HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

ABN 16 823 190 402

Head Office
QQ Block
QEII Medical Centre
6 Verdun Street, Nedlands
WA 6009 Australia

PO Box 7214
Shenton Park WA 6008

T: +61 8 6151 0700
F: +61 8 6151 0701
reception@perkins.uwa.edu.au
perkins.org.au

Associate Prof Fang-Xu Jiang

Head, Islet Cell Development Program
Level 7, QQ Block, QEII Medical Centre
6 Verdun Street, Nedlands
WA 6009, AUSTRALIA
Telephone: (08) 6151 0758
Facsimile: (08) 6151 0701
E-mail: fangxu.jiang@perkins.uwa.edu.au

11 Aug 2015

Dr Lian-Sheng Ma
President and Company Editor-in-Chief

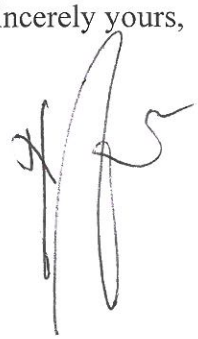
Dear Dr Ma,

Re: ESPS Manuscript NO: 19824 (Multipotent pancreas progenitors: inconclusive but pivotal topic).

Thanks for reviewing and remarking positively to our above manuscript. We have addressed most comments and revisions have been highlighted. A point-by-point response has been attached below. A core tip has also been included.

We wish that you could make a favorable decision to publish our MS.

Sincerely yours,



Fang-Xu Jiang
cc.

Responses to reviewers

Reviewer 1

"This is a very nice review article summarizing the current knowledge of multipotent pancreas progenitors cells and recommending future research directions. If anything can be added, I would recommend that the authors discuss a model of simultaneous expansion of exocrine and endocrine components: the glucagon receptor KO mice and humans with inactivating glucagon receptor mutations (such as P86s). Considering the expansion of both exocrine and endocrine components in these conditions, a potential MPP population may be stimulated and give rise to both."

Thanks for your positive remarks on our manuscript. As the MS focused on the self-renewable multipotent pancreatic progenitors, the addition of contents regarding expansion of exocrine and endocrine tissues of the pancreas might affect the major theme of the review. Glucagon receptor knockout in mice and mutation in humans are definitely interesting areas, but we are not aware that knockout or mutant pancreases contain more or less putative multipotent pancreatic progenitors. Thus we decided not to add these extra data. We will be happy to, should the editor requests us doing so.

Reviewer 2

"The authors reviewed literature related to multipotent pancreatic progenitor cells (MPP) that is expected to exist in adult pancreas but have not been established, and discussed ways that facilitate future advances in this field toward possible regenerative therapy for diabetes mellitus. More than 90 references are cited and nicely summarized. However, a few problems remain to be reconsidered as follows. 1. Reported findings of differentiation, de-differentiation trans-differentiation etc. in both in vitro and in vivo experiments seem to be handled in the same levels of scientific significance. However, phenomena unlikely to happen in adult living pancreas may be caused by artificial means in vitro. Even in vivo, acinar to islet trans-differentiation caused by forced expression of three islet genes (ref. 35) does not seem likely to occur in physiological condition. Physiological likelihood may be considered more important."

Thanks for your positive comments on our manuscript. We did not completely understand what the above remarks required us to do. However, *in vitro* as well as *in vivo* experiments regarding differentiation, de-differentiation or transdifferentiation are expected to have similar levels of scientific significance. Acinar to islet transdifferentiation is an important proof-of-concept study, though its clinical significance remains unclear.

"Is the reference 35 of 2008 a recent report?"

We have replaced the word "recent" with "previous".

"2. A few numerals such as "(19%)" (page 11, the last line), "5.1 +/- 5.4" and "8.2+/-6.9" (page 17, 7th and 8th lines from the bottom, respectively) need detailed description to understand. It seems suitable to omit these numerals and describe them in a qualitative manner."

Yes, we agree. 19% has been revised as 1/5 (page 11). "5.1±5.4 cells" and "8.2±6.9" cells have been changed to "only 5 cells and slightly increasing to 8 cells (page 17).

"3. Some words and expressions may need reconsideration as follows. "pandemic" (abstract, line 5) is usually used for infectious diseases."

No, a *pandemic* is an outbreak of global proportions, not necessarily only being used for describing "infectious diseases".

"The remaining 90% of cases are of type 2 diabetes mellitus" (page 3, lines 10-11) ignores other specific types and gestational diabetes."
Generally, type 1 diabetes is an autoimmune-caused diabetes. All other diabetes mellitus is categorized as type 2 diabetes, including gestational diabetes and monogenic diabetes.

"The former is not found for "The latter" (page 4, line 10)."
The latter here means "the posterior foregut endoderm" (page 4, line 10).

Does "between 8 and 21 weeks of age" (page 13, line 13) mean 8 to 21 weeks old after birth?"
"between 8 and 21 weeks of age" should be "between 8 and 21 weeks of gestation" (page 14, line 4).

"4. Other minor problems are as follows. Probably, "PSC" (page 4, 3rd line from the bottom) appears without full spelling."
Should be pluripotent stem cells (PSC).

"o fraction of the PF cells" (line 8 in the fiure legend of Fig. 1) may need correction."
Should be a fraction...