

Regenerative Medicine: Confusion or Complacency?

The subject of Regenerative Medicine is currently at an inflexion point.¹ There has been an enormous amount of financial investment, along with basic and clinical research, but despite these efforts there is only one tried and tested use of stem cells and that is bone marrow transplantation (using haemopoietic stem cells) which was first developed in 1957.² The rest of Regenerative Medicine is currently confused with the identification of multiple stem cell types,³ many clinical trials⁴ but no real progress to a safe and effective routine stem cell-based procedure for any disease.

Perhaps the most studied stem cells (apart from haemopoietic stem cells) to date are mesenchymal stem cells (MSC) which are found in adipose tissue,⁵ umbilical cord tissue⁶ and even inside teeth.⁷ Despite this apparent abundance of MSC for potential clinical use there have been many problems along the way such as complicated and expensive isolation and preparation of MSC, lack of standardisation of MSC preparations, licensing issues in some countries and unreliable clinical outcomes. As a result, MSC technology has staggered to an almost halt with little or no standardised treatments available.

The second types of stem cell which caused great excitement, and even greater hype and cost, are embryonic stem cells (ESC)⁸ and induced Pluripotent Stem Cells (iPSC).⁹ The problems relating to ESC are that they are made by destroying a human embryo which causes considerable legal, ethical, religious and moral objections. They are also technically difficult to create and require extensive regulatory approval making them extremely expensive. The problems relating to iPSC are that they are 'man made' from normal body cells (e.g. skin cells) by the introduction of new genes into the skin cell to 'turn it into' a stem cell. The reservations here are cost, safety and efficacy and once again neither ESC nor iPSC have reached routine clinical practice.

Thankfully, there is one stem cell type which is readily available, cheap to produce and potentially very safe and effective. These stem cells have an unusual name and equally unusual properties. The name of the stem cells is human Very Small Embryonic Like (hVSEL) stem cells.¹⁰ These hVSEL stem cells are present in every tissue in the body (including blood) and they are pluripotent meaning that they can, in theory, regenerate any tissue type in the body.¹¹ The fact that they are termed 'embryonic like' does not mean that they are embryonic stem cells, it simply means that they carry some of the surface antigens seen on embryonic stem cells.¹² These hVSEL stem cells may be quiescent in normal physiology or may be the ultimate source of all other stem cell types in normal homeostasis.¹³ It has also been shown that hVSEL are mobilised during disease or injury and may be contributing to tissue repair in these circumstances.¹⁴⁻¹⁵

