Report Workshop Kyoto

Local workshop: **The Life Sciences in Society: High Hopes and Difficult Issues**
Held on 29 November 2008, Kyoto
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This workshop was held as part of the tasks outlined in the ESRC SCI fellowship 'Human Embryonic Stem cell Research (hESR) in East Asia: An Institutional Approach to Bioethical Reorientation' (RES-350-27-0002)

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The idea for this workshop developed in the spring of 2008. For years it has been difficult to stimulate debate on issues related to human embryonic stem cell research Only a few social groups in society, such as the scientists themselves, some extremist religious groups and the Anti-Eugenics Network seemed to have been motivated to put forward their views (Kato 2006; Sleeboom-Faulkner 2008). The large public, however, hardly recognised the concepts of stem cell research or pluripotency. In late 2007, with the appearance of the work on iPS by Yamanaka and Takehashi, this situation changed. The news that Japanese researchers had succeeded in discovering iPS and working out how genetic factors could trigger reprogramming, hijacked the imagination of the broad public about the possibilities of iPS to lead the world in stem cell research and finding clinical applications for therapies based on iPS.

Although not all themes in the life sciences speak so clearly to the imagination of the public as clearly as iPS, there is no doubt that themes related to animal-human hybrids, human embryonic stem cell research, foetal research, iPS and chimeras for stem cell research are important themes, which raise concern in people from many walks of life once they find out about them. Moreover, in order for Japanese scientists to proceed with their work related to these research themes, it is important for them to know that they have the support of the public. Scientists in Britain, such as Steven Minger, have felt demonised and persecuted by attacks from members of the public. But scientists in Japan,

especially those specialised in biomedicine, when becoming the centre of a public controversy, could easily risk a scandal leading to ostracization and a discontinuation of their carrier. However, extremist reactions to science projects linked to stem cell research and its clinical applications are rare, and informed public discussions on social and ethical issues linked to stem cell research and its medical applications, on the whole, are exceptional. The degree of difficulty of the themes of debate and the taboos that exist around speaking about 'embryos', 'abortion' and 'oocytes', together with the difficulties associated with discussing life- and death issues do not lend themselves to lively and informed debate.

One aim of the workshop *The Life Sciences in Society: High Hopes and Controversy* was to address this problem by trying out a formula for informed debate-seminars among a limited number of professional people from various walks of life. Examples of such professions and social groups are: nurses, stem cell research scientists, doctors, housewives, secretaries, housewives, sociologists, legal scholars, pensioners, etc. Such diverse group members were expected to approach bioethical and social issues from different perspective, which was hoped to generate new ideas on how to deal with potential controversy on practices in stem cell research and its applications. The output of the workshop would take the form of a report, a media release, and two articles co-authored by the main organisers of the workshop.

Aims of the workshop in short:

- Stimulate informed discussion relevant to policy-makers, scientists and the public
- Generate new ideas on practices in stem cell research, as views held by diverse members of the public could timely identify unforeseen social problems and ethical issues
- Find new ways of creating constructive debate on bioethical and social issues related to the life sciences

Planned output of the workshop:

- Report of the workshop and evaluation

- Media release on the basis of our findings
- Article written by the organisers of the workshop

The workshop was jointly financed by Kyoto University and the ESRC. Kyoto University provided the funding for the location of the workshop, public transport, recording equipment, and the documents and materials used. The workshop also benefited from the dedication of two researchers and two MA students. The ESRC bared the expenses for refreshments, lunch and a small buffet, and the cost of the transcription of the workshop. As the entire workshop was held in Japanese, documents were provided and discussed in Japanese. Unfortunately, a lack of time does not allow me to provide a full English translation of them. But the planned articles based on an analysis of the discussions held in the workshop will be published in English.

All of the discussions during the workshop were recorded with permission of the participants. Participants were also asked if they wanted their views to remain unanimous. It was pointed out that they could indicate this after filling out the anonymous evaluation forms. Though the issue of unanimity did not attract much attention, we decided not to use the names of participants in our analysis anyway. During the workshop, photographs were taken of participants engaging in discussion and a group photo. Permission was asked for their use in the lecture room and in reports. Reimbursement of all transport expenses was provided for.

