP) in the upper scalp as a new autologous treatment option for AGA.
METHODS: Ten male patients (age range, 25-72 years), suffering from AGA at stage II to III according to the Norwood-Hamilton scale, have been treated with a single injection of autologous PRS (ACPSVF: combination of PRP and SVF) in the upper scalp. Preinjection and 6 and 12 weeks postinjection changes in hair density were assessed using ultra high-resolution photography (Fotofinder).
RESULTS: Hair density was significantly increased after 6 weeks and 12 weeks postinjection (P = 0.013 and P < 0.001). In hair-to-hair matching analyses, new hair grew from active follicles. Furhtermore nonfunctioning hair follicles filled with hyperkeartotic plugs, up to today assumed incapable of forming new hair, proved to grow new hair. No side effects were noted after treatment.
CONCLUSIONS: A single treatment of platelet-rich stroma injected in the scalp of patients with AGA significantly increased hair density within 6 to 12 weeks. Further research is required to determine the optimal treatment regimen. Preferred options to our opinion include the repetition of PRS or additional treatments with PRP.

18. Ziering Medical, Marbella, Spain; Ziering Medical, Los Angeles, CA, USA; The Hospital Group, Bromsgrove, Worcestershire, Ziering Medical, Birmingham, Ziering Medical, London, UK, Kerastem Technologies, San Diego, CA, USA; Hair follicle growth by stromal vascular fraction-enhanced adipose transplantation in baldness; Stem Cells Cloning. 2017 Jul 6;10:1-10. doi: 10.2147/SCCAA.S131431. eCollection 2017.
Abstract
Great interest remains in finding new and emerging therapies for the treatment of male and female pattern hair loss. The autologous fat grafting technique is >100 years old, with a recent and dramatic increase in clinical experience over the past 10-15 years. Recently, in 2001, Zuk et al published the presence of adipose-derived stem cells, and abundant research has shown that adipose is a complex, biological active, and important tissue. Festa et al, in 2011, reported that adipocyte lineage cells support the stem cell niche and help drive the complex hair growth cycle. Adipose-derived regenerative cells (also known as stromal vascular fraction [SVF]) is a heterogeneous group of noncultured cells that can be reliably extracted from adipose by using automated systems, and these cells work largely by paracrine mechanisms to support adipocyte viability. While, today, autologous fat is transplanted primarily for esthetic and reconstructive volume, surgeons have previously reported positive skin and hair changes post-transplantation. This follicular regenerative approach is intriguing and raises the possibility that one can drive or restore the hair cycle in male and female pattern baldness by stimulating the niche with autologous fat enriched with SVF. In this first of a kind patient series, the authors report on the safety, tolerability, and quantitative, as well as photographic changes, in a group of patients with early genetic alopecia treated with subcutaneous scalp injection of enriched adipose tissue. The findings suggest that scalp stem cell-enriched fat grafting may represent a promising alternative approach to treating baldness in men and women.

19. Park BS, Kim WS, Choi JS, Kim HK, Won JH, Ohkubo F, Fukuoka; Hair growth stimulated by conditioned medium of adipose-derived stem cells is enhanced by hypoxia: evidence of increased growth factor secretion; H.Biomed Res. 2010 Feb;31(1):27-34.
Abstract
Adipose-derived stem cells (ADSCs) and their secretomes mediate diverse skin-regeneration effects, such as wound-healing and antioxidant protection, that are enhanced by hypoxia. We investigated the hair-growth-promoting effect of conditioned medium (CM) of ADSCs to determine if ADSCs and their secretomes regenerate hair and if hypoxia enhances hair regeneration. If so, we wanted to identify the factors responsible for hypoxia-enhanced hair-regeneration. We found that ADSC-CM administrated subcutaneously induced the anagen phase and increased hair regeneration in C(3)H/NeH mice. In addition, ADSC-CM increased the proliferation of human follicle dermal papilla cells (HFDPCs) and human epithelial keratinocytes (HEKs), which are derived from two major cell types present in hair follicles. We investigated the effect of hypoxia on ADSC function using the same animal model in which hypoxia increased hairregrowth. Forty-one growth factors in ADSC-CM from cells cultured under hypoxic or normoxic conditions were analyzed. The secretion of insulin-like growth factor binding protein (IGFBP)-1, IGFBP-2, macrophage colony-stimulating factor (M-CSF), M-CSF receptor, platelet-derived growth factor receptor-beta, and vascular endothelial growth factor was significantly increased by hypoxia, while the secretion of epithelial growth factor production was decreased. It is reasonable to conclude that ADSCs promote hair growth via a paracrine mechanism that is enhanced by hypoxia.

