Asian pragmatism

Japan has set up a legal framework to allow the use and generation of human embryonic stem cell lines

Stem cell research is a rapidly developing field. Nearly every other week another article is published that expands scientists' knowledge and explores the cells' therapeutic potential to treat a variety of disorders, such as Parkinson's disease or diabetes. But since this research involves using cells derived from human embryos, which are destroyed in the process, it has

governing the distribution and handling of fertilised eggs and the cell lines created from them. However, these cells can only be used for basic research—the guidelines prohibit any other purpose—and fertilised eggs can only be obtained from married couples after written consent and without compensation.

To date, the government's Bioethics

filed on the cell lines created at Wisconsin University, associate professor Ryuichi Nishinakamura from the University of Tokyo said: 'At this point, I wonder, even if Japan gets access to them, will [researchers] find anything new?'

The guidelines were reportedly well-received, but the approval process has been far from automatic. The recent success of Tanabe's application, for example, came only after an extended debate, since the guidelines were originally created with research at academic institutions in mind. The review process has also raised separate concerns about both the adequacy of researchers' previous work with stem cells and the composition of the internal review committees.

Nevertheless, having this debate on public record is a critical step for Japan, thinks Shin-ichi Nishikawa, professor of molecular genetics at Kyoto University, who plans to use stem cell lines imported from Australia. He contrasts the 'practical' approach of the US administration in approving the use of 64 pre-existing cell lines with Japan's approval process, in which the suitability of each cell line has to be debated. Indeed, imported cells from pre-existing cell lines are subjected to the same criteria, such as derivation and handling, written consent or the

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also sparked an intense debate about its ethical and moral implications. Indeed, these have been regarded as so important that various countries have now drafted legal frameworks to balance the potential therapeutic applications against the ethical concerns of using human embryos. While the debate and the legislation process in the USA, the UK and Germany have raised an intense media interest, Japan's pragmatic decision to legalise research using human embryonic stem (ES) cells has been virtually ignored by the international media.

Last year, the government of Prime Minister Junichiro Koizumi approved the use of ES cell lines for basic research. The legal situation not only allows researchers to import and use existing cell lines but also to generate new ones from fertilised human eggs. Soon after this ruling, in September 2001, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) issued 10 pages of guidelines to regulate the use and development of ES cells. These guidelines lay out a two-tier approval process for applicants, first at the institutional and then at the governmental level. Researchers must explain the prospect and nature of their research proposal, prove their proficiency and experience in using stem cells from other species, name the principal researchers and regularly submit reports on their progress. Furthermore, applicants must identify those in charge of the internal ethical review, who judge the criteria

Committee has approved three applications and two more are being considered. Two of those that have been approved came from Kyoto University, one for developing a new cell line and one for the use of imported cells. In addition, the first corporate applicant, the pharmaceutical giant Tanabe Seiyaku, received approval on June 18 to use stem cells for research in collaboration with scientists from Kyoto University. Internal review boards at both Shinshu University and Tokyo University have also approved their scientists' research plans, and the government committee is currently considering their bids.

The sole application for generating a new cell line, submitted by Norio Nakatsuji from the Department of Development and Differentiation at Kyoto University's

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Institute for Frontier Medical Sciences, was the first to be accepted at the end of March. It would give Japanese researchers easier access to ES cells. The researchers may be able to develop their own cell line within 4–8 weeks, but, for the time being, the imported alternative is quicker, especially since the search for fertilised eggs has yet to find a willing donor couple. However, generating their own cell lines is seen as an important step for Japanese biologists. With over 30 patents already

source of the fertilised egg, as those created domestically.

