Creation of Cell Sheet Engineering using Temperature Responsive Polymeric Materials and Invention of Cell Sheet Regenerative Therapy

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In 21st century, Tissue Engineering Regenerative Medicine is highly expected as innovative therapies because it may regenerate the mass production volumes of cells and engineered tissues for advanced therapies. With tremendous research efforts by fusing biomedical scientists and physicians, we are getting close to enjoy effective regenerative medicine.

Smart/Intelligent materials have ability change their structure in response to outer circumstances such as physical and chemical stimuli. Response rate of structural and functional change of smart/intelligent materials can be controlled due to understanding of kinetics as well as equilibrium state of the materials. I have proposed new concept of smart/intelligent materials and have succeeded to show actual biomedical applications. I have focused on molecular design of temperature responsive surfaces and have achieved on-off biomedical functions using temperature switch.

I invented smart surfaces which respond to outer signal of temperature change and shows cell adhesive at 37 ℃ and non-adhesive at room temperature. After cells are proliferated by culture, cells and cell sheets are harvested with temperature change from 37℃ to room temperature without any damage of membrane structure of cell surfaces and bioactivity change. Therefor fabricated cell sheets maintain adhesive proteins at basal side and successfully can be transplanted to targeted tissues and organs. Because poly(N-isopropyl acrylamide) (PIPAAm) are coated with nano-level controlled thickness on the surface of culture dishes. I have proposed this novel system of cells and cell-layers arrangement called "cell sheet engineering" by utilization of smart/intelligent surfaces. Based on this break-through technology achieving a hundred percent transplantation efficiency of living cells, we have initiated the project to promote "cell sheet engineering" to treat patients after long animal preclinical study. We have started seven first-in-human clinical studies of the cell sheet engineering therapy. By using oral mucosal cell sheet, cornea epithelium deficient disease based on collaboration with Professor K. Nishida and prevention of stricture and recovery from endoscopic submucosal dissection surgery for esophageal epithelial cancer have been treated by collaboration with Professor. T. Ohki. Also periodontal ligament cell sheet for periodontal disease (Professor T. Iwata), nasal mucosal cell sheet for middle ear to prevent adhesion of tympanic membrane (Professor H. Kojima), fibroblast sheet for prevention of air leaking with pneumothorax (Professor M. Kanzaki) and chondrocyte sheet for treatment for osteoarthritis of cartilage (Professor M.Sato). Also our team have collaborated with Professor Y. Sawa, Osaka Univ. and succeeded in treating cardio-myopathy using myoblast cell sheet.

Main interest of our cell sheet tissue engineering therapies is moving from autologous to allogenic using polydactyly cells and mesenchymal stem cells. PMDA approved the autologous myoblast sheet as a tissue engineering product for heart failure, autologous oral mucosal cell sheet for treatment of cornea epithelium deficient disease and autologous chondrocyte sheet for osteoarthritis od cartilage. From this point of view, cell sheet engineering with the smart/intelligent surface is a highly promising tool for tissue engineering and regenerative medicine.

In 2016 University of Utah has initiated "Cell Sheet Tissue Engineering Center (CSTEC)" organized by new system of coordination between School of Medicine and College of Pharmacy. I started new research on allogeneic cell sheet therapy using juvenile chondrocyte and mesenchymal stem cells. I would like to present my new concept of allogeneic regenerative therapy for knee cartilage and kidney. Our lab, CSTEC at Utah is developing new allogeneic cell sheet therapies. Juvenile cartilage-derived chondrocyte (JCC) has been identified as a quality source for neocartilage regeneration due to its immune tolerant acceptability and proliferative activity. Its availability also allows chondral defect treatment in a single-stage surgical procedure. With close collaboration with department of orthopedic we have established juvenile cartilage-derived chondrocytes (JCCs) as a prominent cell source and confirmed the safety and efficacy of engineered JCC sheets in preclinical translational research. JCCs exhibited stable and high growth potential in vitro over passage 10, supporting possibilities for scale-up to mass production for commercialization. JCC sheets contained highly viable, densely packed cells, showed no anchorage-independent cell growth, expressed mesenchymal surface markers, and lack MHC II expression. In nude rat focal osteochondral defect models, stable neocartilage formation was observed at 4 weeks by JCC sheet transplantation without abnormal tissue growth over 24 weeks, in contrast to the non-treatment group showing no spontaneous cartilage repair. Regenerated cartilage was safranin-O positive, contained type II collagen, aggrecan, and human vimentin, and lacked type I collagen, indicating that the hyaline-like neocartilage formed originates from transplanted JCC sheets rather than host-derived cells.