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Human ES cell research plans approved by institutional review board

October 17, 2003 – The RIKEN Kobe Institute institutional review board has approved research plans submitted by scientists at three of its laboratories for the use of human embryonic stem cells (ES cells) in experiments designed to unlock some of the fundamental biological secrets of cell differentiation and the developmental potential of stem cells, and to contribute to the scientific basis of the emerging field of regenerative medicine. Under Japanese regulations, institutional review board approval must be obtained before the research plans can be submitted to the office of the minister of the Ministry Education, Sports, Culture, Science and Technology (MEXT) for review and final authorization.

The Laboratory for Organogenesis and Neurogenesis, headed by Yoshiki Sasai, plans to conduct investigations into guiding ES cells to produce specific types of nerve cells which are lacking or deficient in a wide range medical problems including Parkinson's disease, and visual and gastrointestinal disorders. Shin-ichi Nishikawa's Laboratory for Stem Cell Biology will study the differentiation of human ES cells into fat cells and mesodermal stem cells, which may provide a useful platform for investigations into the biochemical and cellular processes at work in metabolic disorders such as diabetes. The third plan, submitted by the Hitoshi Niwa, head of the Laboratory for Pluripotent Cell Studies, seeks to develop a system for stably maintaining lines of ES cells without using culture media of non-human origin, such as the feeder cells and serum commonly used to maintain ES cells in vitro. The three projects propose to make use of a newly-derived line of ES cells, provided by Norio Nakatsuji's lab in the Kyoto University Institute for Frontier Medical Sciences. Pending the MEXT minister's approval, work with the cells is slated to begin in December 2003.

ES cells are of great interest to biologists and medical researchers for their pluripotency, the ability to give rise to all types of cell in the body. This is achieved during the process of differentiation, in which cell division results in two cells, one or both of which has a different, more highly specified, character than its parent cell. ES cells are also notable for their ability to self-renew through cell division – one of the daughter cells produced when the stem cell divides retains its undifferentiated, pluripotent state, leaving it capable of generating more pairs of differentiated and undifferentiated cells in subsequent divisions.

These properties of ES cells have made them a very popular subject of study in recent years. Much of the research to date, however, has been done using ES cells obtained from mice, or other non-human species. While the findings gained from such studies provide important insights into basic biological mechanisms and processes, in order to realize the medical potential of ES cells and to shed light on differences between species, it is necessary to conduct experiments using human ES cells as well.

ES cells are obtained from the inner cell mass of the blastocyst, a hollow structure formed at a very early stage of embryonic development. Human ES cell lines are usually established using cells taken from unused embryos created in vitro fertilization clinics. It is common for such clinics to create more embryos than will ultimately be used to attempt fertilization. Unused embryos are generally disposed of after a child is born from a successful fertilization attempt. Embryos at the blastocyst stage are not viable until they are implanted into a uterus; at this stage, the embryo is incapable of developing into an individual on its own. Thus, new human ES cell lines can be obtained in a manner compatible with prevailing ethical standards; cells once destined to be discarded are used in research with the potential to make a contribution to improved medical care.

The therapeutic potential of ES cells is illustrated by the Sasai proposal, which will seek to test a method for guiding the differentiation of ES cells into specific types of neurons at high efficiencies. This method, called SDIA (for Stromal cell Derived Inducing Activity), has been tested in both mouse and primate, and provides a means to controlling the differentiation of ES cells in culture. Previous studies using cells from these animals have shown that a wide range of central and peripheral nervous system neurons can be induced by adding different combinations of growth factors to cells cultured on a bed of stromal cells, which are found in

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bone marrow. The ability to guide the differentiation of neural cells will be necessary to realize the promise of cell replacement therapies in the treatment of degenerative disorders including Parkinson's disease, in which cells producing the neurotransmitter dopamine are deficient, Hirschsprung's disease, in which enteric neurons fail to develop in sufficient numbers in the large intestine, resulting in chronic constipation, and retinitis pigmentosa, a condition involving the progressive loss of light-sensitive neurons in the retina.

The Nishikawa lab will focus on a similar guidance of differentiation; in this case, of steering ES cells to produce adipocytes (fat cells) and mesodermal stem cells. The ability to generate these types of cells could lead to a number of therapeutic and research applications, including the production of cells to be used in the reconstruction or replacement of soft tissues and in the screening of biologically active materials. One possible application for such cells would be in the replacement of breast tissue removed in mastectomy, an issue which, while not life-threatening, has very real implications to post-operative quality of life. ES cell-derived adipocytes could also be used in studies of fat metabolism and the growth and differentiation of fat cells. These mechanisms are affected in disorders such as diabetes and obesity, two increasingly common metabolic disorders. As many cell lineages, such as blood and heart cells, are derived from mesoderm cells, the ability to precisely guide their differentiate sows promise in the establishment of cells of potential use in cell therapy.

In order for human ES cells to fulfill their medical promise, it will first be necessary to be able to grow and maintain them under clearly defined culture conditions and free from potential contamination. The most common method for growing ES cells in culture uses beds of 'feeder' cells, taken from mice, as well as serum derived from calves. ES cells grown under such conditions cannot be used for transplantation into humans due to the risk of contamination by pathogens present in the animal-derived culture media, and to the lack of complete data on their composition. Hitoshi Niwa is planning to investigate means of stably maintaining cultures of human ES cells without resorting to either feeder cells or serum, thereby providing a medically acceptable alternative to current technologies.