Evaluation:

The evaluation (14 responses) showed that participants were ‘satisfied’ to ‘extremely satisfied’ about having attended the workshop. But the evaluation forms showed an important and recurrently problem: participants had experienced frustration as a result of a lack of information. The participants had wanted more information about the case-studies as they often felt the lack of information when make up their mind in favour or against a stance. This problem requires closer attention, as it may be widespread. It is questionable if providing more data would entirely solve the problem, though it should be considered. For the case-studies were chosen exactly because people have to make their

mind up about their views and courses of action on the basis of imperfect information. However, in societies where people expect the media and scholars to feed them with pre-chewed arguments, it was hard for some participants to form their own views. This was also illustrated by the way some participants thought that they were expected to compromise their views in group discussion so as to create one 'group view' that the rapporteur could present afterwards as their view. Using the location of Kyoto University, actually, contributed to this problem, especially as some of the organisers and participants were clearly regarded and treated as 'professors': guidance was expected.

Format of the workshop (see programme):

- The collection of case-studies of potential controversial issues linked to stem cell research and its clinical applications among the Japanese public;
- One explanative informal lecture on iPS, hESR and regulation;
- Small groups discussions, 3 groups of 4-5, themes introduced by the rapporteur (members of the organising team);
- Reporting on the discussions per group by a rapporteur;
- General discussion.

The organisers looked for participants for c. three weeks, aiming to recruit participants from various social and professional backgrounds. Fifteen people showed interest. In total the workshop counted 15 participants, 2 organisers, 2 co-organisers, and two assistants. The background of the participants was as following: three patients in wheelchair, of which one had his own business in facilities for handicapped persons (and one spouse); one physician/researcher; two citizens; one stem cell scientist; one former pharmacist; two legal scholars; one bioethicis; one student from the agriculture department; one former nurse; and, two philosophers.

Three groups were formed, which rotated in each session so that the composition of groups changed in each session. Each group had a rapporteur, who made notes that were presented as the views of the group during the general discussion at the end of each session. This system worked quite fluently. One problem occurred when some of the

participants though that the groups had to present one ‘group view’ at the end. We could have prevented this by emphasising that multiple views could be presented.

OVERVIEW OF THE CASE-STUDIES

Case 1 and 2: Patient freedom and safety

1. Medical tourism and private stem cell start-up-clinics in Europe
2. Somatic stem cell therapies in India

Case 3 and 4: Ethical and normative issues in SCR

3. Hybrid research in the UK
4. Using pluripotent cells to create gametes and embryos

Case 5 and 6: On speeding up clinical applications and regulation:

5. Encouraging hESR to succeed in research and applications for iPS?
6. Receiving the benefits from advanced regenerative medicine.

SESSION 1:

Case 1 and 2: Patient freedom and safety

The first two cases concern issues important to Japanese society in the sense that new stem cell therapies are being developed in the world, but little is known by the public about the safety issues involved. Due to stringent safety criteria for experimental research and a situation in which national health insurance does not usually cover experimental therapies, many patients have to pay for new treatments themselves. Alternatively, some go abroad to seek healthcare. Introducing two case-studies on the theme of experimental stem cell therapy situated in the Netherlands and in India, forces the discussion to take into consideration differences in socio-economic environment and tempts the discussion to make a distinction between the level of respectability of ‘scientific’ enterprises in so-called advanced countries and a developing country.

CASE 1: **Medical tourism and private stem cell start-up-clinics in Europe (the Netherlands)**[1]

"We have had some spectacular results… a man from South Africa is walking again after years in a wheelchair." (Niels van Gent, Manager PMC Rotterdam)

"We employ manners of healing that have evolved for thousands of years in the Middle East and Far East, which have proven to be effective, and without risk." (PMC website, August 2007)

Up to date there exists no approved clinical trial or treatment involving stem cells beside bone marrow stem cells, neither by the US Food and Drug Administration (FDA) nor the UK Medicines and Healthcare products Regulatory Agency (MHRA). In 2005 the preventive health care centre "Preventief Medisch Centrum" (PMC) started to treat patients with human cord blood stem cell injections for GBP 12.500[2] (CNY 188.000) claiming they "target cells in a manner specific to an individual's condition". Investigations showed these stem cells were actually research grade umbilical cord blood cells "not intended for use in humans" ordered via a Swiss company from a clinic in Pakistan.