20. Batch JA, Mercuri FA, Werther GA; Identification and localization of insulin-like growth factor-binding protein (IGFBP) messenger RNAs in human hair follicle dermal papilla; J Invest Dermatol. 1996 Mar;106(3):471-5.
Abstract
The role of the insulin-like growth factors (IGFs) in hair follicle biology has recently been recognized, although their actions, sites of production, and modulation by the insulin-like growth factor-binding proteins (IGFBPs) have not to date been defined. IGF-I is essential for normal hair growth and development, and may be important in regulation of the hair growth cycle. In many culture systems, IGF-I actions are modulated by the IGFBPs. Thus, if IGFBPs are produced in the human hair follicle, they may play a role in targeting IGF-I to its receptor or may modulate IGF-I action by interaction with matrix proteins. We have used in situ hybridization to localize messenger RNA for the six IGFBPs in anagen hair follicles. Anti-sense and sense RNA probes for the IGFBPs (IGFBP-1 to -6) were produced, and 5-micrometer sections of adult facial skin were probed. Messenger RNA for IGFBP-3, -4, and -5 were identified, with predominantly IGFBP-3 and -5 mRNA found in the dermal papilla, and to a lesser extent IGFBP-4 mRNA. IGFBP-4 mRNA was also found at the dermal papilla/epithelial matrix border. Messenger RNAs for both IGFBP-4 and -5 were also demonstrated in the dermal sheath surrounding the hair follicle. Messenger RNAs for IGFBP-1, -2, and -6 were not identified. These studies demonstrate specific localization of IGFBP mRNAs in hair follicles, suggesting that they each play specific roles in the local modulation of IGF action during the hair growth cycle.

21. Elmaadawi IH, Mohamed BM, Ibrahim ZAS, Abdou SM, El Attar YA, Youssef A, Shamloula MM, Taha A, Metwally HG, El Afandy MM, Salem ML; Stem cell therapy as a novel therapeutic intervention for resistant cases of alopecia areata and androgenetic alopecia; J Dermatolog Treat. 2018 Aug;29(5):431-440. doi: 10.1080/09546634.2016.1227419. Epub 2018 Mar 6.

ABSTRACT

BACKGROUND: Management of alopecia areata (AA) and androgenetic alopecia (AGA) is often challenging as patients may be resistant to currently available modalities of treatment. The use of stem cells may be a novel option for resistant cases.

OBJECTIVE: To evaluate the safety and efficacy of the use of autologous bone marrow derived mononuclear cells(including stem cells) as compared to follicular stems cells for the management of resistant cases of AA and AGA.

METHODS: This study included 40 patients (20 AA patients and 20 AGA patients), all patients were treated with a single session of intradermal injection of autologous stem cells (SCs) therapy. They were divided into four groups according to the applied modality [either autologous bone marrow derived mononuclear cells (bone marrow mononuclear cells [BMMCs] or autologous follicular stem cells [FSC]).

RESULTS: Six months after stem cell therapy (SCT) injection, there was a significant improvement, confirmed by immunostaining and digital dermoscopy. The mean improvement in all groups was "very good". There was no significant difference between both methods in either type of alopecia. No serious adverse events were reported.

CONCLUSION: Autologous BMMCs and FSC seem to be a safe tolerable and effective treatment for the management of both resistant AA and AGA.