

RATIONALE SEFFILLER®

Numerosi studi hanno identificato nel tessuto adiposo uno dei tessuti con la più alta concentrazione di cellule staminali mesenchimali adulte (ADSCs) ed in particolare nella sua componente stromale (SVF Stromal Vascular Fraction).

Le provate capacità rigenerative delle cellule staminali mesenchimali (ADSCs) vengono sfruttate in numerose branche mediche quali la chirurgia ricostruttiva, dermatologia, vulnologia, ortopedia, chirurgia vascolare, cardiologia, ginecologia, otorinolaringoiatria e proctologia oltre che nelle terapie *antiaging* nel campo della Chirurgia e Medicina Estetica.

Tale metodica deve avere le seguenti caratteristiche:

- permettere il prelievo del tessuto nel modo meno traumatico possibile per il tessuto stesso;
- prelevare il tessuto adiposo nel piano più superficiale possibile per avere un tessuto più ricco in termini di cellule staminali mesenchimali (ADSCs);
- prelevare cluster cellulari contenenti adipociti, tessuto stromale (SVF) e cellule staminali mesenchimali (ADSCs) di dimensioni ridotte per favorirne l'attecchimento nel sito ricevente;
- minima manipolazione del tessuto prelevato per conservare la maggior vitalità cellulare possibile ed evitare l'utilizzo di dispositivi per la frammentazione tissutale, rendendo così la metodica più rapida e meno costosa;
- essere il meno traumatica possibile per il paziente e ridurre al minimo le complicanze da prelievo quali ematomi, sieromi, infezioni ed irregolarità cutanee;
- tessuto da impiantare deve essere sufficientemente fluido da poter essere innestato con aghi o cannule sottili, in modo da essere il meno traumatico possibile per il sito ricevente. Nella tecnica di preparazione del tessuto da innestare, la parte del PRELIEVO è quella in cui i Medici che non abbiano una specifica preparazione nell'aspirazione del tessuto adiposo sottocutaneo incontrano maggiori difficoltà: questa difficoltà porta molto spesso i Medici ad avvalersi della collaborazione di specialisti in Chirurgia Plastica (aumentando i costi della procedura e rendendo più complessa l'organizzazione della terapia, che spesso richiede diversi trattamenti) oppure a rinunciare alla terapia rigenerativa esponendo il paziente a possibili complicanze legate a manovre di prelievo non corrette.

IMPIANTO TISSUTALE S.E.F.F.I. e MicroS.E.F.F.I. (SUPERFICIAL ENHANCED FLUID FAT INJECTION)

Dal 2015 Gennai et al. hanno pubblicato diversi studi (vedi riferimenti bibliografici) sulle nuove tecniche di innesto di tessuto SEFFI e MicroSEFFI. Queste tecniche mirano a innestare il tessuto adiposo autologo, compresa la frazione stromale (SVF) e le cellule staminali derivate dal tessuto adiposo (ADSC) in esso contenute, al fine di ottenere un miglioramento trofico dei tessuti e un ripristino dei volumi persi. Gli Autori hanno dimostrato che si può prelevare il tessuto adiposo attraverso apposite cannule con fori laterali molto piccoli, in modo da selezionare piccoli cluster cellulari, per cui non è necessario effettuare manipolazioni per fluidificare il tessuto.

SEFFI e MicroSEFFI sono ormai tra le tecniche più utilizzate destinate alla rigenerazione dei tessuti e al ripristino dei volumi per il ringiovanimento del viso e di altre zone del corpo. Queste tecniche sono considerate procedure chirurgiche minimamente invasive, quindi richiedono esperienza chirurgica, in particolare nella liposuzione, e strutture adeguate.

Alla luce di queste evidenze, la Terapia Autologa Rigenerativa è sempre stata solo nelle mani dei chirurghi plastici e non è stata aperta a medici estetici o dermatologi.

Il dottor Gennai crede fermamente che la Terapia Autologa Rigenerativa Estetica debba poter essere eseguita anche da Medici Estetici senza specifica preparazione nell'intervento di liposuzione: per questo ha sviluppato, standardizzato e brevettato* un'apposita guida, cioè un dispositivo finalizzato al prelievo di tessuto adiposo in modo sicuro, facile, efficace, anche senza alcuna abilità chirurgica di liposuzione.