In October 2006 the Netherlands Health Care Inspectorate (Inspectie voor de Gezondheidszorg) temporarily stopped the stem cell treatment after hearing concerns by a neurologist at the Erasmus Medical Centre at the end of 2005, and after a patient showed serious symptoms following stem cell admission at the PMC (Sheldon, 2006). According to an Inspectorate report, the clinic acted irresponsibly in regard to patient safety, as "it is unable to demonstrate the origin, suitability, and safety of its stem cells". Furthermore it stated that the "safety and quality of the stem cells used […] cannot be established". Subsequently the government issued a ban on application of stem cell therapy by private clinics, which came into effect in January 2007.

[1] Courtesy of Bionet.

[2] Stem cells were administered prior a consultation pack (GBP 240) which included a medical check-up by a local physician (GBP 175) and standard blood and urine tests (extra fee: GBP 65). 80% of patients were referred from Great Britain to PMC in the Netherlands by a "franchise system" (Personal communication, TS).

Eventually PMC discovered a workaround for national legal restrictions in relocating its stem cell activities to an apartment block in the Belgian city Antwerp, just 80 km away from Rotterdam. Beside PMC there are at least another 30 clinics/companies providing stem cell therapy featuring "tomorrow's treatments today" – leaving the scientific community concerned (Enserink, 2006) and numbers are constantly rising.

Questions for discussion CASE 1:

1. Do you think that the authorities where right to stop the experimental umbilical cord stem cell therapy? Why?
2. If the safety and sources of the umbilical stem cell were to be established, would you allow the therapy?

CASE 2: **Experimental somatic stem cell therapies in India**

India is a country with very little healthcare, and when people become ill they do not have money to pay for treatment. However, there are many people with for instance liver disease, eye problems and spinal cord injury.

An Indian company X from Chennai, together with foreign research institutions, decided to provide new stem cell therapies and methods to clients and patients. The foreign companies and researchers support the Indian company, and also support Indian university researchers and students to develop their new therapies.

The therapies, after animal research, require testing on humans before marketing. Company X made links with the India's official regulator of stem cell research (Stem Cell Task Force (SCTF) of Indian Council of Medical Research (ICMR)) and asked for permission to apply their therapies onto humans. They received permission, but supervision of research trials and human subject research in India is loose. Moreover, often research is outsourced to other hospitals that have no permission.

The company provides a mixture of therapies that can be done cheaper in India to attract medical tourism and partly experiments with new therapies on patients with little hope left or no money, although the therapies tested properly.

But consider the following cases:

- The company provides therapy for liver cirrhosis due to viral infections and alcoholism using patients own bone marrow stem cells. The treatment has not proved to be effective yet, but is the only hope to many patients.

- Autologous stem cell treatment for ischaemic heart disease is provided at the Vijaya health centre to many patients.

- Half a dozen eye hospitals in India are collaborating with a foreign research centre to create the inner layer of the cornea (endothelium). It may allow 14,000 eye transplants a year. X hopes to make the endothelium available on a commercial scale and set up a Corneal Endothelial Stem cell (CES) bank at a cost of $8 million. The project is based on the findings of a foreign scientist, who in 2002 found that the endothelium of the cornea contains stem cells (cells in initial stages of development) that can be multiplied several times in the laboratory.

- S Laser Technology Limited has decided to tie up with Chennai based company X for technological collaboration to develop non-rejectable stents for Cardiac patients. The stent is likely to save post surgery expenditure. At present post surgery medicine cost per month, during first year, is around Rs. 3000 to 5000.

- Patients are treated in Chennai with autologous stem cell therapy for spinal cord injury at Hospital L in India. Hospital L had just signed an agreement with the company X, backed by a foreign-based biotherapy institute and decided to take on cases as the first 'experiment' in stem cell therapy. "This case, according to the stem cell therapy project coordinator of Hospital L has showcased the potential of stem cell therapy to bring people with paraplegia back to normalcy in a quick and effective manner.

Questions for discussion CASE 2:

Do you think that the authorities in India should to stop the therapy? Why?

Do you think foreign scientists should collaborate with such companies?

THE THREE GROUP DISCUSSIONS: CASE 1 AND CASE 2

Questions for discussion CASE 1: Medical tourism and private stem cell start-up-clinics in Europe

1. Do you think that the authorities where right to stop the experimental umbilical cord stem cell therapy? Why?
2. If the safety and sources of the umbilical stem cell were to be established, would you allow the therapy?

