September 24, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 21866-revised manuscript.doc).

Title: High-risk corneal allografts: a therapeutic challenge

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Name of Journal: *World Journal of Transplantation*

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Reviewer's comments: This is well prepared review covering different aspects of corneal allotransplantation (experimental models, clinical observations, mechanisms of rejection, stem cells, arteficial corneas, etc). From the reason of this large extent the authors had to simplify some statements (as for example: murine corneal allografts demonstrate 50% graft survival, description of corneal graft rejection (which can be different in normal and "high-risk" recipients), the statement that PSC are able to differentiate into limbal stem cells, etc). Nevertheless, the paper is well prepared by the authors having the experience with experimental and clinical corneal transplantation and thus it can be accepted as it is.

We thank the reviewer for thorough reading of this manuscript and the supportive comments. The manuscript has been revised and improved according to the suggestions of reviewers:

(1) **Introduction, 1st paragraph, line 10, sentences were re-structured for clarification.**

More importantly, corneal grafts performed in "high-risk" recipients have a much reduced acceptance rate with a 5-year survival of 54.2% compared to 91.3% in recipient eyes that have not been overtly inflamed. The "high-risk" recipients were defined by the collaborative corneal transplantation studies as two or more quadrants of the cornea vascularized or a previous graft had been rejected.

(2) **Experimental corneal allograft, 1st paragraph, line 3, sentence was rephrased.**

Similar to human corneal grafting, murine corneal allografts performed in an uninflamed graft bed, despite being mismatched for both major and minor histocompatibility complex antigens, half of the grafts failed, whereas in the inflamed "high-risk" graft bed, almost all of the grafts failed and with an increased tempo depending on the level of major histocompatibility complex (MHC)/non-MHC antigens mismatch

(3) **Embryonic and induced pluripotent stem cells, 2nd paragraph, line 6, additional information was added and the sentences were rearranged**

PSC are able to differentiate into limbal stem cells (LSC) in vitro, confirmed by expression of LSC markers ABCG-2 and p63α at both cellular and molecular levels. The successful engraftment of these differentiated LSC seeded scaffold demonstrated significant reconstruction of ocular surface with functional re-epithelization, minimal corneal scars and corneal vascularization in an experimental model of alkali burn in rabbits. Hence, PSC could potentially

be used to replace damaged LSC which is a characteristic feature found in many "high-risk" ocular pathologies

Thank you again for publishing our manuscript in the *World Journal of Transplantation.*

Sincerely yours,

Lucia Kuffová
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