Da questa idea originale SEFFILINE ha sviluppato SEFFILLER®, un dispositivo medico dove tutti i componenti necessari al trattamento sono presenti nella scatola e mono-uso, per consentire ai medici estetici di eseguire trattamenti autologhi rigenerativi in ambulatorio in modo sicuro, facile ed efficace.

*Brevetto italiano

DISPOSITIVO MEDICO SEFFILLER®

Mette a disposizione dei Medici Estetici che vogliono eseguire la terapia rigenerativa il kit per rendere la procedura di prelievo, preparazione ed innesto SEMPLICE, SICURA, RAPIDA, EFFICACE ed ECONOMICA.

SICURO

Il dispositivo medico è monouso, quindi riduce i rischi di contaminazioni e trasmissione di malattie. La guida brevettata rende sicuro il prelievo anche per medici senza specifica esperienza nel prelievo del tessuto adiposo sottocutaneo.

SEMPLICE

La nostra guida brevettata permette al Medico, anche senza specifica esperienza nell'aspirazione del tessuto sottocutaneo, di prelevare il tessuto nel piano corretto e riducendo al minimo il rischio di eseguire manovre che possano danneggiare il paziente.

RAPIDO

Il nostro dispositivo medico è monouso e *"all-in-one"*, senza necessità di apparecchiature esterne quali aspiratori; inoltre la procedura è eseguibile in anestesia locale anche in regime ambulatoriale. Richiede minima manipolazione del tessuto. Il tutto semplifica e riduce i tempi della procedura.

EFFICACE

Il dispositivo medico brevettato *"guida"* il prelievo nel piano corretto superficiale dove è presente la massima concentrazione di cellule staminali mesenchimali (ADSCs). Inoltre la cannula di prelievo determina la selezione di clusters cellulari di minima dimensione riducendo la manipolazione successiva quindi preservando la massima vitalità cellulare. Le ridotte dimensioni dei clusters cellulari favoriscono l'attecchimento e permettono l'innesto con aghi o cannule di ridotte dimensioni nel piano superficiale favorendo l'effetto rigenerativo e diminuendo il traumatismo del sito ricevente.

ECONOMICO

I dispositivi medici della linea SEFFILINE®, essendo monouso *"all-in-one"*, rendono la metodica estremamente economica in quanto può essere eseguita anche in ambulatorio, in anestesia locale, senza la collaborazione del chirurgo esperto in prelievo di tessuto adiposo.

La procedura SEFFILLER® può essere usata in combinazione con altre procedure di medicina estetica quali: tossina botulinica, filler, peeling, resurfacing laser, fili di trazione, needling, ecc.

