

What is RES™?

Regenerative Epithelial Suspension - RES™ is an autologous suspension composed of the cells¹ and wound-healing factors necessary to regenerate natural healthy skin.

Avita Medical's unique regenerative technology enables clinicians to rapidly create and apply RES™ at the point of care in a simple 30-minute procedure.

The regenerative mechanism is within the suspension...

Activated

- Disaggregation of skin cells removes contact inhibition, inducing the “free edge” effect,² which initiates a cascade of wound healing cell signals.¹⁴
- Growth factors and cytokines are rapidly secreted by “free edge” keratinocytes and fibroblasts to orchestrate proliferation, migration, angiogenesis and matrix re-modelling processes which are essential for skin regeneration.³⁻¹³
- In preclinical experiments RES™ has been shown to exhibit the characteristics of cells in the “free edge” state. Investigators found that large numbers of viable cells from RES™ adhere to a wound bed almost instantly and displayed typical proliferative and migratory morphologies as early as day 1 post-harvest. Key proteins associated with activation were shown to increase and decrease, in accordance with the literature.¹⁴

Available

- RES™ is available within minutes at the point of care and delivers non-cultured disaggregated epithelial skin cells which trigger signaling across the surface of the wound, overcoming the usual limitations of the wound edge. (Figure 1).^{1,15-19}

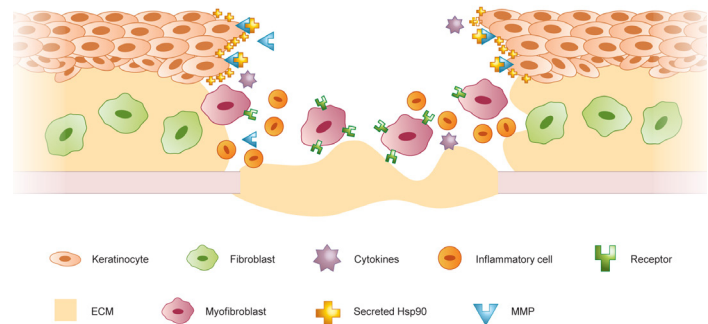
Autologous

- RES™ is safe, as it is produced from the patient's skin. In addition, there is no risk of graft failure due to rejection.²⁰

Complete

- The multi-phenotype skin cells¹ contained in RES™ are essential in the normal cellular processes for effective wound healing and restoration of normal functionality (e.g. durability, pigmentation, minimal contracture).²¹
- Melanocytes contained in RES™ survive to localize to the epidermal side of the dermal-epidermal junction and evenly distribute melanin throughout the epidermis for pigmentation of the new skin.²²
- Application of RES™ increases the number of resident fibroblasts in the wound to reduce migration and wound tension,²³⁻²⁵ which reduces the incidence of contracture.

