LETTER TO THE EDITOR

The path forward

Dear Editor

Today, September 12th, 2015, is the one year anniversary of the world's first induced pluripotent stem (iPS) cell clinical research, conducted by Dr Masayo Takahashi at Riken.

The first patient was in her mid-seventies and suffering from exudative (wet type) age-related macular degeneration (AMD). She had a series of 18 anti-vascular endothelial growth factor (VEGF) ocular injections for both eyes to cope with the constant recurrence of the disease. The results presented by Dr Takahashi showed that, after the removal of the subretinal fibrotic tissue and implantation of the iPS-cell-derived retinal pigment epithelial (RPE) cell sheet, the patient experienced no recurrence of neovascularization at the 6 month point and was free from frequent anti-VEGF injections. Her visual acuity was stabilized and there have been no safety related concerns so far. The 1 year results will be released shortly.

Riken was preparing a second autologous iPS cell line, but has faced confusion regarding safety regulations from specialists in various fields. Unlike the first case, after the generation of the second iPS cell-derived RPE cells, Riken identified six genetic mutations which were not present before the reprogramming.

There has since been debate on how to evaluate the safety profile of the RPE cell sheet in the Japanese scientific community.

The result of tumorigenicity testing has proven the final RPE cells to be safe. Furthermore, the presence of genetic mutation does not necessarily mean that these RPE cells can be tumorigenic. Furthermore, to date, there is no regulation with which medical professionals are obligated to check gene modification for organ transplantation, mesenchymal stem cell injections or autologous cell therapy.

The fact remains that we do not have clear guidelines today on which the whole community can reach a consensus that "the second" RPE cells are safe enough for implantation.

As a pioneer of iPS cell clinical application, Riken took the responsible decision not to rush ahead with the second patient's RPE cells, which could potentially damage the whole field of regenerative medicine. The last thing they wanted to do was to slow down the whole field and end up not being able to cure the patients who otherwise could have been cured by taking more careful steps.

Although therefore, the cells were widely thought to be safe to use, after careful consideration, they made the decision that they would not implant another autologous cell sheet until such guidelines could be officially authorized.

They are now coordinating the discussions at the Ministry of Education, Culture, Sports, Science, and Technology, and also at the Ministry of Health, Labor and Welfare to carefully discuss these issues with key opinion leaders in the field including government officials, regulatory experts, scientists and toxicologists. Further detailed information surrounding the new guidelines will be published by Dr Masayo Takahashi in *Cell and Gene Therapy Insights* once a consensus has been reached.

The torch has been shared by Riken with Healios to bring this innovation to the patients who are waiting globally. CiRA (Kyoto University) has generated the world's first clinical use allogeneic iPS cell line with full characterization, including whole genome sequences.

Obviously this allogeneic cell line does not have genetic mutations that cause debate. This cell line will match roughly 17% of the Japanese population (HLA 3 locus) and Healios is moving forward to conduct an allogeneic RPE cell suspension injection which is freezable and ready for injection clinically, free from the above concerns around genetic mutations.

Under the Japanese government's leadership, as part of a growth strategy, Pharmaceutical law has been de-regulated significantly for cell and gene therapy, referred to as the PMD Act. Under this new regulation, Healios intends to initiate clinical trials in 2017 to file a biological license application in 2019 to obtain approval for the world's first iPS cell based product in 2020.

I see the path forward to be not an easy one. It never has been. I am sure that we will face many hurdles to bring iPS cell technology to patients globally. But we are not afraid of this responsibility. We welcome these challenges. The fact is that we are facing even greater challenges than gene mutations, including the most rapidly aging global society in the history of human race. If there is one generation which can solve this issue, it is our generation. We must cope with this situation with the power of regenerative medicine and pass the torch to the next generation with hope, respect and some wisdom.

I am happy to spend my life to make the world a slightly better place and you have my commitment until the day I take my last breath. Healios is committed "to be the change in an ever evolving world through enrichment of living."

We will keep you posted…

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FINANCIAL DISCLOSURE & ACKNOWLEDGEMENTS

Healios has global exclusive license from Riken regarding the related know-how and intellectual properties to commercialize RPE cell product and conducting joint research with Dr. Masayo Takahashi's lab to commercialize RPE cell technology.

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