1-MH-P-01-01

Recent Progress in iPS Cell Research and Application

Shinya Yamanaka

Center for iPS Cell Research and Application, Kyoto University, Japan

The appeal of induced pluripotent stem cells (iPSCs) is that they can proliferate almost indefinitely and differentiate into multiple lineages. Although originally generated from fibroblasts, they can be made from various somatic cells, which significantly expands their medical application. As a result, cell-based therapies, disease mechanisms and new drug development are being studied worldwide using iPSCs.

We are currently establishing optimal technologies for the efficient generation of safe iPSCs. More specifically, we are investigating an integration-free method that avoids chromosomal damage using episomal vectors. We have proposed the use of L-Myc as an alternative to oncogenic c-Myc in order to reduce the risk of tumorigenicity while maintaining iPSC induction at high efficiency. Furthermore, for iPSC induction without the need for conventional feeder cells or culture materials from different species but consistent with regulatory requirements for medical practice, we replaced feeder cells with a recombinant laminin-based matrix and developed a culture medium free of animal-derived constituents (xeno-free). Regarding quality control, some marker genes for neural differentiation-defective clones were identified, indicating the possibility of screening out low-quality iPSCs before use, which would expedite application for regenerative medicine.

In 2014, the world's first clinical study using iPSCs was initiated to study the transplantation of iPSC-derived RPE (retinal pigment epithelium) sheets for age-related macular degeneration. In addition, iPSC studies have recently shown major progress for other disorders, such as corneal diseases, blood diseases and Parkinson's disease, giving expectation that iPSC-based regenerative medicine will be widely used in the near future. To push these efforts, we are proceeding with an iPSC stock project in which iPSC clones are being established from donors with a homologous HLA haplotype, which is associated with decreased immune response and therefore less risk of transplant rejection, with the aim of quality-assured iPSCs for future cell therapies.

1-MH-P-02-02

The Accident of Fukushima Dai-ichi Nuclear Power Station, Radiation and Future of Energy in The World

Akito Arima

President, Japan Radioisotope Association, Japan

This paper consists of three main subjects. They are as follows;

§1 The earthquake and tsunami on 11 March , 2011 and the accident of Fukushima Dai-ichi Nuclear Power Station
§2 Radio activities in sea water and in towns in the vicinity of Fukushima Dai-ichi Nuclear Power Station
§3 Future of energy in the world

In §1, I discuss briefly the earthquake and tsunami on 11 March, 2011 and their grave consequences, and then the accident of Fukushima Dai-ichi Nuclear Power Station.

In §2, the accident of Fukushima Dai-ichi is compared with that of Chernobyl. The amount of Cesium-137 emitted in the Fukushima accident is one-sixth of that in the Chernobyl. The highly contaminated areas due to the Fukushima accident are about 6% of those due to the Chernobyl accident. I then examine the recent status of the radioactivity density in sea water inside and outside of the port next to Fukushima Dai-ichi. One important fact is that the densities of radioactive ^{134}Cs, ^{137}Cs and gross β-emitters in sea water outside of the port are almost non-detectable.
After Fukushima Daiichi Nuclear Power Plant Accident, one of the biggest concerns raised by Japanese citizens, especially Fukushima residents, has been the degree of radiation exposure dose to environmental sources , such as sea or soil , and its negative influence on human health.
It is the question of how seriously human health is affected by each unit of radiation dose in a low level but long term contaminated area, which is quite different from the short time but high radiation exposure dose caused by atomic bombing at Hiroshima and Nagasaki.
People want to know, under the existing situation, the radioactive level below which human health can be kept free from damage. They also try to find out the level beyond which human health will start suffering, and its expected degree of damage.

§3, I wish to discuss a future prospective of the world population and the demand for primary energy and electricity. Because of rapid increase of the world population and economic development, the global warming is becoming a serious problem. The development of renewable energy has to be promoted in order to solve the energy crisis as well as to prevent the global warming problem. However, the development of renewable energy will require sufficient resources of time and budget. The effort of Germany to increase electricity generation by renewable energy is discussed as an example.

Finally it is pointed out that human beings cannot help depending on all kinds of energy sources including both renewable energy and nuclear energy which do not cause the emission of CO_2.

3-D-SL-01-01

Health Effects of the Fukushima Nuclear Accident and Research on Low Dose Radiation

Kenji Kamiya[1,2]

[1]Research Institute for Radiation Biology and Medicine, Hiroshima University, Japan, [2]Fukushima Medical University, Japan

In the Fukushima nuclear accident which occurred on March 11, 2011, a large amount of radioactive material was released into the environment, in consequence, we need to elucidate effects of radiation on the human body and broaden knowledge about countermeasures to protect from these effects.