REFERENCES

1. Gennai A., Bernardini F. P.; Superficial enhanced fluid fat injection (SEFFI and MicroSEFFI) in facial rejuvenation; *CellR4* 2017; 5 (1): e2239
2. Gennai A., Zia S., Roda B., Maggio A., Bonsi L., Alviano F., Zattoni A., Reschiglian P., Bernardini F.P., SEFFI (Superficial Enhanced Fluid Fat Injection) for aesthetic and clinical regenerative treatments, *Global Journal of Dermatology & Venereology*, 2020, 8, 32-40
3. Martina Rossi; Barbara Roda; Silvia Zia; Ilaria Vigliotta; Chiara Zannini; Francesco Alviano; Laura Bonsi, Andrea Zattoni, Pierluigi Reschiglian, and Alessandro Gennai; Characterization of the Tissue and Stromal Cell Components of Micro-Superficial Enhanced Fluid Fat Injection (Micro-SEFFI) for Facial Aging Treatment; *Aesthetic Surgery Journal* 2018, 1–12
4. Francesco P. Bernardini, Alessandro Gennai; Superficial Enhanced Fluid Fat Injection for Volume Restoration and Skin Regeneration of the Periocular Aesthetic Unit. An Improved Fat Grafting Technique to enhance the beauty of the eye; *JAMA Plastic Facial Surgery* January-February 2016 Vol. 18 n. 1
5. Francesco P. Bernardini, Alessandro Gennai, Luigi Izzo, Alessandra Zambelli, Erica Repaci, Ilaria Baldelli, G. Fraternali-Orcioni, Morris E. Hartstein, Pier Luigi Santi, and Rodolfo Quarto; Superficial Enhanced Fluid Fat Injection (SEFFI) to Correct Volume Defects and Skin Aging of the Face and Periocular Region; *Aesthetic Surgery Journal* 2015, 1–12
6. Pignata G, Gennai G, Bernardini F; Rejuvenation of the centre of the face: a new paradigm Endoscopic lifting with fat grafting; *Plsr Aesthet Res* 2018;5:23
7. Tabanella G., Ferlosio A., Orlandi A., Gennai A., Adipose-derived mesenchymal stem cells transplantation for socket preservation: a clinical report, *EC Dental Science, Case Report*, 2019
8. Gennai A, Zambelli A, Repaci E, et al., Skin Rejuvenation and Volume Enhancement with the Micro Superficial Enhanced Fluid Fat Injection (M-SEFFI) for Skin Aging of the Periocular and Perioral Regions. *Aesthet Surg J.* 2017;37(1):14-23.
9. Gennai A., Bernardini F-P, Rejuvenation faciale par lifting endoscopique avec le petite incision incision vertical associée à une injection superficielle de graisse: un repositionnement endoscopique, une regeneration tissulaire et une restauration volumetrique (La technique R3); *J. Med. Esth. Et Chir. Derm.* Vol. XXXIV, 174, juin 2017, 87-95
10. Gennai A., Bernardini F-P, R3 facial rejuvenation through minimal incisions vertical endoscopic lifting (MIVEL) and superficial enhanced fluid fat injection (SEFFI): endoscopic repositioning, tissue regeneration volume restoration; *Aesthetic Medicine*, vol. 1, No. 2, July-Sept 2015
11. Singer NG, Caplan AI Mesenchymal stem cells: mechanisms of inflammation. *Annu Rev Pathol* 2011; 6:457–478
12. Delarosa O, Dalemans W, Lombardo E Mesenchymal stem cells as therapeutic agents of inflammatory and autoimmune diseases. *Curr Opin Biotechnol* 2012; 23:1–5.
13. Krampera M, Glennie S, Dyson J et al Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigenspecific T cells to their cognate peptide. *Blood* 2003; 101:3722–3729
14. Delarosa O, Sánchez-Correa B, Morgado S et al. Human adipose-derived stem cells impair natural killer cell function and exhibit low susceptibility to natural killer-mediated lysis. *Stem Cells Dev* 2012; 21:1333–1343.
15. Planat-Benard V, Silvestre JS, Cousin B, et al. Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. *Circulation.* 2004;109:656 – 663.
16. Madonna R, Geng Y.J. and De Caterina R. Adipose Tissue-Derived Stem Cells: Characterization and Potential for Cardiovascular Repair; *Arterioscler Thromb Vasc Biol* 2009; -1728
17. Coleman S.R., Saboeiro A. Fat Grafting to the Breast Revisited: Safety and Efficacy *Plastic and Reconstructive Surgery*, March 2007.

