

IPS Cells Are Man-Made Cancer Cells

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(Received 2008-01-21; accepted 2008-02-13; published 2008-02-13*)

HIGHLIGHT

Yamanaka's iPS cells are expected to provide a great hope for therapeutic cloning. However, by definition and nature, these iPS cells are just some man-made cancer cells.

ABSTRACT

Recent high-profile publications have regarded iPS (induced pluripotent stem) cells as potential therapeutic stem cells for regenerative medicine. However, based on the fact that the inducing/reprogramming factors contained in iPS cells are known oncogenes and their expression have been associated with various cancers, I will announce iPS cells as man-made cancer cells. These safety-problematic cells should not be put into any therapeutic use.

KEY WORDS

Yamanaka, iPS cells, Stem cell, Cancer, Reprogramming, Criticism, Negligence, Editorial misconduct

In 2006 Takahashi and Yamanaka announced that, with just four factors (Oct3/4, Sox2, c-Myc and Klf4), they can produce pluripotent stem cells from mouse embryonic and adult fibroblast cultures (Takahashi and Yamanaka, 2006). Since then, these so-called "induced pluripotent stem (iPS) cells" have been reported in high-profile in various top journals despite some strong criticisms (Liu, 2008). Experts in the stem research field have heralded the creation of iPS cells as a milestone for therapeutic cloning (Zaehres and Scholer, 2007), even though the real safe therapeutic value of these magic cells have not yet proven at all.

The therapeutic value of the first-generation iPS cells was actually seriously questioned due to the presence of Myc, a well known oncogene (Battey et al., 1983; Dominguez-Sola et al., 2007). Thus, efforts have been made to eliminate Myc, the unexpected ingredient in the stem cell cocktail (Knoepfler, 2008). It turned out, the so-called one of the "essential" four components of the original iPS cell cocktail is not essential at all because iPS

cells were still "generated" without using Myc (Nakagawa et al., 2008; Yu et al., 2007).

The elimination of Myc has been regarded as a major achievement in creating the second-generation iPS cells that are described as "safer" than the first-generation iPS cells (Pera and Hasegawa, 2008). However, are these Myc-free iPS cells really safe?

Here I wish to raise a caution that all other three inducing/reprogramming factors still remained in the Takahashi/Yamanaka cocktail for second-generation iPS cells are all oncogenes by definition and their over-expression has all been associated with this or that kind of cancer.

For examples, it has been shown that Oct3/4 gene is expressed in adult human breast stem cells (Trosko, 2006) and bladder cancer (Atlasi et al., 2007). Interestingly, some abnormal effects with the ectopic expression of Oct-4 was already known to a leading iPS research group (Hochedlinger 2005).

Sox2 has been shown to be expressed in human gastric carcinoma (Li et al., 2004), stomach

adenocarcinomas (Tsukamoto et al., 2005), pancreatic carcinoma (Sanada et al., 2006b), vater adenocarcinoma (Sanada et al., 2006a), malignant glioma (Schmitz et al., 2007), breast cancer (Rodriguez-Pinilla et al., 2007) and brain tumors (Phi et al., 2008).

KLF4, once believed to be a tumor-suppressor, is now also shown as an oncogene (Rowland and Peeper, 2006). KLF4 is often over-expressed in squamous cell carcinoma (Foster et al., 2005; Foster et al., 1999). Up to 70% of primary human breast cancers show over-expression of KLF4 (Foster et al., 2000) and nuclear localization of KLF4 has been found as a predictor of poor outcome of breast cancer (Pandya et al., 2004).

In a different four-factor cocktail for “inducing” pluripotent stem cells, Nanog and Lin28 were used in addition to Oct4 and Sox2 (Yu et al., 2007). However, forced expression of Nanog in hematopoietic stem cells has been shown to result in a T-cell disorder (Tanaka et al., 2007).

So far the known iPS cell cocktail component that has not been found in an association with cancer is Lin28. However, this component is shown as not absolutely required for “inducing” iPS cells (Yu et al., 2007).

Thus, all essential iPS cell-inducing/reprogramming factors are oncogenes and their over-expression has been linked with cancers. When iPS cells are full of such oncogenes and the expression of these genes is already at elevated level in the iPS cells, how can we say these iPS cells are safe for therapeutic use?

Come on! Let us face the reality and say iPS cells are man-made cancer cells.

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* This paper was submitted to *Cell* on Jan. 21, 2008. *Cell* never responded to me despite my repeated inquiries. The publication here is the same as submitted to *Cell* except for the added highlight and keywords.

** This publication is sent to *Cell* as a record.

Appendixes

Cover letter for submission to *Cell*

Dear *Cell* Editors,

I am submitting a very important manuscript entitled "IPS cells are man-made cancer cells" to be published in an appropriate section in *Cell*.

Sincerely yours,

Shi V. Liu MD PhD
2008-01-21

Inquiry sent to *Cell*

Editors of *Cell*,

On Jan. 21, 2008 I submitted a Manuscript "IPS cells are man-made cancer cells".

Since the submission, I have not received any reply from *Cell*. I called *Cell* and left a message to the assistant to the *Cell* editor. But no one returned my call.

I know that some editors in *Cell* have developed a hostile attitude towards me simply because some of my submissions are critical not only to *Cell*'s publications but also *Cell*'s publishing practices. However, no matter how much you dislike my expressed views (all of them are proven to be correct); you need to show some basic working ethics and at least give me a reply to let me know your decision.

If *Cell* will repeat its previous practice of just ignoring my submission without any response, I will take further action against this irresponsible and unethical behavior.

I should also remind you that, if *Cell* continues its strong push of the man-made cancer cells named as iPS cells and totally ignoring my warning on the danger of these cells, I will reserve my legal right to sue your negligence that may lead to great harm to humanity.

Shi V. Liu MD PhD
Feb. 1, 2008