Normal wound healing



Wound healing with RES™

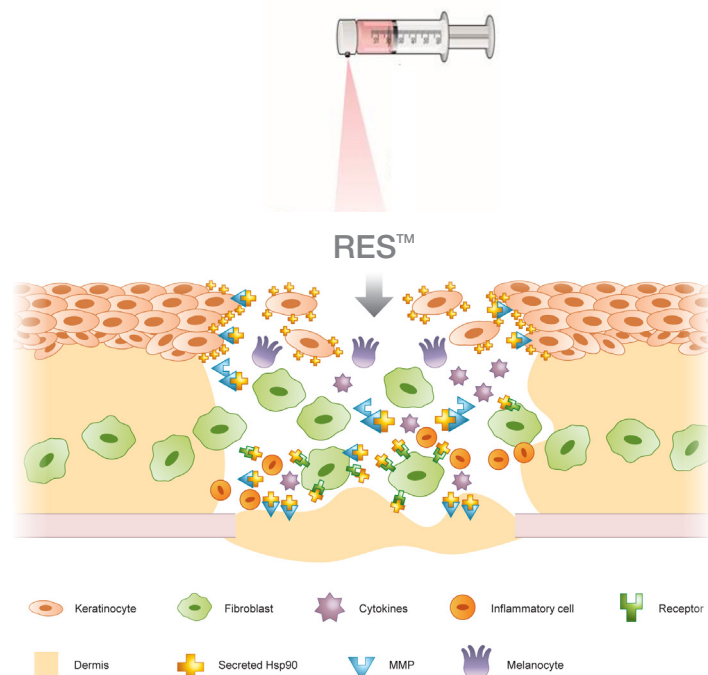


Figure 1

Preparation of RES™

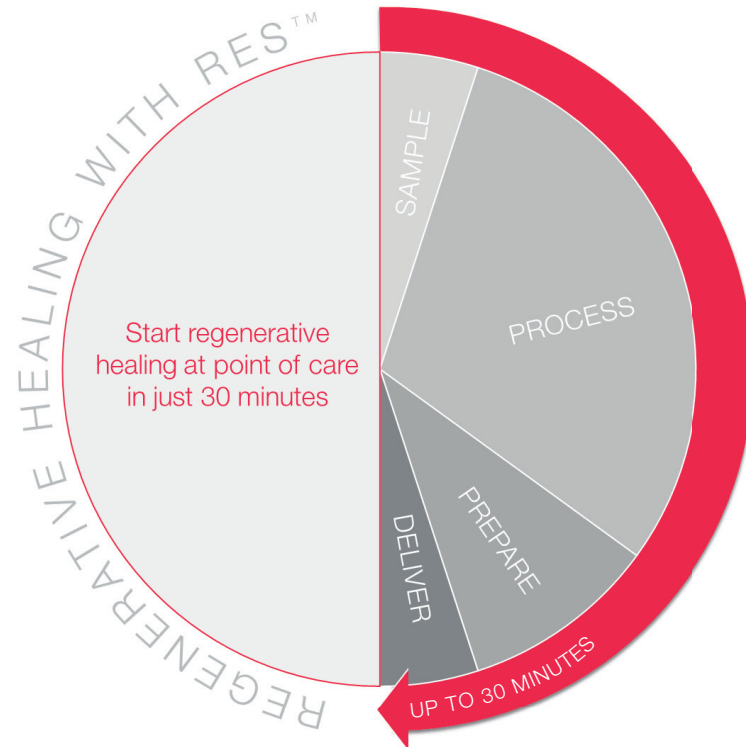


Figure 2



RES™ can be used to:

- **Restart** healing in unresponsive wounds, providing improved healing rates and time to wound closure.²⁶⁻³¹
- **Repair** burns, achieving definitive closure with less donor skin and improved functional and aesthetic outcomes.^{15,32,33}
- **Restore** pigmentation and improve the aesthetic appearance of damaged skin.^{2,19,34-42}

