

## 33244- Answers to reviewer's comments.

### COMMENTS TO AUTHORS

*The manuscript entitled "Skeletal muscle generated from induced pluripotent stem (iPS) cells - induction and application" is well written and interesting for readers. However, I would recommend to update section 5 "Heterogeneity of human iPS clones in differentiation potential". Ref 26 is outdated because same group demonstrated later that isogenic iPSC clones were indistinguishable for isogeneic ESC (Choi et al 2015). It was also demonstrated that there was no somatic memory in completely reprogrammed iPSCs generated from various isogenic somatic cell types and "the best iPSC clone" selection criteria was suggested (Shutova et al, 2016) and scorecards for iPSCs utility were also introduced (Bock et al 2011).*

### Answers to reviewer's comments.

We deeply appreciate your comments. We rewrote the section 5 as follows, and cited the paper by Shutova et al.

#### **Heterogeneity of human iPS clones regarding the differentiation potential**

Human iPS cells are heterogeneous in the myogenic differentiation potential. Some iPS clones efficiently differentiate into the skeletal muscle lineage, while others do not. The heterogeneity is found even among iPS clones derived from the same donor using the same method. Although the molecular basis is largely unknown, one possibility is that some clones are incompletely reprogrammed and cannot respond to differentiation signals properly. If the induction protocol is appropriate, completely reprogrammed iPS clones are expected to efficiently differentiate into the skeletal muscle lineage. Recently, using integrative analysis of reprogramming in a human isogenic system, Shutova et al. identified criteria to select the best iPS line <sup>[26]</sup>.