Questions for discussion CASE 2: Experimental somatic stem cell therapies in India

1. Do you think that the authorities in India should to stop the therapy? Why?
2. Do you think foreign scientists should collaborate with such companies?

Group 1 debated the cases from the perspectives of doctors, patients and ordinary citizens and concluded that it is in the interest of the patients that the therapy should be offered. And, if safety is confirmed, such therapy should also be accessible by ordinary citizens. Medical professionals should accept it if the government brings a halt to therapies for the reason of high risk. One discussion in group 2 proceeded from the view of the individual as independent and capable individual, using as a criteria the ability of providers to explain the risk and procedures to patients, who then should chose whether to purchase the therapy. If they cannot, some group 1 members argued, the therapy should be prohibited. If risk and effectiveness can be explained, the therapy should be on offer. In group 3, some argued that it is all right if safety is the main criterion, but others said that you cannot judge a therapy on the basis of safety alone: there should be evidence that it works. The scientist from group 3 argued, however, that whether therapies are recognised by the FDA or just under research, safety remains an issue. Even with documents, you do not know for sure.

Two problems played in all three groups: one linked to the global nature of medicine and one to the ambiguous character of some research. If is not clear whether the stem cell therapy is conducted for research purposes or for clinical application, the overall view was that the therapy should be offered for free. If in one's country this research is forbidden, patients will go to other countries that carry the burden of

experimental research and clinical trials (group 1, 2). All groups expressed doubts about its desirability. There was awareness that high safety levels entail high costs. On the other hand, it was argued that any medical behaviour is accompanied by risk. Avoiding all risk when providing therapy is difficult.

If in India the therapies mentioned were provided scientifically and safety, group 1 thought that the therapy prices were low. Group 2 expressed the view that in itself it is not a problem that research is done in a place where it is made easy to conduct and advance one's research. When facilities for collaborative research are not good, one has to work according to existing conditions. But, it was countered by members of both group 2 and 3, there is a need for a system that supervises research. If the system does not work well, it is not good for Japan to invest in it. Some persons of group three wanted to prohibit any experimental therapy in India. They thought that doing research that you cannot do at home oversees is not defendable: even if the research is good, it was argued, it is no good if the authorities themselves are not properly organised.

Some voices from group three expressed the view that you should not get biomaterials from aboard either, be it organs or umbilical cord blood. Another problem group 3 pointed out was the differences in healthcare systems and provision between countries. These differences cause some patients, who can afford it by cannot acquire it at home, to travel abroad for care, while they cause some patients, who cannot afford healthcare, to receive experimental treatment at home.

GENERAL DISCUSSION SESSION 1 (extracts)

There were various points of view on the issue of how to decide whether to prohibit a therapy and to whom:

- Risk is different per patient. It also makes a difference whether you have insurance or not. If you do not have enough coverage, people without money use such therapies as a way of getting care.
- The problem is that financially vulnerable cannot but participate in experimental trials. This, however, does not mean that such trials should take place.
- But as long as there are patients that want the therapy, it should not be prohibited.

- From a broader perspective the therapy should be prohibited. It is a different dimension. The solution should lie in the hand of policy-makers.
- The problem is standards. It is the standard for who will receive what kind of therapy. Without knowing the standard there is not solution. But who determines the standard is the problem.
- If there is no law, such as in Japan, then the medical association with make guidelines. On this basis the government creates policies.
- If the criteria for therapies and safety are determined beforehand, then there is no sense in doing research.
- Risk will never be zero. It is not an issue of first establishing standards. First a number of groups do research. After years, one can establish criteria on the basis of this.
- Whether this is possible is doubtful. Searching for therapy on the basis of dreams is no good. You need to know if a therapy can be trusted.
- If the standards are high then research does not progress and therapies cannot be created. In Japan clinical research is a hurdle.
- As long as the risk-benefit ratio is not clear, the therapy should be researched, following research protocol. Such protocols differ per country.

SESSION 2:

Case 3 and 4: Ethical and normative issues in SCR

Some questions regarding the use of cybrids, the embryo and human cloning are thought to be especially relevant to what we think of as the West. Apart from in the case of human cloning, this idea is also dominant in mainstream debates in the media and the academic world. Empirical research, however, shows that is not necessarily so. The questions in this session were hoped to stimulate discussion on views of cybrids and artificial embryos for scientific research, and to invite normative views about cybrid and embryo creation.