Clinical References

1. Wood FM, Giles N, Stevenson A, Rea S, Fear M. Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell® kit. *Burns* 2012; 38:44-51.
2. Singer AJ, Clark RAF. Cutaneous wound healing. *New England Journal of Medicine* 1999; 341(10):739-746.
3. Mizutani H, Black R, Kupper TS. Human keratinocytes produce but do not process pro-interleukin-1 (IL-1) beta, different strategies of IL-1 production and processing in monocytes and keratinocytes. *Journal of Clinical Investigation* 1991; 87:1066-1071.
4. Wood LC, Elias PM, Calhoun C, Tsai JC, Grunfield C, Feingold KR. Barrier disruption stimulates interleukin-1 α expression and release from a pre-formed pool in murine epidermis. *Journal of Investigative Dermatology* 1996; 106:397-403.
5. Zepfer K, Häffner A, Spohoo LF, De Luca D, Tang HP, Fisher P, et al. Induction of biologically active IL-1 β -converting enzyme and mature IL-1 β in human keratinocytes by inflammatory and immunologic stimuli. *Journal of Immunology* 1997; 159:6203-6208.
6. Mauviel A, Heino J, Kähäri VM, Hartmann DJ, Loyau G, Pujol JP, et al. Comparative effects of interleukin-1 and tumor necrosis factor- α on collagen production and corresponding procollagen mRNA levels in human dermal fibroblasts. *Journal of Investigative Dermatology* 1991; 96:243-249.
7. Mauviel A, Chen YQ, Kähäri VM, Lledo I, Wu M, Rudnicks L, et al. Human recombinant interleukin-1 β up-regulates elastin gene expression in dermal fibroblasts. *Journal of Biology Chemistry* 1993; 268(9):6520-6524.
8. Kupper TS. The activated keratinocyte: a model for inducible cytokine production by non-bone marrow-derived cells in cutaneous inflammatory and immune responses. *Journal of Investigative Dermatology* 1990; 94:146S-150S.
9. Chen JD, Lapiere JC, Sauder DN, Peavey C, Woodley DT. Interleukin-1 α stimulates keratinocyte migration through an epidermal growth factor/transforming growth factor- α -independent pathway. *Journal of Investigative Dermatology* 1995; 104:729-733.
10. Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya et al. Epithelialization in wound healing: A comprehensive review. *Advances in Wound Care* 2014; 3(7):445-464.
11. Li W, Li Y, Guan S, Fan J, Cheng CF, Bright AM, et al. Extracellular heat shock protein-90 α : linking hypoxia to skin cell motility and wound healing. *EMBO Journal* 2007; 26:1221-1233.
12. Cheng CF, Fan J, Fedesco M, Guan S, Li Y, Bandyopadhyay B et al. Transforming growth factor alpha (TGF α)-stimulated secretion of HSP90 α : using the receptor LRP-1/CD91 to promote human skin cell migration against a TGF β -rich environment during wound healing. *Molecular and Cellular Biology* 2008; 28:3344-3358.
13. Woodley DT, Fan J, Cheng CF, Li Y, Chen M, Bu G, et al. Participation of the lipoprotein receptor LRP1 in hypoxia-HSP90 α autocrine signaling to promote keratinocyte migration. *Journal of Cell Science* 2009; 122:1495-1498.
14. Georgopoulos, N and Dunnill, C. Skin Integrity Institute, University of Huddersfield. Personal communication. 2016
15. Zajicek R, Pafcuga I, Suca H, et al. Healing of widely meshed autografts using freshly isolated autologous epidermal cells and acellular Xe-Derma xenoderms. *Hojeni ran* 2012;6(2):12-18.
16. Foster K, Richey K, Pressman M, Caruso D. Compassionate use of ReCell and meshed autografts in three patients with extensive burn injury. Presented at: The 47th Annual Meeting of the American Burn Association; 2015 Apr 21-24; Chicago, USA.
17. Gravante G, Di Fede MC, Araco A, Grimaldi M, De Angelis B, Arpino A, Cervelli V, Montone A. A randomized trial comparing ReCell® system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. *Burns* 2007; 33:966-972.
18. Wood F, Martin L, Lewis D, Rawlins J, McWilliams T, Burrow S, Rea S. A prospective randomized clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. *Burns* 2012; 38:830-839.
19. Komen L, Vrijman C, Tjin EP, Krebbers G, de Rie MA, Luiten RM, van der Veen J4, Wolkerstorfer A. Autologous cell suspension transplantation using a cell extraction device in segmental vitiligo and piebaldism patients: A randomized controlled pilot study. *J Am Acad Dermatol*. 2015 Jul;73(1):170-2