18. Coleman S.R . Hand Rejuvenation with Structural Fat Grafting. *Plastic And Reconstructive Surgery*, 2002: 1731-44.
19. Madonna R, Geng Y.J. and De Caterina R. Adipose Tissue-Derived Stem Cells: Characterization and Potential for Cardiovascular Repair; *Arterioscler Thromb Vasc Biol* 2009; -1728
20. Caplan, A. I. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J. Cell. Physiol.* 2007; 213(2):341–347.
21. Satija, N. K.; Singh, V. K.; Verma, Y. K.; Gupta, P., et al. Mesenchymal stem cell-based therapy: A new paradigm in regenerative medicine. *J. Cell. Mol. Med.* 2009; 13(11–12):4385–402.
22. Garcia-Olmo D, Garcia-Arranz M, Garcia LG et al. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn’s disease: a new cell-based therapy. *Int J Colorectal Dis* 2003;18:451–454.
23. F. de la Portilla et al. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn’s disease: results from a multicenter phase I/IIa clinical trial *Int J Colorectal Dis* 2013; 28:313–323.
24. Salemi S, Rinaldi C, Manna F, Guarneri GF, Parodi PC. Reconstruction of lower leg skin ulcer with autologous adipose tissue and platelet-rich plasma. *J Plast Reconstr Aesthet Surg.* 2008 Dec;61(12):1565-7.
25. Cervelli V, Gentile P, De Angelis B et al. Application of enhanced stromal vascular fraction and fat grafting mixed with PRP in post-traumatic lower extremity ulcers. *Stem Cell Res.* 2011 Mar;6(2):103-11
26. Mingliang Sun, Yunfan He, Tao Zhou, Pan Zhang, Jianhua Gao, and Feng LuA dipose Extracellular Matrix/Stromal Vascular Fraction Gel Secretes Angiogenic Factors and Enhances Skin Wound Healing in a Murine Model *BioMed Research International* Volume 2017, Article ID 3105780, 11 pages
27. V. Falanga, “Wound healing and its impairment in the diabetic foot,” *e Lancet*, vol. 366, no. 9498, pp. 1736–1743, 2005.
28. S. H. Lee, J. H. Lee, and K. H. Cho, “E ffects of human adipose- derived stem cells on cutaneous wound healing in nude mice,” *Annals of Dermatology*, vol. 23, no. 2, pp. 150–155, 2011.
29. M. Isakson, C. de Blacam, D. Whelan, A. McArdle, and A. J. Clover, “Mesenchymal stem cells and cutaneous wound healing: current evidence and future potential,” *Stem Cells International*, vol. 2015, Article ID 831095, 12 pages, 2015.
30. L.Pan,J.Tang,H.Liu,andB.Cheng,“Sympatheticnerves:How do they a ffect angiogenesis, particularly during wound healing of so tissues?” *Clinical Hemorheology and Microcirculation*, vol. 62, no. 2, pp. 181–191, 2016.
31. Suzuki E, Fujita D, Takahashi M, et al. Adipose tissue-derived stem cells as a therapeutic tool for cardiovascular disease. *World J Cardiol.* 2015;7:454–65.
32. Bourin P, Bunnell BA, Casteilla L, et al. Stromal cells from the adipose tissue- derived stromal vascular fraction and culture expanded adipose tissue- derived stromal/stem cells: a joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). *Cytotherapy.* 2013;15:641–8.
33. Gimble JM, Bunnell BA, Frazier T, et al. Adipose-derived stromal/stem cells. *Organogenesis.* 2013;9:3–10.
34. Nguyen A, Guo J, Banyard DA, et al. Stromal vascular fraction: a regenerative reality? Part 1: current concepts and review of the literature. *J Plast Reconstr Aesthetic Surg.* 2016;69:170–9.
35. Hass R, Kasper C, Böhm S, et al. Different populations and sources of human mesenchymal stem cells (MSC): a comparison of adult and neonatal tissue- derived MSC. *Cell Commun Signal.* 2011;9:12.
36. Katlin B. Stivers, Jason E. Beare, Paula M. Chilton, Stuart K. Williams, Christina L. Kaufman, and James B. Hoying Adipose-derived cellular therapies in solid organ and vascularized-composite allotransplantation *Curr Opin Organ Transplant* 2017, 22:490–498



