What are considered 'good facts'?

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ABSTRACT

In the January edition of the *Journal of Medical Ethics*, Fujita and Tabuchi (hereafter, Authors) responded that we misunderstood the 'facts' in our previous article. Our article's method was twofold. First, it appealed to normative analysis and publicly accessible materials, and second, it targeted a policy-making approach to public funding. We specifically did not focus on the Center for iPS Cell Research and Application or induced pluripotent stem stock projects. The Authors raised five criticisms, including transparency of our interpretation of public funding policy. We reply to these criticisms by clarifying facts, and demonstrating new data (facts), and asking the Authors what qualifies as a 'good fact' in medical ethics. We note that in some cases, it might be possible to examine to what extent facts are 'true', while in other cases, 'facts' are laden with 'values', which cannot be confirmed or falsified with observation alone. The level of 'good' implicit in a fact is a challenging issue that goes well beyond science and makes metaethical assumptions about the relationships between facts and values more broadly.

We appreciate the Response.[1] Before addressing each criticism, we clarify two points. First, our article[2] appealed to normative analysis and publicly accessible materials. Second, our central target was a policy-making approach to public funding, not Center for iPS Cell Research and Application (CiRA) or induced pluripotent stem cell (iPSC) stock projects.

With this in mind, our key concerns were twofold.

1. Timing: why, in 2013, without a single successful example of the clinical application of iPSC transplantation available, were massive public funds poured into the iPSC stock project? Why was a project of this scale embarked on in 2013, rather than waiting until successful cases of clinical application occurred? Was this sequence of events logical?
2. Process: what was the decision-making process that led the Japanese government to devote large amounts of public funds in this manner? Was the process transparent? Was it fair? Was it ethically justified?

Box 1 Japan Science and Technology Agency (JST) project content

With clinical application as the ultimate goal, this project will secure the standardisation and safety of induced pluripotent stem cells (iPSCs) and serve as the necessary R&D to establish an iPSC stock bank for regenerative medicine. To this end, we propose the following within the time frame of 10 years.

- Elucidate the reprogramming mechanism of iPSCs.
- Establish a method for consistent generation of uniform quality iPSCs based on a molecular reprogramming mechanism, and with that, work towards improved safety and high efficiency of safety confirmation tests for iPSCs.
- Establish and fine tune protocols for generating and evaluating high-quality iPSCs (with good proliferation capacity and multipotency and so on) with low risk of cancerisation.
- Consider a culture protocol that will enable maintenance of iPSC quality.
- An immunological analysis of iPSCs employing measures that reduce the likelihood of immunorejection for allotransplantation.
- Create an iPSC stock bank for regenerative medicine and contribute iPSCs to research institutions such as the 'Center of Excellence for Practical Use According to Disease and Tissue'.

At project completion, we aim for the work described above to have established a highly efficient method of establishing iPSCs, to have developed a method to confirm the safety of the cells and to have created an iPSC stock bank for regenerative medicine that will cover the majority of the Japanese population (p. 22).

Cited from reference 7, p. 22 (authors' translation).

The primary criticisms by Fujita and Tabuchi (hereafter, Authors)[1] are based on the claim that we misunderstood the 'facts'. Yet the Authors neglect to bear in mind that we draw only on publicly accessible facts; they also ignore the broader question of what constitutes 'good facts'. They also neglect to address the normative analysis that represents our central theses.

One postpublication 'fact' was that Dr. Yamanaka submitted a proposal to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) that CiRA wished to terminate iPSC stock bank and transfer control over to a public interest incorporated foundation; there was reportedly 'no opposition' to this move by MEXT's expert committee.[3 4] At the same time, Dr. Yamanaka reported a plan to establish a technology that would enable a generation of autologous iPSCs from patients' own cells in a cost-effective manner, in 'several years'.[3–5] Subsequently, on 21 December 2018, CiRA posted on the Internet that its bank achievement rate was 32%.[6]

Before replying to the Authors' five criticisms, we respond to their criticism in the Introduction.