CASE 1: Hybrid research in the UK

Just as iPS is important to understand pluripotency and the reprogramming of life, the research of somatic cell nuclear transfer [The lecture explains SCNT] is important to understand the regeneration of life. For by inserting the DNA of adult cells into an oocyte, it is possible to study the reproductive mechanisms of cells. The aim of this kind of research is not to create clones to be used for therapy: the purpose is basic research [explained in lecture]. The problem is that this form of hESR requires oocytes. And as discussed, oocytes are very hard to come by. This is also true in the UK.

To get around the problem, scientists have tried to use the oocytes of cows, rodents and other animals to clone cells. This was done for the first time in China by Sheng Huizhen from Shanghai. But protest ensued about the alleged mixing between two species. A scientists in the UK, Steven Minger, claims that there is so little DNA in the oocyte of the cow, that it can hardly be regarded as the mixing of species, and he asked Parliament to allow scientists to experiment with the oocytes of mammals. After much disagreement and discussion, his lab and some other research institutes have received permission.

In the new Human Tissue and Embryos (Draft) Bill a new category has been created of ‘permitted eggs’, ‘permitted sperm’ and ‘permitted embryos’. Alteration of nuclear or mitochondrial DNA is prohibited if eggs, sperm and resulting embryo are destined for implantation in a woman. This category makes space for the creation of ‘inter-species embryos’, which insertion into the womb is not permitted, i.e. inter-species and ‘altered’ embryos are ‘non-permitted’.

Questions for discussion:

1. Do you think that scientists should get permission to insert human DNA into animal oocytes? Why and why not?
2. Do you think inserting DNA in animal embryos should be allowed in order to create medicine or food?

Case 2: **Using pluripotent cells to create gametes and embryos**

The MEXT has decided to explore the lifting of research guidelines that forbid the differentiation of human embryonic stem cell and iPS into gametes for IVF or curing congenital diseases. It will have made a decision on the 17th of November. A committee has been appointed by the MEXT (Ministry of Education, Culture, Sports, and Science and Technology) and MoHWL (Ministry of Health, Welfare and Labour) to discuss the use of differentiated oocytes and sperm for fertilisation. The special committee has decided to condone guidelines to allow the differentiation of pluripotent cells into gametes if they are not implanted into the womb.

In 2003 for the first time oocytes and sperm were created out of the ES cells of mice. The creation of gametes from pluripotent stem cells has become a popular research activity. The idea is that if the mechanism is better understood it will be possible to explain the causes of some kinds of infertility and Down Syndrome, so that new drugs and therapies can be designed to remedy these syndromes. For ARTS research oocytes are sometimes needed. It is very difficult in Japan to obtain these, and it is only possible to obtain them from people that undergo IVF treatment or infertility treatment. But if we can create oocytes through iPS, it may become easy to obtain them. In that case, it is hoped that not only ARTS research will flourish, but also human ES cell research and foetal research.

Furthermore, if research progresses, it is hoped that it will be possible to create non-afflicted sperm and oocytes to facilitate not only research into the mechanism of fertilization but also to make possible the reproduction of those that have become infertile as result of disease or accident. However, it is also thinkable that this technology is used to extend people's life and create children ad random, generating new bioethical problems. Due to lack of experimentation on animals, and because the significance of the use of ES cells in creating gametes is not yet fully understood, it has been forbidden. But, now, depending on the progress of animal research, the use of pluripotent cells from ES cells and iPS cells has been examined.

Questions for discussion:

1. Do you acknowledge the creation of embryos out of in vitro created gametes made from iPS for research purposes?

2. Should in vitro created gametes be used for the creation of embryos in infertility treatment? Should any limits be imposed?

THE THREE GROUP DISCUSSIONS: CASE 3 AND 4

Questions for discussion CASE 3: Hybrid research in the UK

1. Do you think that scientists should get permission to insert human DNA into animal oocytes? Why and why not?
2. Do you think inserting DNA in animal embryos should be allowed in order to create medicine or food?

Questions for discussion CASE 4: Using pluripotent cells to create gametes and embryos

1. Do you acknowledge the creation of embryos out of in vitro created gametes made from iPS for research purposes?
2. Should in vitro created gametes be used for the creation of embryos in infertility treatment? Should any limits be imposed?