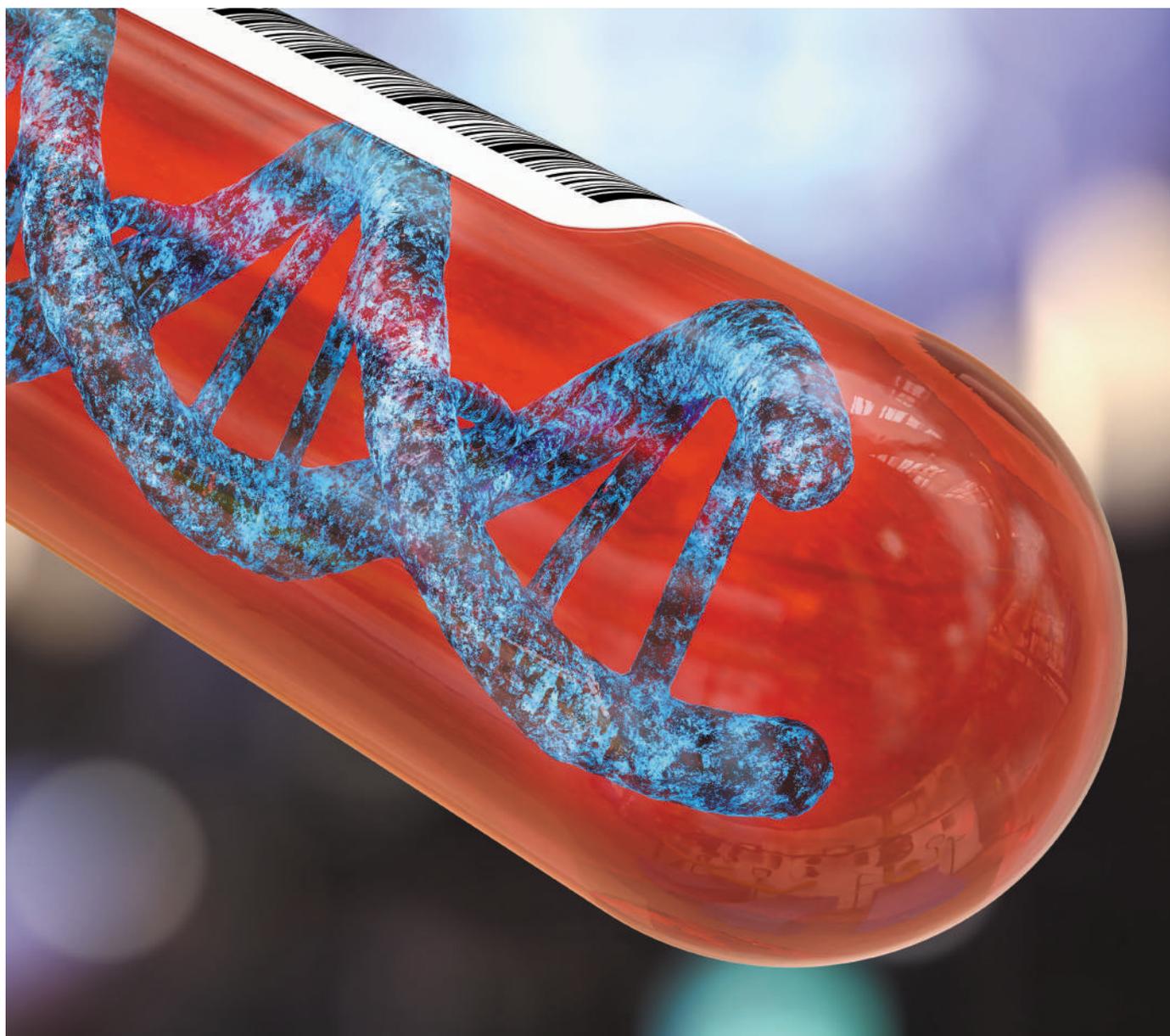
The most exciting thing is that hVSEL can be easily obtained by taking a blood sample from the patient and preparing Platelet Rich

Plasma (PRP) which contains millions of hVSEL stem cells. These hVSEL stem cells in PRP can then be activated using modulated laser light to make them highly safe and effective autologous reparative stem cell technology.¹⁶ The mechanism of action of the modulated laser light on hVSEL stem cells is still to be fully defined but a mechanism has been proposed using the principles of Quantum Mechanics which is once again a first in stem cell technology.¹⁷ It has since been found that the modulated laser does in fact interact with other stem cell types most notable umbilical cord blood derived expanded MSC which have been shown to be extremely effective in the treatment of end stage heart failure.¹⁸ In the same study we reported the safety and efficacy of autologous laser activated hVSEL stem cells in the treatment of end-stage heart failure.

Much more work is needed on laser activated autologous hVSEL stem cells, but they represent an easy to obtain, cheap to process and potentially a safe and effective treatment for a wide range of pathologies. The impact alone on global heart disease could be massive and similar as yet unpublished results have been obtained in neurological disease, neurological trauma and type 2 diabetes. Since hVSEL stem cells are pluripotent they can not only repair stem cell numbers in any stem cell compartment but also repair the damaged or diseased stem cell niche.¹⁹ The stem cell technology needed to provide safe, effective and affordable treatments in the future needs to be identified and focussed on now. If we continue with confused, complex and expensive technology then regenerative medicine will have a very poor, if not non-existent, future.