The public funding allotted to Japan Science and Technology Agency (JST) 'Core hub for iPSC research' is 2.7 billion Japanese yen per year for 10 years, that is, a total budgeted amount of 27 billion yen.[7] As cited in our article, this is roughly a quarter of 110 billion yen.[2 8] This is a 'true' fact. The JST's application for the project mentions the following (box 1).[7]

We then ask the Authors to clarify what 'the amount being spent on building and supplying the iPSC stock' encompasses. The application to the JST stated that this project would '*Establish a method for consistent generation of homogenous, high quality, with less cancerization risk iPSCs based on a molecular reprogramming mechanism*'. Is it irrational for us non-specialists to think that this is one part, a critically necessary component, of the establishment of iPSC stock bank?

Moreover, a newspaper reported in FY 2014, the MEXT determined to invest 9.0 billion yen in 1 year to CiRA to facilitate iPSC stock project. It included cost for constructing a building to be used as a core facility (five floors above ground, two below, for a total of roughly 7500 m^2).[9]

If this is a 'fact', then our question is: 'Are the infrastructure funds used to follow through with the iPSC stock project not included in the funds designated to create the iPSC stock bank?' As non-specialists,

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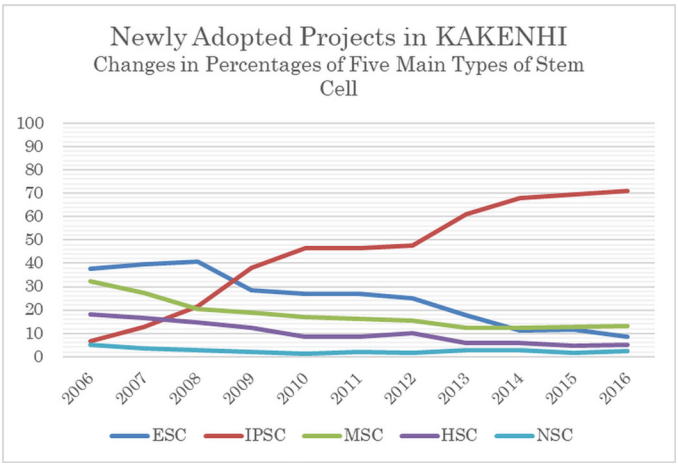

Figure 1 We conducted a search of the *KAKENHI* database[18] to determine the newly accepted topics for each fiscal year. Search terms were 'iPS cell OR artificial pluripotent stem cell AND human' for iPS cells and 'ES cell OR embryonic stem cell AND human' for ES cells. Using this method, 'English abbreviation OR Japanese translation AND human' were used as search terms for the five main stem cell types. The proportion of research studies pertaining to each type of stem cell is shown assuming the sum of all stem cell studies is 100. HSC, haematopoietic stem cell; MSC, mesenchymal stem cell; NSC, neural stem cell.

we consider infrastructure funds be part of the iPSC stock bank.

Below, we address each of five criticisms.

Objection 1: can Japanese citizens access the meeting minutes from the deliberations and resources cited by the Authors? We were unable to find these by means of internet searches. As a result, it was impossible to know what kinds of discussions occurred, the basis of the calculations and the process through which the budget distribution proposal was confirmed. A final summary of the draft budget of the Ministry of Finance (2013) was accessible on the internet.[8] Within this massive document (115 pages), we found the following:

- For iPSC research, continuous and steady support of 9.0 billion yen × 10 years, total 110 billion (p. 24).
- Construct iPSC stock bank of regenerative medicine grade (p. 90).

After the Ministry of Finance proposal, it was approved by the Diet. How long was the deliberation for this one line of the proposal in the lengthy document in the Diet? Can this really be called 'transparent'?

The Authors advocate that the government fulfilled the necessary level of transparency because the proposed budget progressed through the process to be approved by the Diet. However, 'Transparency' is not achieved merely by following the perfunctory protocol, but rather must include an aspect of 'Accountability' in the form of offering a sufficient explanation.

