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Mulhouse Strategy to Expand Ex Vivo Very Small Embryonic Like Stem Cells (VSELs) – Recent Study Published in *Stem Cell Reviews and Reports*

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Very small embryonic like stem cells (VSELs) are a population of developmentally early stem cells that may differentiate across germ layers [1–4]. These rare small cells have been identified in adult tissues including bone marrow (BM), mobilized peripheral blood (mPB), umbilical cord blood (UCB), and other organs such as for example gonads. VSELs remain quiescent due to epigenetic changes in genes involved in insulin/somatotrophic signaling [1]. This phenomenon prevents their unleashed proliferation and potential risk of teratoma formation [1]. The presence of these cells in postnatal tissues challenges a hierarchy of stem cell compartments in hematopoietic and non-hematopoietic organs. Accumulating data indicate that these pluri/multipoint stem cells may in a controlled way give rise to tissue specific stem cells. This is challenging some dogmatic concepts; as recently discussed in an excellent review [2].

Since VSELs without a doubt exist in BM [3, 4] a major question is: what is their relationship to other populations of stem cells in this organ? Are they precursors of long term repopulating hematopoietic stem cells, mesenchymal stroma cells and endothelial progenitors? [1–4]. The phenotype of most primitive hematopoietic stem cell (HSCs) is still not very well known and competing phenotypes have been described in the literature. However, in several published studies in the past VSELs have been demonstrated to possess hematopoietic potential (reviewed in [1–4]). Nevertheless, one of the problems with their hematopoietic specification was needing to employ as a feeder layer murine OP-9 stroma cells [1]. This has been recently omitted by expanding these small cells in a feeder layer free medium supplemented with nicotinamide, FSH, LH, BMP-4, FGF-2 and KL [1].

On top of this, an exciting story has been recently published in a current issue of Stem Cell Reviews & Reports from a group of investigators from Mulhouse, France [5]. Dr. Lahlil from Dr. Henon group and colleagues have successfully employed for the expansion of purified VSELs a small molecule UM171 that is a pyrimido-[4,5-b]-indole derivative. VSELs as reported were in their hands significantly expanded without feeder cells and more importantly expanded cells preserved their capacities to differentiate into hematopoietic and endothelial cells. The link between VSELs, HSCs and endothelial progenitors has been already postulated by other investigators [1–4]. What Lahil et al. noticed is that more than 1000 genes become downregulated in freshly isolated VSELs, but after 12 days of expansion and stimulation expanded VSELs restored the expression of some downregulated genes known as key regulators of cell proliferation and differentiation. The authors postulate that properties of such pluripotent expanded cells make them potential candidates for clinical applications in regenerative medicine [5].

The small molecule UM171 has been successfully employed in the past by Dr. Guy Sauvageau's team, to expand ex vivo of human UCB cells that after successful expansion were capable of reconstituting human hematopoiesis for at least 6 months in a model of immunocompromised mice. However, the potential target for UM171 is still unknown and seems to be independent of suppression of the aryl hydrocarbon receptor. Recently the same groups employed this molecule to expand $CD34^+$ UCB cells into cells with multilineage repopulation activity as demonstrated in the elegant model of serial transplants. The expanded cells expressed the endothelial protein C receptor (EPCR/CD201, PROCR). The expression of EPCR raised again a question of relationship of expanded cells to endothelial lineage. Interestingly UM171 also expanded in the

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hands of Dr. Lahlil's group UCB-purified VSELs into endothelial cells [5]. To support this further, Smadja and other investigators (reviewed in [1–4]) postulated a link between VSELs, HSCs and endothelial progenitors.

The data reported by Lahlil et al. confrim that VSELs are a population of stem cells that can be specified into HSCs. Thus the positive expansion results of $CD34^+$ or $CD133^+$ cells in presence of UM171 [5] or nicotinamide [1] may in fact depend on the expansion of most primitive $CD34^+/CD133^+$ VSELs. It is well known that asymmetric stem cell division is crucial to maintain the "true expansion" of stem cells – and this important feature of VSELs during hematopoietic expansion has been nicely demonstrated by Bhartiya et al. [3].

In conclusion, this interesting study by Lahlil et al. [5] demonstrates that ex vivo expansion of VSELs is feasible without feeder layer cells or retroviral vectors. Since these cells express several pluri/multipotency markers we are looking forward to see the application of VSELs cells in clinical trials to treat hematopoietic- and non-hematopoieic disorders and organ damages.

References

1. Ratajczak, M. Z., Bartke, A., & Darzynkiewicz, Z. (2017). Prolonged growth hormone/insulin/insulin-like growth factor nutrient response signaling pathway as a silent killer of stem cells and a culprit in aging. *Stem Cell Reviews, 13*(4), 443–453. https://doi.org/10.1007/s12015-017-9728-2.
2. Bhartiya, D. (2017). Pluripotent stem cells in adult tissues: Struggling to be acknowledged over two decades. *Stem Cell Reviews, 13*(6), 713–724. https://doi.org/10.1007/s12015-017-9756-y.
3. Ganguly, R., Metkari, S., & Bhartiya, D. (2018). Dynamics of bone marrow VSELs and HSCs in response to treatment with gonadotropin and steroid hormones, during pregnancy and evidence to support their asymmetric/symmetric cell divisions. *Stem Cell Reviews, 14*(1), 110–124. https://doi.org/10.1007/s12015-017-9781-x.
4. Smadja, D. M. (2017). Bone marrow very small embryonic-like stem cells: New generation of autologous cell therapy soon ready for prime time? *Stem Cell Reviews, 13*(2), 198–201. https://doi.org/10.1007/s12015-017-9718-4.
5. Lahlil R, Scrofani M, Barbet R, Tancredi C, Aries A, Hénon P. (2018). VSELs maintain their pluripotency and competence to differentiate after enhanced ex vivo expansion. *Stem Cell Reviews*. 8 May 2018. https://doi.org/10.1007/s12015-018-9821-1.