Although the most well-known cell lines, and those most likely to be used, have been created at Wisconsin University, Nishikawa chose to use a cell line created by a colleague in Australia from a fertilised egg donated from Singapore. 'I thought the important thing was to get cells from a variety of sources,' he said, 'then applying and getting the ethical committee to discuss it.' Through this

choice, he specifically hoped to expand the debate surrounding the ethical standards set in the Japanese guidelines. The discussion is important in itself, Nishikawa argues. 'That is a process for the Japanese to get used to dealing with such issues,' he said. And this is not limited to issues surrounding stem cell research. It is less than 10 years since the first ethics committee was established at a medical university, he noted, so 'for Japan I think this is a very precious experience we are having now.'

Today, there are an estimated 100–200 researchers in Japan working on stem cells, and they are almost exclusively funded by the government. This has not always been the case. In the early stages, the corporate community was also involved in supporting stem cell research at universities. Nishinakamura recalls the research climate in Japan. In the mid-1990s, he said, hardly anyone in Japan was focusing on stem cell research. Nevertheless, pharmaceutical companies had more resources to devote to experimental research and were happy to benefit from the free publicity that resulted from the publication of research they funded and to have direct feedback from researchers. For instance, AmGen, a pharmaceutical company headquartered in Thousand Oaks, CA, helped the Institute of Medical Science at the University of Tokyo (IMSUT) to open a new Department of Stem Cell Regulation in 1994. Then, James Thomson's group at the University of Wisconsin announced the creation of the first ES cell lines in 1998, which sparked a boom in Japan. 'Absolutely everyone started doing stem cells,' Nishinakamura said.

In the past 2–3 years, however, the initial excitement about the potential for ES cells has cooled. Early research results are being questioned. And AmGen has decided to pull the funding for IMSUT's Department of Stem Cell Regulation as of

April 2003, forcing the staff to look for new jobs. 'The big pharmaceutical companies aren't that interested,' Nishinakamura explained. 'There's still a long road ahead. It's not going to make money in six months.'

Eventually, Japan's top bioethics committee will have to consider commercial applications and therapeutic cloning

And other routes of private funding for research do not play a significant role in Japan. The country has no private grant-giving organisations akin to the Michael J. Fox Foundation in the USA, which funds research, including stem cell therapy studies, into Parkinson's disease. Furthermore, the role of venture capital in biotechnology remains small. But interest and awareness are growing and, as government support for these businesses increases, this is set to change. In the meantime, some researchers worry that Japan will fall behind in stem cell research, even though the climate itself is not inhospitable. There has been no apparent migration of researchers out of Japan and, in one well-publicised case, two researchers left the USA to continue their research in the Asian archipelago.

The Japanese government is also anticipating further developments in stem cell research and the guidelines for deriving and handling ES cells are scheduled to be reviewed and amended to reflect technological changes sometime within the next 2 years. Government officials say there is no plan yet for when this review might take place or what issues it will address. But the use of stem cells for clinical research is bound to top the list, particularly the use of ES cells. The current guidelines, written by the ministry that oversees the nation's universities, cover

only basic research. As responsibility for clinical research and applications will involve the Health and Welfare Ministry, which is currently writing up its own guidelines covering treatment with adult (somatic) stem cells, MEXT cannot and will not move ahead on new rules, researchers and officials say, until the Health and Welfare Ministry's guidelines are released.

Following on from clinical use, the nation's top bioethics committee will have to consider commercial applications and therapeutic cloning, Japanese researchers think. While a policy of open disclosure has governed this first stage of ES cell use in Japan, the commercial consequences, for example through developing ES cell cultures for drug screening, will require a new kind of regulation.

The extent to which stem cell treatments will become standard medical practice remains to be seen. 'I cannot say that this can be a critical technology for commercial purposes, but I think this is a critical technology for treatment,' said Nishikawa. As an example, he likes to point to the >500-year history of blood transfusions, a kind of metaphor. One thing we can understand from blood transfusion history is the way one technology creates many other new medical technologies, he said. 'For example, heart surgery cannot be imagined without blood transfusion.' In a larger context, he expects the debate about the use of stem cells to expand into a more general debate about the nature of disease itself. The progress of ES cell research, Nishikawa said, will 'ask us to define what the medical field is'.

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