37. Wang RX, Yu CR, Dambuza IM, et al. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat Med* 2014; 20:633 – 641.
38. Aarabi S, Bhatt KA, Shi Y, Paterno J, Chang EI, Loh SA, et al. (2007) Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *Faseb J* 21: 3250–326
39. Liu S, Jiang L, Li H, Shi H, Luo H, Zhang Y, et al. (2014) Mesenchymal stem cells prevent hypertrophic scar formation via inflammatory regulation when undergoing apoptosis. *J Invest Dermatol* 134: 2648– 2657.
40. Sophie Domergue, Claire Bony, Marie Maumus, Karine Toupet, Eric Frouin, Valérie Rigau, Marie-Catherine Vozenin, Guy Magalon, Christian Jorgensen, Danièle Noël Comparison between Stromal Vascular Fraction and Adipose Mesenchymal Stem Cells in Remodeling Hypertrophic Scars PLOS ONE | DOI:10.1371/journal.pone.0156161 May 26, 2016
41. Elizabeth Brett, MS; Elizabeth R. Zielins, MD; Monica Chin, BS; Michael Januszyk, MD; Charles P. Blackshear, MD; Michael Findlay, MD; Arash Momeni, MD; Geoffrey C. Gurtner, MD; Michael T. Longaker, MD, MBA; Derrick C. Wan, MD Isolation of CD248-expressing stromal vascular fraction for targeted improvement of wound healing *Wound Rep Reg* (2017) 25 414–422 VC 2017
42. Nie, C. et al. Locally administered adipose-derived stem cells accelerate wound healing through differentiation and vasculogenesis. *Cell Transplant.* 20 (2), 205-216 (2011).
43. Shin, L., & Peterson, D. A. Human mesenchymal stem cell grafts enhance normal and impaired wound healing by recruiting existing endogenous tissue stem/progenitor cells. *Stem Cells Transl Med.* 2 (1), 33-42 (2013).
44. Kato, Y., Iwata, T., Washio, K., Yoshida, T., Kuroda, H., Morikawa, S., Hamada, M., Ikura, K., Kaibuchi, N., Yamato, M., Okano, T., Uchigata, Y. Creation and Transplantation of an Adipose-derived Stem Cell (ASC) Sheet in a Diabetic Wound-healing Model. *J. Vis. Exp.* (126), e54539, doi:10.3791/54539 (2017).
45. Hea Gu, MD1; Jae Sun Lee, MS2; Deok-Woo Kim, MD3; Eul-Sik Yoon, MD, PhD3; Eun-Sang Dhong, MD, PhD Neovascular potential of adipose-derived stromal cells (ASCs) from diabetic patients *Wound Rep Reg* (2012) 20 243–252 © 2012
46. Slavkovsky, R. et al. Zucker diabetic fatty rat: a new model of impaired cutaneous wound repair with type II diabetes mellitus and obesity. *Wound Repair Regen.* 19 (4), 515-525 (2011).
47. Michael H. Carstens, Arturo Gómez, Ronald Cortés , Elizabeth Turner , Cecilia Pérez Marlon Ocon , Diego Correa Non-reconstructable peripheral vascular disease of the lower extremity in ten patients treated with adipose-derived stromal vascular fraction cells *Stem Cell Research* 18 (2017) 14–21
48. Bura, A., Planat-Benard, V., Bourin, P., Silvestre, J.-S., Gross, F., Grolleau, J.-L., Saint-Lebesse, B., Peyrafitte, J.-A., Fleury, S., Gadelorge, M., Taurand, M., Dupuis-Coronas, S., Leobon, B., Casteilla, L., 2014. Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia. *PubMed — NCBI. Cytotherapy* 16, 245–257.
49. Rehman, J., Traktuev, D., Li, J., Merfeld-Clauss, S., Temm-Grove, C.J., Bovenkerk, J.E., Pell, C.L., Johnstone, B.H., Considine, R.V., March, K.L., 2004. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation* 109, 1292–1298.
50. Rennert, R.C., Sorkin, M., Januszyk, M., Duscher, D., Kosaraju, R., Chung, M.T., Lennon, J., Radiya-Dixit, A., Raghvendra, S., Maan, Z.N., Hu, M.S., Rajadas, J., Rodrigues, M., Gurtner, G.C., 2014. Diabetes impairs the angiogenic potential of adipose-derived stem cells by selectively depleting cellular subpopulations. *Stem Cell Res. Ther.* 5, 79.
51. Sumi, M., Sata, M., Toya, N., Yanaga, K., Ohki, T., Nagai, R., 2007. Transplantation of adipose stromal cells, but not mature adipocytes, augments ischemia-induced angiogenesis. *Life Sci.* 80, 559–565.
52. Agnes S. Klar, Jakub Zimoch, and Thomas Biedermann Skin Tissue Engineering: Application of Adipose-Derived Stem Cells *Hindawi BioMed Research International* Volume 2017, Article ID 9747010, 12 pages



