

Format for ANSWERING REVIEWERS



September 29, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 12988 Review.doc)

Title: The Vital Roles of Stem Cells and Biomaterials in Skin Tissue Engineering

Author: Abu Bakar Mohd Hilmi and Ahmad Sukari Halim

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 12988

The manuscript has been improved according to the suggestions of reviewers:

- 1) Format has been updated
- 2) Revision has been made according to the suggestions of the reviewer

Reviewer 1

This review is titled as "The vital roles of stem cells and biomaterials in skin tissue engineering". The content of this manuscript collectively deals with several types of somatic stem cells such as EpiSC, HFSC, etc. Scope of this review article seems to be rather diverse in many technical aspects. Reader of this manuscript cannot figure out the solid image of this reviews. In which point the author want to focus? Tissue engineering of skin? Stem cell biology? Cell transplantation therapy about skin in dermatology or that in plastic surgery? Biomaterials and biopolymers?

Based on the title, the manuscript is focused on the most important of stem cells and biomaterials that are mainly involved in skin tissue engineering. Cells transplantation therapy in dermatology or plastics surgery and biopolymers are not included therein.

Artificial epidermis consisting of cultured keartinocytes, and artificial dermis consisting of cultured fibroblasts on the suitable scaffold are two major categories of tissue-engineered medical products (TEMPs) in a clinical use. Therefore I suggest that the author should focus on cell biological aspect of EpiSC derived from ectodermal lineage, and also on the induction of fibroblasts from cells of mesodermal lineage much more in detail.

Artificial epidermis and dermis involved many types of cells and not limited to keratinocytes and fibroblasts as briefly mentioned in Table 1. The contribution of fibroblasts and EpiSC in TEMP for clinical use however, is included before on pages 11-12.

In my impression, HFSC is also an important factor in stem cell biology field, but still is not in tissue engineering for clinical application. Hair itself can be substituted by wigs or also by other bio-mimetic technologies. However severe burns and would of the skin should be absolutely treated with cell-based artificial skin for keeping the life of patients. If the authors have a strong interest in cell transplantation therapy using various types of stem cells contained in the skin, rather than in the artificial skin, it is also necessary to describe various types of stem cells contained in the skin tissues as described briefly in line 3-12 of page 6 in much more detail (see a review article; J. Li et al., *Inter. J. Mol. Sci.* 14, 11626-11642 in Open Access, as an example).

Various types of stem cells contained in skin tissue are already included comprehensively on page 5.

The author summarized cell-based artificial skin in Table 1. However the information is not comprehensive and does not cover all the products in the World (for example, only products of companies in USA, UK, Switzerland, Malaysia were cited). Name of company should be written in the Table 1.

The skin substitutes in Table 1 contain the current skin substitutes; therefore other skin substitutes are excluded. The name of company is not included in the current review to avoid favouritism of business.

The author wrote as described below in line 8-10 from bottom of page 4. "Stem cells that are able to differentiate into one cell type are known as unipotent stem cells, such as epidermal stem cells (EpiSC) which regenerate differentiated epidermis.⁴" However usually unipotent immature cell is called as "progenitor cell", rather than the stem cell. Somatic stem cell (tissue stem cell) is defined as the cell having both self-renewal activity and multipotency.

Unipotent immature cells are named progenitor cells. Meanwhile, epidermal stem cells are unipotent stem cells as explained by Cédric Blanpain and Elaine Fuchs in "Epidermal Stem Cells of the Skin" *Annu Rev Cell Dev Biol.* 2006 ; 22: 339-373.

The author wrote as described below in line 3-7 from top of page 10. "Currently, fish skin, seaweed, jellyfish and other marine sources are in high demand for isolating collagen and are the ideal sources for skin tissue engineering because prion disease transmission to humans is eliminated if marine-based sources are used compared with mammalian-based sources." However it is not true. Seaweed does not contain collagen, as same as in case of other plants.

Seaweed contains large quantity of collagen as performed by Sher Bahadar Khan, Zhong-Ji Qian, BoMi Ryu, and Se-Kwon Kim in "Isolation and Biochemical

Characterization of Collagens from Seaweed Pipefish, *Syngnathus Schlegeli*”
Biotechnology and Bioprocess Engineering 2009, 14: 436-442.

Reviewer 2

General Comments The quality and readability of the manuscript is high, and the discussion of skin-resident stem cells is interesting. Major areas of deficiencies are:

The interaction between the discussed stem cell source and various biomaterials is lacking. The review fails to cover in sufficient detail the composition and application of tissue engineered skin products currently used clinically (as shown in Table 1.) Expansion of the review to detail and discuss these clinically applied products, their advantages and disadvantages as well as clinical outcomes would significantly improve the manuscript and increase interest to the readers.

The composition and clinical application of tissue engineered skin products are included on pages 9 and 10

The main and short titles are appropriate, while the short title neglects to mention biomaterials, which seem to be a main point of this manuscript

Short title has reached maximum words, therefore neglects to mention biomaterials therein.

The abstract contains appropriate information for the review, however some topics are raised in the abstract but not discussed in the review (eg. Fabrication methods, storage, cost, use of serum etc.).

Fabrication methods are included on page 11. Storage, cost, use of serum have never been explained in the abstract of current review.

A clear link between biomaterials and stem cells and the advantages of each (together and separate) is not clearly stated.

The advantages of stem cells alone have been included before on page 5 entitle Skin Stem Cells. The advantages of biomaterials have been included before on page 6 entitle Biomaterials. The combination of them has been included on Table 1.

Figure 2 does not support the authors comments that HFSC are rapidly proliferating, with the figure apparently showing a single cell (of many) dividing once over 12 hours.

Figure 2 supports the proliferation of HFSCs. The figure is about an observation of HFSCs using live imaging technique which is able to determine the population

doubling time (PDT). PDT of HFSCs has been demonstrated in “A simple culture method for epithelial stem cells derived from human hair follicle, Cent Eur J Bio (2013).” Based on the live imaging (Figure 2), the cell was proliferating on about 13 hours post- culture which are considered rapidly proliferating. Other cells however, was proliferating later on.

Figure 3 is not self-explanatory and it is not clear why this example was used when there are many successful clinical examples. The Table is appropriate, but would benefit from additional information, such as separating the biomaterial and cell types (currently both listed under “biomaterial source” and perhaps comparison of the clinical outcomes for each of these products. More information and clear descriptions for the tables and figures could be included, as described above. Figures and tables are not adequately explained in captions or in the text

Figure 3 is important for answering core tips section. More information and description are adequately explained on page 15 (Figure 3) and page 14 (last paragraph).

3) References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*

Sincerely yours,

Mohd Hilmi Abu Bakar

Mohd Hilmi Abu Bakar,
The first author.