REFERENCES

1. Edgar, L., Pu, T., Porter, B., Aziz, J.M., La Pointe, C., Asthana, A. & Orlando G. Regenerative medicine, organ bioengineering and transplantation. *Br J Surg.* 107(7), 793-800 (2020).
2. Simpson, E. & Dazzi, F. Bone Marrow Transplantation 1957-2019. *Front Immunol.* 10, 1246 (2019).
3. Zakrzewski, W., Dobrzyński, M., Szymonowicz, M. & Rybak, Z. Stem cells: past, present, and future. *Stem Cell Res Ther.* 10(1), 68 (2019).
4. <https://www.nih.gov/health-information/nih-clinical-research-trials-you> (accessed 07/04/2022)
5. Mushahary, D., Spittler, A., Kasper, C., Weber, V. & Charwat, V. Isolation, cultivation, and characterization of human mesenchymal stem cells. *Cytometry A.* 93(1), 19-31 (2018).
6. Xie, Q., Liu, R., Jiang, J., Peng, J., Yang, C., Zhang, W., Wang, S. & Song, J. What is the impact of human umbilical cord mesenchymal stem cell transplantation on clinical treatment? *Stem Cell Res Ther.* 11(1), 519 (2020).
7. Hollands, P., Aboyeji, D. & Orcharton, M. Dental pulp stem cells in regenerative medicine. *Br Dent J.* 1, 5-9 (2018).
8. Vazin, T. & Freed WJ. Human embryonic stem cells: derivation, culture, and differentiation: a review. *Restor Neurol Neurosci.* 28(4), 589-603 (2010).
9. Ohnuki, M. & Takahashi, K. Present and future challenges of induced pluripotent stem cells. *Philos Trans R Soc Lond B Biol Sci.* 370(1680), 20140367 (2015).
10. Ratajczak, M.Z., Zuba-Surma, E.K., Machalinski, B., Ratajczak, J. & Kucia, M. Very small embryonic-like (VSEL) stem cells: purification from adult



- organs, characterization, and biological significance. *Stem Cell Rev.* 4(2), 89-99 (2008).
11. Kucia M, Machalinski B, Ratajczak MZ. The developmental deposition of epiblast/germ cell-line derived cells in various organs as a hypothetical explanation of stem cell plasticity? *Acta Neurobiol Exp (Wars)*. 66(4), 331-341 (2006).
 12. Kucia M, Zub a-Surma EK, Wysoczynski M, Wu W, Ratajczak J, Machalinski B, Ratajczak MZ. Adult marrow-derived very small embryonic-like stem cells and tissue engineering. *Expert Opin Biol Ther.* 7(10), 1499-1514 (2007).
 13. Ratajczak, M.Z., Zuba-Surma, E.K., Wysoczynski, M., Ratajczak, J., & Kucia, M. Very small embryonic-like stem cells: characterization, developmental origin, and biological significance. *Experimental hematology*, 36(6), 742-751. (2008).
 14. Hénon, P. Key Success Factors for Regenerative Medicine in Acquired Heart Diseases. *Stem Cell Rev Rep.* 16(3), 441-458 (2020).
 15. Ratajczak, J., Zuba-Surma, E., Paczkowska, E., Kucia, M., Nowacki, P. & Ratajczak, M.Z. Stem cells for neural regeneration--a potential application of very small embryonic-like stem cells. *J Physiol Pharmacol.* 62(1), 3-12 (2011).
 16. Hollands, P., Aboyeji, D.R. & Ovokaitys, T. The action of modulated laser light on Human Very Small Embryonic-Like (hVSEL) stem cells in Platelet Rich Plasma (PRP) *CellR4* 8, e2990 (2020).
 17. Brindley, J., Hollands, P. & Ovokaitys, T. A Theoretical Mechanism for the Action of SONG-Modulated Laser Light on Human Very Small Embryonic-Like (hVSEL) Stem Cells in Platelet Rich Plasma (PRP) *CellR4* 9, e3201 (2021).
 18. Ovokaitys, T., Paronyan, A., Hayrapetyan, H. & Hollands P. Intravenous SONG-modulated laser-activated allogeneic cord blood mesenchymal stem cells for the treatment of end-stage heart failure: a preliminary clinical study, *CellR4* 9, e3280 (2021).
 19. Lane, S.W., Williams, D.A. & Watt, F.M. Modulating the stem cell niche for tissue regeneration. *Nature Biotechnology* 32(8), 795-803 (2014)

Peter Hollands



Peter trained at Cambridge University under the supervision of the co-inventor of IVF and Nobel Laureate Professor Sir Bob Edwards FRS. He has worked in various IVF clinics in the UK, Canada and Nigeria and has held executive positions in several stem cell companies. Peter has written a book on stem cell technology called 'The Regeneration Promise'. His second book 'The Fertility Promise' is an explanation of IVF and assisted reproduction.

Email: peterh63@hotmail.com