53. B. Puissant, C. Barreau, P. Bourin et al., "Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells," *British Journal of Haematology*, vol. 129, no. 1, pp. 118–129, 2005.
54. L. Cai, B. H. Johnstone, T. G. Cook et al., "IFATS collection: human adipose tissue-derived stem cells induce angiogenesis and nerve sprouting following myocardial infarction, in conjunction with potent preservation of cardiac function," *STEM CELLS*, vol. 27, no. 1, pp. 230–237, 2009.
55. W.C.Gao, X.Qiao, S.L.Ma, and L.Cui, "Adipose-derived stem cells accelerate neovascularization in ischaemic diabetic skin ap via expression of hypoxia-inducible factor-1 α ," *Journal of Cellular and Molecular Medicine*, vol. 15, no. 12, pp. 2575–2585, 2011.
56. Adas Darinskas, Mindaugas Paskevicius, Gintaras Apanavicius, Gintaris Vilkevicius, Liutauras Labanauskas, Thomas E. Ichim and Rytis Rimdeika Stromal vascular fraction cells for the treatment of critical limb ischemia: a pilot study *J Transl Med* (2017) 15:143 DOI 10.1186/s12967-017-1243-3
57. Stolzing A, Jones E, McGonagle D, Scutt A. Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies. *Mech Ageing Dev.* 2008;129:163–73.
58. Han SK, Kim HR, Kim WK. The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. *Wound Repair Regen.* 2010;18:342–8.
59. Compagna R, Amato B, Massa S, Amato M, Grande R, Butrico L, de Franciscis S, Serra R. Cell therapy in patients with critical limb ischemia. *Stem Cells Int.* 2015;2015:931420.
60. DONG-SIC CHAE, SEONGHO HAN, MINA SON & SUNG-WHAN KIM Stromal vascular fraction shows robust wound healing through high chemotactic and epithelialization property *Cytotherapy*, 2017; 19: 543–554
61. Smith AN, Willis E, Chan VT, Muffley LA, Isik FF, Gibran NS, et al. Mesenchymal stem cells induce dermal fibroblast responses to injury. *Exp Cell Res* 2010;316(1):48–54.
62. Luigi Clauser, MD, DMD Antonio Lucchi, MD, Ilaria Tocco-Tussardi, MD, Chiara Gardin, PhD, Barbara Zavan, PhD Autologous Fat Transfer for Facial Augmentation and Regeneration Role of Mesenchymal Stem Cells *Atlas Oral Maxillofacial Surg Clin N Am* 26 (2018) 25–32
63. Luigi Clauser., Letizia Ferroni., Chiara Gardin, Riccardo Tieghi, Manlio Galie, Giovanni Elia, Adriano Piattelli, Paolo Pinton, Eriberto Bressan, Barbara Zavan Selective Augmentation of Stem Cell Populations in Structural Fat Grafts for Maxillofacial Surgery *PLoS ONE* 9(11): e110796. doi:10.1371/journal.pone.0110796
64. Luigi C. Clauser, MD, DMD, PhD Giuseppe Consorti, MD Giovanni Elia, MD Manlio Galié, MD, DMD Riccardo Tieghi, MD Three-Dimensional Volumetric Restoration by Structural Fat Grafting *Craniofacial Trauma Reconstruction* 2014;7:63–70
65. Ogura F, Wakao S, Kuroda Y, et al. Human adipose tissue possesses a unique population of pluripotent stem cells with nontumorigenic and low telomerase activities: potential implications in regenerative medicine. *Stem Cells Dev.* 2014;23(7):717-728.
66. Lendeckel S, Jodicke A, Christophis P, et al. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report. *J Craniofacial Surg.* 2004;32(6):370-373.
67. Rossi M. AF, Ricci F., Vignoli F., Marchionni C., Valente S., Zannini C., Tazzari P. L., Vignoli M., Bartoletti E., Bonsi L. In vitro multilineage potential and immunomodulatory properties of adipose derived stromal/stem cells obtained from nanofat lipoaspirates. *CellR4.* 2016; 4 (6):e2212.
68. Michalek J, Moster R, Lukac L, et al. Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis. *Cell transplantation.* 2015.
69. Gotoh M, Yamamoto T, Kato M, et al. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients. *Int J Urol.* 2014;21(3):294-300.