The majority of all group members agreed to permit the creation of cybrids, because of its potential benefits for society in future. However, some from group three insisted that there would be many views about this in society. As it is a normative issue, one should be totally open about the research and discuss its future consequences. Some member of group three were prepared to tolerate it as a compromise. All groups said it was easier to accept the use of cybrids than the use of ES cells, as the latter requires the destruction of embryos. But the group was also adamant in it requiring a clear limit to creating embryos, not using this technology for reproductive aims: creating an individual through this technology should absolutely forbidden. Some said it was inevitable that someone would try it. People agreed that violation should be punished severely. Various individuals of group 1, though not opposing the technology, expressed a feeling of abhorrence about the use of cybrids.

There was much controversy on the question of creating embryos out of iPS gamets. Those in favour thought it would be important to do in order to understand the mechanism of normal embryo development and help couples with infertility problems. A majority seems to have been against for various reasons. One reason was that even if the embryo is obtained in vitro from iPS cells, it is ethically problematic to destroy embryos intentionally, also for research purposes. A second reason, based on a slippery slope argument, was that it could lead to human cloning. A third reason, also a slippery slope argument, was that it would lead to using these embryos for IVF treatment. A majority was against using such iPS embryos for reproductive purposes. Those in favour, however, argued that it was important to cure infertility. One person argued that it is better to use one's own iPS embryo for creating offspring then receiving sperm or oocyte from a third, unrelated, person. One civilian, being flabbergasted by these novel reproductive possibilities, found the ideas hard to accept: 'I cannot understand it using the everyday way of thinking I have used until now'. The arguments against included, one, the danger of developing such technologies to the children that have to live with the consequences of mistakes; two, the acceptability of being a result of such technology to the resultant children; the possible commercial exploitation of such technologies; the pressure on couples to have children in a society with a low birth rate, making childlessness a source of shame. There was no agreement on where the limit should be set.

GENERAL DISCUSSION SESSION 2 (extracts)

This discussion shows that public discussion in Japan is experience as problematic:

- There were many things I did not know about and amazed me. Does research go this far? What do we call research? I am interested to know how far and in what direction all this will go! (housewife)
- The problem is that information does not get communicated. There are many people that do not know about this. Those that do not make a point of finding out about it do not know.
- The reason that people do not participate in discussion is that they think that even if they participate their view will not be taken into account.
- A large part of the population is not interested.

- But when in the news, people somehow do find out about it.
- Those uninterested think that their efforts have been in vain. They think that what starts cannot be stopped.
- As a housewife, I think that my friends and acquaintances, who have not heard about this, want to reflect on this. They just do not know about it. If there would be a platform like this, they soon would form an opinion. There would be anxiety about the future. Now I finally start to understand some of the topics that were discussed on television. The common people do not get such information.
- Even though iPS has been a much discussed topic on TV, many people do not know understand its implications.
- People are not concerned with topics other than their income.
- Is it not so that researchers do not communicate this with citizens because they fear a hysterical reaction? Thinking that you should not wake sleeping children…
- When I wanted to use cells from aborted foetuses, I started a discussion, being aware of the problematic nature of it. But the discussion soon put an end to it. Not making a problem of it and furthering one's research would have been better perhaps. However, I thought I would follow due procedures… The majority of society tends to agree with the views of the masse media. When clashes with expert committees occur, the discussion just stops. If you want to get on with research, doing things extra becomes a brake to research. But you cannot just sit still and do nothing. It is characteristic for the Japanese to be bad at holding discussion.

SESSION 3

Case 5 and 6: **On speeding up clinical applications and regulation:**

Regulation regarding research protocols for new research applications, and permission to use of human embryonic stem cells hESR have been criticised as being strict and review committees have been critisized as slow. Now that the Japanese public is enthusiastic about iPS, the government wants to devise new regulation to facilitate the development of research applications in a clinical setting. Similarly, the testing of foreign drugs on the

Japanese has been problematic for decades, and culminated in the so-called ‘drug-lag’. This drug lag, especially in the area of cancer drugs, has led to the phenomenon of ‘medical refugees’. Both problems are related to how the Japanese bureaucracy deals with new drugs, safety issues in research, and with issues related to Japanese identity.

