

Left: Immunohistochemical stain of the engineered artery
 Von Willebrand Factor (upper), Calponin (lower)
 Right: SEM image of the Engineered Vessels / Luminal surface

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RESEARCH TOPIC

Strong, flexible artery developed with internal diameter of 6 mm

Reference

1)Iwasaki K, Kojima K, Kodama S, Paz A. C, Chambers M, Umezu M, Vacanti C. A., "Bioengineered Three-Layered Robust and Elastic Artery Using Hemodynamically-Equivalent Pulsatile Bioreactors", *Circulation*, **2008**, 118:S52-S57

Key words

Tissue engineered artery, Bioreactor, Arteries, Elasticity, Vascular grafts

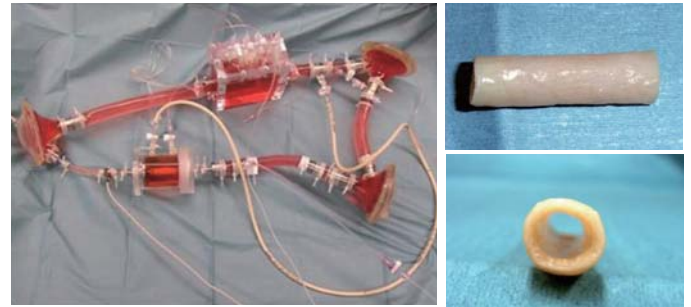


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Strong, flexible artery developed with internal diameter of 6 mm

Progress in embryonic stem (ES) cells and induced pluripotent stem (iPS) cell research has heightened expectations on the possible use of regenerative medicine for the restoration of damaged tissues and associated functions. Technologies have been developed to induce the differentiation of stem cells in cell culture into particular cell types, such as pulsating cardiomyocytes and oxygen-carrying erythrocytes. However, various challenges such as creating a 3-D structure based on several types of cells and ensuring the correct functioning of tissues, associated with these techniques remain. Kiyotaka Iwasaki, Associate Professor at Waseda Institute for Advanced Study, has successfully developed a tissue-engineered artery using the 3 types of cells that constitute arteries and polymer sheets that are eventually absorbed in human body. This tissue-engineered artery has laminar structure, strength, and elasticity that are similar to that of human arteries.



Left: Hemodynamically-equivalent pulsatile flow-and-pressure bioreactor
Right: Elastic artery engineered in vitro

Arterial walls are strong and flexible as they must withstand significant amounts of pressure of up to approximately 100 mmHg. However, diseases such as hyperlipidemia induce atherosclerosis, in which arterial walls are rendered hard and brittle. Though atherosclerosis progresses without any subjective symptoms, it may lead to ischemic stroke, myocardial infarction, and angina. Thus, the prevention of atherosclerosis has become a problem with social implications.

Ever since his undergraduate days, Iwasaki has been involved in the development of prosthetic valves and artificial hearts, the development of reliable test systems and methodologies as an alternative to animal trials for the investigation of practical performances of such devices, and the development of a novel tissue-decellularization technology which produces cell-free non-immunogenic tissues with growth potential. After attending a meeting of the Tissue Engineering Society International in December 2003, he decided to take on the challenge of developing a tissue-engineered blood vessel. Although artificial blood vessels made of materials such as synthetic fibers have been used in a variety of situations, narrow blood vessels with a diameter of 6 mm or less that could be put to clinical use had not been developed since they are prone to thrombosis. The blood vessel developed by Iwasaki using cells has a diameter of 6 mm and is flexible and withstands high pressure.

First, endothelial cells, smooth muscle cells, and fibroblasts were isolated from the artery of a cow and cultured. (These 3 cell types were used for the generation of arterial media, intima, and adventitia, respectively.) The cells were seeded on sheet bases made from polymer materials, which are absorbed in the body following hydrolysis (such as polyglycolic acid and poly (ϵ -caprolactone)), in order to allow cell growth in the form of a sheet. Iwasaki reveals, "The smooth muscle cell sheet is wrapped around a silicon tube for further culturing. The cultured fibroblast sheet is wrapped around this smooth muscle sheet for culturing, and the inner silicon tube is removed. Thereafter, the tube structure is attached to a proprietary device (pulsatile circulation culture system), and endothelial cells are injected into the lumen to enable cell growth. Subsequently, the tube is placed in a ring where the blood flow and blood pressure conditions are the same as in the body to enable further culturing. The diameter of the blood vessel thus produced is 6 mm, in diameter and 4 cm long and has a thickness of approximately 0.7 mm." The tissue-engineered blood vessel is not associated with any risk of thrombosis, which is commonly found in artificial blood vessels, since the lumen is internally lined with endothelial cells.

The development of the pulsatile circulation culture system was the key to success. In this system, the culture medium circulates instead of blood. The flow rate, pressure, pH, and CO₂ concentration of the system can be controlled whenever desired. Iwasaki increased the flow rate and pressure of the system by small increments, finally achieving the values found in the blood vessels with an internal diameter of 6 mm found in arterial circulation of adults. The elastic fiber namely elastin, which is a source of flexibility, in artery, was produced in large quantities from cells. Iwasaki is eager to make further progress in this field of study, and comments that, "In the future I would like to use bone marrow and iPS cells to create something that can be used to treat patients." Let us hope that he meets with success in his endeavor as soon as possible.

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