70. Granel B, Daumas A, Jouve E, et al. Safety, tolerability and potential efficacy of injection of autologous adipose-derived stromal vascular fraction in the fingers of patients with systemic sclerosis: an open-label phase I trial. *Ann Rheum Dis*. 2015;74(12):2175-2182.
71. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells*. 2014;32(5):1254-1266.
72. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(5):1308-1316.
73. Koh YG, Choi YJ, Kwon OR, Kim YS. Second-Look Arthroscopic Evaluation of Cartilage Lesions After Mesenchymal Stem Cell Implantation in Osteoarthritic Knees. *Am J Sports Med*. 2014;42(7):1628-1637.
74. Maroesjka Spiekman Joris A. van Dongen, Joep C. Willemsen, Delia L. Hoppe, Berend van der Lei and Martin C. Harmsen The power of fat and its adipose-derived stromal cells: emerging concepts for fibrotic scar treatment *J Tissue Eng Regen Med* 2017; 11: 3220–3235.
75. Mohsen Khosravi Maharlooei Mansooreh Bagheri, Zhabiz Solhjoui, Behnam Moein Jahromi, Majid Akrami, Lili Rohani, Ahmad Monabati, Ali Noorafshan, Gholamhossein Ranjbar Omrani Adipose tissue derived mesenchymal stem cell (AD-MSC) promotes skin wound healing in diabetic rats diabetes research and clinical practice 93 (2011) 228–234
76. Jingwei Feng, Kazuhide Mineda, Szu-Hsien Wu, Takanobu Mashiko, Kentaro Doi, Shinichiro Kuno, Kahori Kinoshita, Koji Kanayama, Rintaro Asahi, Ataru Sunaga & Kotaro Yoshimura An injectable non-cross-linked hyaluronic-acid gel containing therapeutic spheroids of human adipose-derived stem cells *Scientific Reports* | 7: 1548 | DOI:10.1038/s41598-017-01528-3.
77. Bilgic S, Durusu M, Aliyev B, Akpancar S, Ersen O, Yasar SM, Ardic S. Comparison of two main treatment modalities for acute ankle sprain. *Pak J Med Sci*. 2015;31(6):1496–1499. doi: 10.12669/pjms.316.8210.
78. Caplan AI. Mesenchymal stem cells. *J Orthop Res*. 1991;9(5):641–650. doi: 10.1002/jor.1100090504.
79. Carter DR, Beaupre GS, Giori NJ, Helms JA. Mechanobiology of skeletal regeneration. *Clin Orthop Relat Res*. 1998;355(Suppl):S41–S55. doi: 10.1097/00003086-199810001-00006.
80. Lendeckel S, Jödicke A, Christophis P, Heidinger K, Wolff J, Fraser JK, Hedrick MH, Berthold L, Howaldt HP. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: case report. *J Cranio-Maxillofac Surg*. 2004;32(6):370–373. doi: 10.1016/j.jcms.2004.06.002.
81. Pak J. Regeneration of human bones in hip osteonecrosis and human cartilage in knee osteoarthritis with adipose-tissue derived stem cells: a case series. *J Med Case Rep*. 2011;7(5):296. doi: 10.1186/1752-1947-5-296.
82. Buckwalter JA. Articular cartilage injuries. *Clin Orthop Relat Res*. 2002;402(1):21–37.
83. Pak J, Chang JJ, Lee JH, Lee SH. Safety reporting on implantation of autologous adipose tissue-derived stem cells with platelet-rich plasma into human articular joints. *BMC Musculoskelet Disord*. 2013;14:337. doi: 10.1186/1471-2474-14-337
84. Pak J, Lee JH, Park KS, Jeong BC, Lee SH. Regeneration of cartilage in human knee osteoarthritis with autologous adipose tissue-derived stem cells and autologous extracellular matrix. *BioRes Open Access*. 2016;5(1):192–200. doi: 10.1089/biores.2016.0024
85. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee*. 2012;19(6):902–907. doi: 10.1016/j.knee.2012.04.001
86. Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, Choi YJ. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy*. 2013;29(4):748–755. doi: 10.1016/j.arthro.2012.11.017.
87. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. *Arthroscopy*. 2014;30(11):1453–1460. doi: 10.1016/j.arthro.2014.05.036