Case 5: **Encouraging hESR to succeed in research and applications for iPS?**

Since the publication of Yamanaka’s iPS in mice in Autumn 2006 [Lecture explains iPS], the world gained important insights into pluripotency. And when his technology was applied onto human cells, many people started to believe that it would be possible to generate pluripotent cells very much like human embryonic stem cells to use in therapies. These therapies include possible cures for Alzheimer’s, Parkinson’s, diabetes and so on. The Japanese government decided to fully support the development of iPS, and the research received the broad support of the public. One of the reasons for this is that the therapy seemed to solve a problem associated with human embryonic stem cell research: the need to use supernumerary (spare) human oocytes and embryos. For even after many discussions had been held on how to source oocytes and embryos bioethically, the question has not been solved satisfactory in Japan [Lecture explains the regulation on oocyte donation]. It is so difficult for scientists to obtain oocytes, that hardly any hESR is being conducted, and this, scientists think, harms Japan’s ability to compete with scientists abroad.

Now, it has become clear that if you want to develop iPS, you need to be able to compare data with those for hESR. If you can’t, it may be difficult to compare the difference cells and to publish new research results.

Questions for discussion:

1. Should regulation be loosened to facilitate hESR in Japan? How? Why?
2. Should hESR be made easier temporarily until iPS is established?

Case 6: **Receiving the benefits from advanced regenerative medicine.**

The government in Japan invests much money in the life sciences, among which regenerative medicine. Considering the rapid progression of Japan as an aging society, it also encourages industrialization to facilitate new therapies and medicine. However, when most hospitals want to develop new therapies it is very difficult for most of them to obtain permission to do so, except for a few licensed hospitals. For, traditionally, it is the companies and the pharmaceutical industry that is able to set up clinical trials under the Pharmaceutical Administrative Law (PAL). Hospitals and research centres however, are regulated under the Medical Administrative Law (MAL), which does not allow trials.

In most cases, the researcher then is not allowed to use grant money or insurance coverage. This means that the patients have to pay if the research is to take place. For instance, one patient with prostate cancer received advanced therapy in February for which he paid 2 million Yen. He found out about the therapy as he knows about medical therapies, and has just enough money to pay for it. Others decide to enter American insurance companies, as these pay out for therapies that are recognised in the USA.

There are many cancer therapies recognised in the USA, which still have to be tested on Japanese people before they will be recognised by the Japanese government. Often this takes much time, and some patient groups claim it takes too long and advise patients to go abroad.

Questions for discussion:

1. Do you think that the government should 'put safety first' and have drug products and therapies tested on Japanese before recognising them?
2. Do you think that it should be made easier for Japanese researchers to try out new therapies on patients?

THE THREE GROUP DISCUSSIONS: CASE 5 AND 6

Questions for discussion Case 5: Encouraging hESR to succeed in research and applications for iPS?

1. Should regulation be loosened to facilitate hESR in Japan? How? Why?

2. Should hESR be made easier temporarily until iPS is established?

Questions for discussion case 6: Receiving the benefits from advanced regenerative medicine.

1. Do you think that the government should 'put safety first' and have drug products and therapies tested on Japanese before recognising them?

2. Do you think that it should be made easier for Japanese researchers to try out new therapies on patients?

The main position of group one and three was in favour of loosening the guidelines for hESR so as to compare ES cells and iPS cells. Nevertheless there was controversy within both groups and group two disagreed. A scientist stated that there are still a lot of things that we do not know about ES cells. In order to the iPS research it seems to him necessary to conduct hESR as well. It is still unclear to what extent ES cells and iPS cells are alike, what their merits and demerits are, and whether they can be treated the same. He claimed that it is a global trend to do research into ES cells and iPS in parallel, and said that Japan could drop out of the race to develop clinical applications because of obstruction to hESR. Persons in group three agreed with this view. The patients present concurred, expressing the view that if it is so that hESR can yield new therapies, then guidelines definitely should be loosened. A scientist from group two put forward the view that only a few certified research groups would do hESR. Then regulation could be loosened, and the number of research groups increased. A scientist from group three opined that, even if iPS does not work, it could support regenerative medicine

Opposing views, however, argued that regulation is so strict exactly because scientists have not been responsible. This is why Professor Hwang could betray the trust of society in science. Researchers, this view argued, do not have the position to accuse others of irrational behaviour, considering that ethics committees are meant to be representatives of the people. If regulation for hESR is temporarily loosened, a member of group two argued, it would be hard to make it stricter again. Therefore it should not be done. Again another view opined that the regulation is strict, because the embryo is regarded as sacred. To have a second discussion about this would be nonsense in principle. A last view mentioned here expressed the pessimistic opinion that both hESR

and iPS research lower the value of life in existence. The research is done with the purpose in mind to perfect human beings. This is a doubtful aim. Therefore research guidelines should not be loosened.