20. Billingham RE, Medawar PB. The technique of free skin grafting in mammals. *Journal of Experimental Biology* 1951; 385-402.
21. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. *Cell* 1975; 6(3):331-343.
22. Navarro FA, Stoner ML, Lee HB, Park CS, Wood FM, Orgill DP. Melanocyte repopulation in full-thickness wounds using a cell spray apparatus. *Journal of Burn Care and Research* 2000; 22(1):41-46.
23. Kwan P, Hori K, Ding J, Tredget EE (2009) Scar and contracture: biological principles. *Hand Clin* 25(4):511-23
24. Sorrell JM, Caplan AI. Fibroblast heterogeneity: more than skin deep. *J Cell Sci*. 2004;117(Pt 5):667-675
25. Grinnell F. Fibroblasts, myofibroblasts, and wound contraction. *J Cell Biol*. 1994, 124(4): 401-404
26. Hu ZC, Chen D, Guo D, Liang YY, Zhang J, Zhu JY, Tang B. Randomized clinical trial of autologous skin cell suspension combined with skin grafting for chronic wounds. *Br J Surg*. 2015;102(2):e117-23.
27. Giraldi E, Ricci E, Spreafico G, Baccaglioni U. Preliminary results with the use of non-cultured Autologous cell suspension to repair non-healing vascular ulcers. *Acta Vulnologica*. 2012. 10, 153-163.
28. De Angelis B, Migner A, Lucarini L, Agovino A, Cervelli V. The use of a non-cultured autologous cell suspension to repair chronic ulcers *Int Wound J* 2013. 12(1):32-9.
29. Trapasso M, Spagnolo F, Marchi F, Strada P, Santi P, Scala, M. Regenerative surgery for the definitive repair of a vasculitic non-healing ulcer using platelet-derived growth factors and noncultured autologous cell suspension. *Plast Reconstr Surg* 2013; 1:1-3.
30. Chant H, Woodrow T, Manley J. Autologous skin cells: a new technique for skin regeneration in diabetic and vascular ulcers. *Journal of Wound Care* 2013;22(10Suppl):S10-5.
31. Using ReCell to Treat Difficult to Heal Chronic Wounds Case Study Jeremy Rawlins FRCS (Plast) Consultant Plastic surgeon.
32. O'Neill TB, Rawlins J, Rea S, et al. Complex chemical burns following a mass casualty chemical plant incident: How optimal planning and organisation can make a difference. *Burns* 2012;38:713-18.
33. Holmes JH. Compassionate use of ReCell in a massive burn injury. Presented at the 17th Congress of the International Society for Burn Injuries, 12-14 October 2014, Sydney, Australia.
34. Yamaguchi Y, Brenner M, Hearing VJ. The regulation of skin pigmentation. *Journal of Biological Chemistry* 2007; 282(38):27557-27561.
35. Navarro FA, Stoner ML, Lee HB, Park CS, Wood FM, Orgill DP. Melanocyte repopulation in full-thickness wounds using a cell spray apparatus. *Journal of Burn Care and Research* 2000; 22(1):41-46.
36. Goodman, G.J. (2008). An automated autologous cell transplantation method for the treatment of hypopigmented scarring. *Dermatologic Surgery*. 34(4):578-581.
37. Cervelli, V., DeAngelis, B., Balzani, A., Colicchia, G., Spallone, D., Grimaldi, M. (2009). Treatment of stable vitiligo by ReCell system. *Journal of Wound Technology*. 17(4), 273-278.
38. Cervelli, V., DeAngelis, B., Spallone, D., Lucarini, L., Arpino A., Balzani, A. (2009, October). Use of a novel autologous cell-harvesting device to promote epithelialization and enhance appropriate pigment in scar. *Clinical and Experimental Dermatology*. 35(7):776-780.
39. Gramlich G.E.M. (2010). Laser Rejuvenation in combination with autologous cell suspension. *Kosmetische Medizin*. 1(10), 25-29.
40. Cervelli, V., Spallone, D., Lucarini, L., Palla, L., Brinci, L., DeAngelis, B. (2010). Treatment of stable vitiligo hands by ReCell® system: a preliminary report. *European Review for Medical and Pharmacological Sciences*. 14, 691-694.
41. Mulekar S.V., Ghwsh B., Al Issa A. and Al Eisa A. (2007, January). Treatment of Vitiligo lesions by ReCell® vs. conventional melanocyte-keratinocyte transplantation: a pilot study. *Brit. J. of Dermatology*. 158(1), 45-49.
42. K.H. Busch, R. Bender , N. Walezko, H. Aziz, M.A. Altintas , M.C. Aust. Combination of medical needling and non-cultured autologous skin cell transplantation (ReNovaCell) for repigmentation of hypopigmented burn scars. *Burns*. 2016