88. Kim YS, Choi YJ, Suh DS, Heo DB, Kim YI, Ryu JS, Koh YG. Mesenchymal stem cell implantation in osteoarthritic knees: is fibrin glue effective as a scaffold? *Am J Sports Med.* 2015;43(1):176–185. doi: 10.1177/0363546514554190.
89. Bui KH-T, Duong TD, Nguyen NT, Nguyen TD, Le VT, Mai VT, Phan NL-C, Le DM, Ngoc NK, Pham PV. Symptomatic knee osteoarthritis treatment using autologous adipose derived stem cells and platelet-rich plasma: a clinical study. *Biomed Res Ther.* 2014;1(1):2–8. doi: 10.7603/s40730-014-0002-9.
90. Michalek J, Moster R, Lukac L, Proefrock K, Petrasovic M, Rybar J, Capkova M, Chaloupka A, Darinskas A, Michalek J Sr, Kristek J, Travnik J, Jabandziev P, Cibulka M, Holec M, Jurik M, Skopalik J, Kristkova Z, Dudasova Z. Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis. *Cell Transplant.* 2015. doi: 10.3727/096368915X686760
91. Fodor PB, Paulseth SG. Adipose derived stromal cell (ADSC) injections for pain management of osteoarthritis in the human knee joint. *Aesthet Surg J.* 2016;36(2):229–236. doi: 10.1093/asj/sjv135.
92. Brody LT, Thein JM. Nonoperative treatment for patellofemoral pain. *J Orthop Sports Phys Ther.* 1998;28(5):336–344. doi: 10.2519/jospt.1998.28.5.336
93. Pak J, Lee JH, Kartolo WA, Lee SH. Cartilage regeneration in human with adipose tissue-derived stem cells: current status in clinical implications. *Biomed Res Int.* 2016;2016:4702674. doi: 10.1155/2016/4702674
94. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med.* 2008;359(11):1108–1115. doi: 10.1056/NEJMoa0800777
95. Pak J, Lee JH, Jeon JH, Lee SH. Complete resolution of avascular necrosis of the human femoral head treated with adipose tissue-derived stem cells and platelet-rich plasma. *J Int Med Res.* 2014;42(6):1353–1362. doi: 10.1177/0300060514546940
96. Saxer F, Scherberich A, Todorov A, Studer P, Miot S, Schreiner S, Güven S, Tchang LA, Haug M, Heberer M, Schaefer DJ, Rikli D, Martin I, Jakob M. Implantation of stromal vascular fraction progenitors at bone fracture sites: from a rat model to a first-in-man study. *Stem Cells.* 2016;34(12):2956–2966. doi: 10.1002/stem.2478
97. Frazier TP, Gimble JM, Devay JW, Tucker HA, Chiu ES, Rowan BG. Body mass index affects proliferation and osteogenic differentiation of human subcutaneous adipose tissue-derived stem cells. *BMC Cell Biol.* 2013;14:34. doi: 10.1186/1471-2121-14-34
98. Jaewoo Pak,#1,2,3 Jung Hun Lee,#1,4 Kwang Seung Park,4 Moonhee Park,4,5 Lin-Woo Kang,6 and Sang Hee Lee Current use of autologous adipose tissue-derived stromal vascular fraction cells for orthopedic applications *J Biomed Sci.* 2017; 24: 9.
99. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7(2):211–228. doi: 10.1089/107632701300062859.
100. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* 2002;13(12):4279–4295. doi: 10.1091/mbc.E02-02-0105
101. Fandong Meng*, Dongmei Zhou*, Wei Li Adipose-derived stem cells as a potential weapon for diabetic foot ulcers *Int J Clin Exp Med* 2017;10(12):15967-15973
102. Konno M, Hamabe A, Hasegawa S, Ogawa H, Fukusumi T, Nishikawa S, Ohta K, Kano Y, Ozaki M, Noguchi Y, Sakai D, Kudoh T, Kawamoto K, Eguchi H, Satoh T, Tanemura M, Nagano H, Doki Y, Mori M and Ishii H. Adipose-derived mesenchymal stem cells and regenerative medicine. *Dev Growth Differ* 2013; 55: 309-318.
103. Nagata H, Ii M, Kohbayashi E, Hoshiga M, Hanafusa T and Asahi M. Cardiac adipose-derived stem cells exhibit high differentiation potential to cardiovascular cells in C57BL/6 mice. *Stem Cells Transl Med* 2016; 5: 141-151.



104. Ribeiro CA, Fraga JS, Graos M, Neves NM, Reis RL, Gimble JM, Sousa N and Salgado AJ. The secretome of stem cells isolated from the adipose tissue and Wharton jelly acts differently on central nervous system derived cell populations. *Stem Cell Res Ther* 2012; 3: 18.
105. Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW and Gimble JM. Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. *J Cell Physiol* 2007; 212: 702-709.
106. Nambu M, Kishimoto S, Nakamura S, Mizuno H, Yanagibayashi S, Yamamoto N, Azuma R, Nakamura S, Kiyosawa T, Ishihara M and Kanatani Y. Accelerated wound healing in healing-impaired db/db mice by autologous adipose tissue-derived stromal cells combined with atelocollagen matrix. *Ann Plast Surg* 2009; 62: 317-321.
107. Bura A, Planat-Benard V, Bourin P, Silvestre JS, Gross F, Grolleau JL, Saint-Lebesse B, Peyrafitte JA, Fleury S, Gadelorge M, Taurand M, Dupuis-Coronas S, Leobon B and Casteilla L. Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia. *Cytotherapy* 2014; 16: 245-257.
108. Bura A, Planat-Benard V, Bourin P, Silvestre JS, Gross F, Grolleau JL, Saint-Lebesse B, Peyrafitte JA, Fleury S, Gadelorge M, Taurand M, Dupuis-Coronas S, Leobon B and Casteilla L. Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia. *Cytotherapy* 2014; 16: 245-257.
109. Jianming Guo^{1,2}, Alan Dardik³, Kacey Fang⁴, Ruixue Huang^{5*} and Yongquan Gu^{1,2*} Meta-analysis on the treatment of diabetic foot ulcers with autologous stem cells *Stem Cell Research & Therapy* (2017) 8:228.