Since carcinogenic risk increases linearly as exposure dose increases, the estimation of the exposure dose should be the basis of health care in any radiation accident.

The outline of exposure dose of residents by the accident is being clarified. The external exposure doses are being estimated by the Fukushima health management survey. The most recent result from 440,000 residents was reported at the 17th Exploratory Committee of Fukushima Health Management Survey, and it showed that 93.9% Fukushima residents were exposed to less than 2 mSv, the average dose was 0.8 mSv. In Soso district, a comparatively higher dose area, approximately 77.6% were exposed less than 1 mSv, the highest value was 25 mSv in one person. The internal exposure is being measured by whole body counter (WBC). The result showed that the committed effective dose in 233,199 persons out of 233,225 (99.989%) was less than 1 mSv.

While the measurement data from thyroid dose measurements is insufficient, Tokonami reported that thyroid equivalent dose was less than 50mSv which is much lower than the average dose measured after the Chernobyl nuclear accident. According to UNSCEAR, the situation of Chernobyl in which thyroid cancer development was observed among many children is unlikely to occur in Fukushima.

In Fukushima, the health effects of low-dose/low dose rate exposure will be a continuous problem. However, these effects haven't been fully elucidated scientifically. Even though low-dose effects are commonly estimated from those of high dose/high dose rate exposure, the possibility is pointed out that the low-dose/low dose rate effects on the organism may be significantly different. In addition, recent studies have found that following radiation exposure, various DNA damage responses are induced in the cell, such as DNA repair, cell cycle arrest and cell death and cellular senescence, and the molecular mechanisms of these responses are still being clarified

Such cellular responses are believed to have some effects on the health risks of radiation, although the magnitude of these effects is unknown.

In addition to epidemiological studies, further studies of radiation effects by low-dose radiation on cell response and DNA, and also studies of effects on stem cells are required in order to elucidate the health risks of low-dose/low dose rate exposure. The progress of these studies is expected in the days ahead.

4-AX1-SL-02

The Evolution of Radiation Therapy; From 3D to 4DRT

Masahiro Hiraoka

Radiation Oncology & Image-applied Therapy, Kyoto University Graduate School of Medicine, Japan

The development of three-dimensional radiotherapy (3D-RT) caused tremendous improvement of therapeutic ratio in clinical radiation therapy. High precision radiation therapy including stereotactic irradiation, intensity modulated radiation therapy (IMRT), and particle therapy using proton or carbon ion are monumental achievements. Those new technologies, however are confronted with organ motions when a tumor in the intra-thoracic and upper-abdominal regions is indicated. Several approaches to challenge the issues have been clinically attempted such as respiratory inhibition with abdominal compression, breath-hold, respiratory gating, and tracking. The irradiation method that target position information is tracked directly or indirectly in real-time during the treatment session, and the treatment beams are adaptively delivered in accordance with the motion information is called four-dimensional radiotherapy (4D-RT).
Among various methods, dynamic tracking irradiation with a gimbaled method has the following advantages;
1) Continuous real-time monitoring of DT is possible with the use of IR system, 2 pairs of fluoroscopy and EPID.
2) Treatment is usually completed within the comparable time of 3D SBRT.

Since 2000, Kyoto University, Institute of Biomedical Research and Innovation and Mitsubishi Heavy Industries, Ltd. have started to develop an innovative image-guided radiotherapy (IGRT) system outside Japan which has several potentials of new radiation treatment technologies such as dynamic tumor tracking irradiation and dynamic wave arc irradiation using a novel gimbaled X-ray head. This system was approved by FDA in 2007, by PMDA(Japan) in 2008 and by CE mark in 2010, and its clinical application started in 2009.
Dynamic tracking SBRT (DT SBRT) was realized for a patient with lung tumor in Sept. 11 2011 and for a patient with liver tumor in 2012. Significant decrease in PTV and the doses of normal tissues (lung V20, V5, liver V15, spinal cord) was shown. Treatment time was almost comparable to the conventional SBRT. Log file analysis showed high accuracy of tumor tracking of the system.
Dynamic tracking IMRT (DT IMRT) was realized for a patient with pancreas cancer in May 2013. In the initial experiences with 6 patients, all of them completed accelerated radiotherapy by DT IMRT in combination with full dose of gemcitabine.
A prospective multi-institutional trial for lung cancer and pancreas cancer is to be started.