The overall view among all three groups that more kinds of medicine should be available to the Japanese people, and all medicine should not first have to be tested on Japanese individuals before made available to the public and covered by national insurance. Nevertheless, there was a little hesitation among some.

The general position was that the MoHWL is overcautious compared to foreign countries: Regulation should be loosened and should not depend on testing Japanese patients first. The meaning of 'safety' and 'ethics' was also discussed. Some argued that it is nonsense to retest medicine already approved by the FDA, advocating that it is fine 'if we have what they have in America'. One scientist said that hurdles to using new medicine are high: testing periods should be shortened and the required number of people to be tested decreased. For, as a patient argued, threatening the life of patients by long waiting times is wrong: Thinking about the life of the patient, it should be loosened. MoHWL perhaps has more problems then the fear of risk and administrative problems

Although most agreed that unnecessary procedures should be avoided, it was also agree that testing on Japanese people is necessary. But it was still thought that in urgent cases it should be up to the patient, even without clinical testing on the Japanese to establish racial safety first. It was generally agreed that when a new system of making available expensive medicine is not created, the interests of the economically vulnerable have to be kept in mind. For in that situation, only the well off could obtain therapies that are only obtainable with private money or private insurance. However, when it comes to IPS clinical research, it was argued that especially in the area of 'life' (reproduction, fertility) great care should be taken when creating new clinical applications: they should not be made available too soon. As a person from group 3 argued, ethics committees should avoid unnecessary processes, but continue to establish safety. Some participants expressed the suspicion that the MoHWL fears taking risks and is struggling with administrative problems.

GENERAL DISCUSSION SESSION THREE (extracts)

From the general discussion it became clear that scruples about hESR are not particular to the West. It also became clear that not everyone in Japan stands behind iPS cell research.

- I am not convinced that in order to do iPS research it is necessary to do hESR.
- IPS cells resemble ES cells, but it is possible that they are unusable. When the Japanese when see something new, they trash what they had before.
- The diameter of history: ES cells work, but I want to use ES cells from other sources then embryos. IPS cell research will maybe survive, but we will not know if we do not use the original, ES cell as a model. We need to find out if we can use them interchangeable. Now we have to support hESR more than ever. The more choice we have, the more chances we have to help the patients. Betting on one method is dangerous. (scientist)
- It is hard to say if it is necessary to loosen regulation.
- I am worried that feelings in life will disappear. In the clinic and in research: how can we deal with this problem.

The general discussion also shows how difficult it is to attain agreement on to what extent the Japanese require separate drug trials as a separate 'race' (sic!). The discussion is intimately linked to the meaning of 'risk' and the fear of dealing with 'risk'.

- There are various kinds of trial cases. There are also individual differences in medicine. There are also racial differences, and also cases with no differences. I am not sure how this is with stem cells.
- Only in cases where there is a genetic difference trials should be done on the Japanese.
- How can we discuss that?
- To doctors and pharma it is only natural that drugs have side effects. But product users do not want to recognise this.
- Though side effects are known to exist, they are hidden. The doctors should communicate such information. But the situation may have improved recently.
- The Japanese cannot accept risk.

- Until recently doctors did not tell the patients about the risks. Only very recently they have started providing patients with a diagnosis and prognosis. Everyone has only recently understood that there is risk, and explanations are only given incidentally.
- If the state has to be responsible for everything, then it is logical that it becomes cautious. If there are side effects you just have to make sure that the people who have received the medicine are insured.
- Insurances differ per kind of medicine.
- Patients in experimental research are not insured. There is no insurance. Apart from the drugs and the equipment nothing is insured.
- I do not understand why the MoHWL is so slow.
- No matter how you explain it, it is a very emotional discussion. One should create a point of departure by means of risk-benefit analysis. This perhaps does not function well in Japan.
- It is argued that because the patient groups are dissatisfied loosening of regulation is needed. How does the MoHWL deal with that? Is the MoHWL not averse to loosening regulation because it has experiences scares in connection with former scandals? What should we think about this?