# Title of Project: Molecular Biomechanics of Vascular Cell Mechano-Responses

Joji Ando
(Dokkyo Medical University, School of Medicine, Professor)

Research Areas : Human Medical Engineering and Medical Bio-Engineering/Biomaterials
Keywords : Biomechanics, Mechanotransduction, Hemodynamic forces, Vascular biology

## 【Purpose and Background of the Research】

Living tissues and cells sense and respond to mechanical forces originating in the environment, and their responses play a critical role in the maintenance of their functions and survival. The mechano-sensing and -response mechanisms, however, have not yet been fully elucidated. In this project, we will focus on the endothelial cells that line the inner surface of blood vessels and investigate how they recognize the mechanical force generated by flowing blood, shear stress, as a signal and transmit it into the cell interior. We will promote the novel research field "molecular biomechanics", in which the mechanisms of shear-stress-induced $Ca^{2+}$ signaling via ATP-operated P2X4 ion channels are analyzed at a nano-scale biomolecular level. In addition, we will use P2X4 knock-out mice to clarify the role of shear stress $Ca^{2+}$ signaling in the control of the circulatory system and we will search for an unknown mechanical-force-mediated bio-regulatory mechanism that is distinct from the mechanisms mediated by the nervous system and endocrine system.

## 【Research Methods】

This project will investigate the following three research topics.

**I. Dynamic behavior of membrane molecules under shear stress:** Cultured endothelial cells will be exposed to controlled levels of shear stress in a flow-loading device and examined by means of various bio-imaging techniques for changes in membrane fluidity, phase transitions of membrane lipids, membrane microdomains such as caveolae and rafts, the state of the cytoskeleton and integrin, and ligand-independent activation of growth factor receptors.

**II. Shear-stress sensing mechanisms:** The intracellular $Ca^{2+}$ concentration of endothelial cells rapidly increase in response to shear stress, and the $Ca^{2+}$ response is mediated by P2X4 channels and by the ATP released from endothelial cells. The molecular mechanisms of the P2X4 activation and ATP release will be investigated by real-time imaging of the $Ca^{2+}$ response and ATP release

**III. Shear-stress signaling and its role in regulation of the circulatory system:** Signal transduction pathways and gene response cascades that are activated downstream of shear stress sensing will be analyzed. P2X4 knock-out mice will be used to identify the role of shear stress in regulation of the circulatory system. In addition, the role of shear stress in organogenesis will be investigated from the standpoint of induction of embryonic stem cell differentiation.

## 【Expected Research Achievements and Scientific Significance】

Clarification of the shear-stress sensing mechanisms will lead to better understanding of vascular mechanobiology. Studies of P2X4 knock-out mice will reveal the role of hemodynamic forces in the control of cardiovascular functions. The fruits of this research will contribute to elucidating the pathogenesis of blood-flow-dependent vascular diseases such as atherosclerosis, hypertension, and thrombosis. Furthermore, the achievements of a "molecular biomechanics" research field should provide valuable information concerning the regulatory mechanisms of a variety of cells that are exposed to biomechanical forces and be helpful in understanding life phenomena that consist of interactions between environmental factors including a mechanical field and genetic factors.

## 【Publications Relevant to the Project】

K. Yamamoto, T. Sokabe, , A. Kamiya, and J. Ando: Impaired flow-dependent control of vascular tone and remodeling in P2X4-deficient mice. Nat. Med. 12:133-137, 2006

K. Yamamoto, R. Korenaga, A. Kamiya, and J. Ando: Fluid shear stress activates $Ca^{2+}$ influx into human endothelial cells via P2X4 purinoceptors. Circ. Res. 87:385-391, 2000

**【Term of Project】** FY2009-2013

**【Budget Allocation】** 156,400 Thousand Yen

## 【Homepage Address and Other Contact Information】

http://square.umin.ac.jp/vascbiol/