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Creating Functional Human Organs
by Transplanting Their "Buds" into Living Organisms
- A Notification of the Start of Research and Development for Products Related to Regenerative Medicine (Three-dimensional Organs) -

In relation to a technology to create functional human organs using pluripotent stem cells (such as iPS cells) developed by a research group, which is led by Professor Hideki Taniguchi and Associate Professor Takanori Takebe of the Department of Regenerative Medicine, Municipal University Corporation Yokohama City University Graduate of Medicine, HEALIOS K.K. entered into an agreement for exclusive and worldwide patent licensing, and launched a joint research project with the group in October 2014.

This technology is based on the concept of imitating the process of intercellular interaction for organ development in a fetus; it is a new cell culture technique to artificially create 3-dimensional organ anlages ("organ buds") by co-culturing 3 types of cells (endodermal, vascular endothelial, and mesenchymal stem cells). For example, in the case of the liver, hepatic precursor cells playing a central role in hepatic function are initially induced from human iPS cells, and subsequently cultured with vascular endothelial cells that create new blood vessels and mesenchymal stem cells mainly involved in intracellular attachment under a special condition to generate a 3-dimensional human liver anlage in approximately 48 hours. Furthermore, this human liver anlage is transplanted into a mouse, so that it will develop to a functional liver with a human vascular structure. In experiments using hepatic failure model mice, the survival rate markedly improved in the transplantation compared with non-transplantation group, confirming the effectiveness of treatment using this technology. These findings were published in the British scientific journal Nature in July 2013, and the technology was selected as one of the 10 breakthroughs (scientific achievements) of 2013 by the American scientific journal Science.

In addition to the liver, the research group has also succeeded in creating 3-dimensional anlages of various organs, such as the pancreas, kidney, intestine, lung, heart, and brain. At present, patients with organ failure whose organs do not appropriately function are generally treated with organ transplantation as a highly effective treatment method to replace their damaged organs with healthy ones. However, the number of donor organs to accommodate yearly increasing needs for organ transplantation is extremely low, and, in this respect, the technology developed by the research group is expected to establish a new treatment concept, such as "organ anlage transplantation therapy", as an alternative method of organ transplantation to help a large number of patients overcome the disease.

Yokohama City University is establishing preparatory procedures to launch a clinical research project to examine urea cycle abnormalities as a representative metabolic hepatic disorder among newborns (within 28 days after birth) in 2019. Urea cycle abnormalities are defined as serious conditions, in which congenital abnormalities in enzymes associated with a metabolic pathway (the urea cycle) to detoxify ammonia and produce urea in the liver lead to hyperammonemia or an increased blood ammonia level, resulting central nervous system impairment. They are fatal, or lead to severe sequelae, such as intellectual and developmental disabilities, if occurring during the neonatal period. In Japan, the number of pediatric patients (children younger than 18 years) with such abnormalities is 286 (based on data from a survey on the status of nationwide registration as part of the Research Program for the Treatment of Specific Chronic Pediatric Diseases 2011); the annual number of newborns with these disorders is estimated at slightly higher than 20. For the complete recovery of these patients, liver transplantation is the only currently available treatment method. Even in mild cases, lifelong treatment with dietary therapy and pharmacotherapy to decrease the ammonia level is necessary. In the scheduled clinical research project by the university, a liver anlage will be injected into the liver through a catheter to create a functional liver, with a view to initially confirming the safety of this procedure.

Aiming to establish systems to conduct clinical studies in the future through joint research, we target metabolic hepatic disorders at present. Involved in approximately 500 functions, including synthesizing various proteins for health and detoxifying/excreting unnecessary, harmful substances using nearly 2,000 types of enzyme, the liver may be regarded as a chemical plant in the body. Metabolic hepatic disorders correspond to a category of hepatic dysfunction or difficulty in producing necessary substances in the liver due to causes, such as a congenital lack of specific enzymes, and the annual numbers of new patients in Japan and Western countries are estimated at approximately 30 and 390, respectively. The market size for enzyme replacement therapy as a representative method to treat it is calculated at 12 to 21 billion yen, based on its annual cost (30 to 50 million yen/patient).

We are planning to subsequently proceed to research and development for alternative methods of liver transplantation in consideration of the current status (annual number of transplantations: slightly higher than 400 in Japan and approximately 10,000 in Western countries; that of patients waiting for transplantation: slightly lower than 400 in Japan and approximately 19,000 in Western countries).

The disease domain that provides us with a particularly important future perspective is hepatic cirrhosis, which is defined by the accumulation of fibers in damaged hepatic cells due to the progression of chronic hepatitis, leading to liver hardening and consequent dysfunction; it may be regarded as a symptom of end-stage chronic hepatitis. The number of patients with hepatic cirrhosis is 400,000 to 500,000 (Hepatic Cancer White Paper; Japan Society of Hepatology) in Japan. Among these, the number of patients continuously receiving treatment in medical institutions is 56,000 (Patient Survey 2011; Ministry of Health, Labour, and Welfare), and the annual number of deaths from the disease not involving hepatic cancer is approximately 17,000 (Hepatic Cancer White Paper; Japan Society of Hepatology). Liver transplantation is the only available treatment method for complete cure at present, suggesting that the need for treatment using the new technology is high when its favorable therapeutic effects on patients with hepatic cirrhosis are confirmed.

In October of this year, our laboratory was set up in the University-Industry Cooperation Laboratory that had been newly organized within the Yokohama City University Advanced Medical Research Center. The early establishment of systems to achieve our goals has been the purpose of this utilization of the University laboratory. Through collaboration with Yokohama City University, we aim to determine optimal transplantation techniques, and promote approaches for the actual use of regenerative medicine technologies by establishing methods for large-scale production of human liver anlages that are applicable to humans, as well as methods to evaluate and transplant these anlages in the future.

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