Objection 2: we discussed criticism 2 by the Authors at length in our article,[2] including the likelihood that incidental findings obtained from this project would benefit all citizens as a broader standard. The Authors' response appears to suggest that 'the broader standard is sufficient, and all citizens can benefit'. However, when we published our article, the project's final goal was bank achievement covering 80% of Japanese citizens,[2] and as non-specialists, we were unable to foresee the potential incidental benefits that might emerge from the project. To take this one step further, as the Authors indicated so clearly above, the 'incidental projects' are just that — incidental and come with no guarantee. That is precisely why we argued that the investment of 'public' funding could not be justified. Unfortunately, the achievement rate is 32%. If findings emerged that would benefit the entire population even more than an 80% achievement rate, then we ask that these 'good facts' be publicised. If the reprogramming mechanism of iPSCs was elucidated as described in the initial JST project objectives, that is, to an extent that many citizens would benefit, then this should be explained in a manner that the general population can understand.

A statement like, 'we were able to establish technology to generate high quality iPSCs as well as a method to generate iPSCs with low risk of cancerization', falls short of being justifiable from our perspective of a broader standard. One reason is that these technologies are necessary to generate autologous iPSCs, too. A project other than an iPSC stock project could have researched this independently. CiRA is also on the brink of accomplishing excellent research using autologous iPSCs. Indeed, we have praised those studies as being highly ethical.[10] Truly, if there are (incidental) good facts that would greatly benefit the Japanese population, then even retrospectively, we would offer our praise and agree the iPSC stock project was meaningful from the perspective of a broader standard. However, this nonetheless would be an argument based on hindsight.

Objection 3: would it be clearer to the Authors if 'Q&A' was restated as 'Public Comments'? The Symposium[11] cited by the Authors is held once a year and has 1000 attendees with a 5-hour conference comprising primarily lectures. Recording audio or taking pictures is forbidden. The meeting minutes are supposedly publicised, but this is not the case. A recording was distributed, but it could have been edited, and thus the time spent on Q&A cannot be accurately estimated. The CiRA website[12] is maintained reasonably well. However, it maintains only a 'Questions' section where anonymous questions are impossible. Their informational bulletins are unilateral. Aside from this, the many events, seminars and symposiums held by CiRA are of high value.

How would the Authors define 'procedural justice'? In Japan, for example, when guidelines were drafted for human embryonic stem cells (ESCs), even for revision in 2014, the government held a Public Comment session,[13] and the Committee handled each and every comment that was made.[14 15] Admittedly, while Public Comment does have limitations, we feel that these sessions represent a 'bare minimum' requirement. Do the Authors truly believe that one annual symposium and postings on a website are sufficient for procedural justice?

Objection 4: the sources cited by the Authors report that, in 2012, cancer research received 3636 billion yen, while regenerative medicine received 4499 billion yen. In 2013, cancer received 3629 billion yen (no change), while regenerative medicine received 8993 billion yen, a roughly 200% increase.[16 17] We believe it unfair that the Authors decided to leave out this 'true fact'. Moreover, within this regenerative medicine research budget, let us examine figure 1, which analyses *KAKENHI* (competitive public research funding).[18] Over the past 10 years, the

proportion of stem cell research funded shows that ESC research have decreased by 0.23-fold, and those using mesenchymal stem cell have decreased by 0.40-fold, while the proportion of iPSC research increased 10.92-fold. Some specialists have noted that this decrease in ESC research funding has slowed Japan down in its ESC clinical application behind other countries. Would the Authors still advocate that public funding policies are not biased towards regenerative medicine, especially, iPSC research?

Objection 5: we reiterate that if the social benefits obtained thus far were extremely beneficial to all citizens, these 'good facts' should be explained in a manner the general population can understand based on scientific data accessible to all. If the 'good facts' are such that citizens are offered benefits, then we would accept the social benefits theory.

While we understand the need for a nation to classify some information, given the massive amount of public funding involved with this particular project, the amount of resources and data that remain unpublicised seem to be large and disproportionate. Some 'facts' might be possible to examine to what extent those facts are 'true'. However, some 'facts' in this discussion already include 'values'. The level of 'good' in a fact is a challenging issue that goes beyond science and assumes a value theory.

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