

## Research Center for Medical Sciences Institute of Clinical Medicine and Research

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### General Summary

In addition to performing our own research activities, in 2016 we continued to engage in an educational laboratory course program with the assignment of students of the third-year grade from the School of Medicine in 2016. We also fulfilled research support duties for registered researchers from the University Hospital at Kashiwa campus (Departments of Gastroenterology; Laboratory Medicine; Diabetes, Metabolism and Endocrinology; and General Internal Medicine) so that doctor physician-researchers could work freely. Their research work has been progressed efficiently.

### Research Activities

#### *Mechanism of islet injury and beta cell regeneration in diabetes mellitus*

Pancreatic islet structure includes peripheral nerve fibers that are non-endocrine cells, capillaries, and ectoderm oriented, such as neural crest-derived peri-islet Schwann cells also make up the islet structure. It has been estimated that the function of the Schwann cell might have the same functions as the same as the function of allogeneic astrocytes and Schwann cells in the other tissues of the nervous system. These functions might include the supplementation of nutrients to the blood vessels and the endocrine cells and shielding cells from exogenous stress, but the functions remain unclear.

Research to elucidate the structure-function relationship of the islet compartment structure and molecules for the cell to cell communication should be helpful to understand the origins of pancreatic islet failure in diabetes mellitus. We have already started a study of "beta cell protection from metabolic stress" through the islet architecture. Experiments in 2016 showed that, in the co-culture conditions of MIN6, a murine established beta cell line, and IMS32, a murine established Schwann cell line, significantly higher in GSIS (glucose-stimulated insulin secretion) or insulin secretory capacity than in MIN6 of a single culture system. When expression of mRNA for the molecule that performs intercellular communication, gapjunction, was knocked-out with RNA interference technology, GSIS was lowered than in the control. This phenomenon was considered as a protective effect from the Schwann cells via intercellular communication.

#### *Search for novel biomarker in skin gas with gas chromatography*

Continuing from the previous fiscal year, we searched for a methodology for of detection with skin-derived gas-by-gas chromatography to find novel biomarkers for metabolic or physical stress including systemic inflammation.

*Study of the change of the body components during treatment of diabetes mellitus by sodium-dependent glucose co-transporter SGLT2 inhibitor*

In the treatment of type 2 diabetes by with dietary restrictions and medication, changes of body composition change associated, in particular, with the possibility of muscle loss and body fat increase, have become a problem. Sodium-dependent glucose co-transporter (SGLT2) inhibitor is known to cause body weight loss accompanied by body fat reduction, but details of body-composition change are not known. Furthermore, concerns have been raised about a possible worsening prognosis because of a decrease in skeletal muscle mass (sarcopenia). To clarify these issues, we have performed a multicenter, open-labeled follow-up clinical study with of an SGLT2 inhibitor on in Japanese patients with type 2 diabetes. So far 11 medical facilities are involved in this prospective study. In the analysis, body fat mass was found to have continued to decrease efficiently for up as long to as 52 weeks with dual-energy X-ray absorptiometry, DXA. Skeletal muscle mass decreased slightly during the initial 12 weeks yet showed no further decrease after 24 weeks.

### Publications

**Sakai S<sup>1</sup>, Kaku K<sup>2</sup>, Seino Y<sup>3</sup>, Inagaki N<sup>4</sup>, Haneda M<sup>5</sup>, Sasaki T, Fukatsu A<sup>6</sup>, Kakiuchi H<sup>1</sup>, Samukawa Y<sup>1</sup>** (<sup>1</sup>Taisho Pharmaceutical Co., Ltd., <sup>2</sup>Kawasaki Medical Sch, <sup>3</sup>Kansai Electric Power Hosp, <sup>4</sup>Kyoto Univ, <sup>5</sup>Asahikawa Medical Univ, <sup>6</sup>Yachiyo Hosp). Efficacy and Safety of the SGLT2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus Stratified According to Baseline Body Mass Index: Pooled Analysis of Data From 52-Week Phase III Trials. *Clin Ther*. 2016; **38**: 843-62.

**Yanai H<sup>1</sup>, Hirowatari Y<sup>2</sup>, Ito K<sup>3</sup>, Kurosawa H<sup>4</sup>, Tada N, Yoshida H** (<sup>1</sup>Natl Center for Global Health and Medicine Kohnodai Hosp, <sup>2</sup>Saitama Prefectural Univ, <sup>3</sup>Yaesu Sakura Dori Clinic, <sup>4</sup>Inzai General Hosp). Understanding of Diabetic Dyslipidemia by Using the Anion-Exchange High Performance Liquid Chromatography Data. *J Clin Med Res*. 2016; **8**: 424-6.

**Shibahara-Sone H<sup>1</sup>, Gomi A<sup>1</sup>, Iino T<sup>1</sup>, Kano M<sup>1</sup>, Nonaka C<sup>1</sup>, Watanabe O<sup>1</sup>, Miyazaki K<sup>1</sup>, Ohkusa T** (<sup>1</sup>Yakult Central Institute). Living cells of probiotic *Bifidobacterium bifidum* YIT 10347 detected on gastric mucosa in humans. *Benef Microbes*. 2016; **7**: 319-26.

**Akasaki Y, Kikuchi T, Homma S, Koido S, Ohkusa T, Tasaki T, Hayashi K, Komita H, Watanabe N, Suzuki Y, Yamamoto Y, Mori R, Arai T, Tanaka T, Joki T, Yanagisawa T, Murayama Y.** Phase I/II trial of combination of temozolomide chemotherapy and immunotherapy with fusions of dendritic and glioma cells in patients with glioblastoma. *Cancer Immunol Immunother*. 2016; **65**: 1499-509.

**Manita D<sup>1</sup>, Yoshida H, Hirowatari Y<sup>2</sup>** (<sup>1</sup>Tosoh Corporation, <sup>2</sup>Saitama Prefectural Univ). Cholesterol Levels of Six Fractionated Serum Lipoproteins and its Relevance to Coronary Heart Disease Risk Scores. *J Atheroscler Thromb*. 2017 Sep; **24**: 928-39. Epub 2016 Dec 26.

### Reviews and Books

**Kajihara M, Takakura K, Kanai T, Ito Z, Matsumoto Y, Shimodaira S<sup>1</sup>** (<sup>1</sup>Shinshu Univ), **Okamoto M<sup>2</sup>** (<sup>2</sup>Kitasato Univ), **Ohkusa T, Koido S.** Advances in inducing adaptive immunity using cell-based cancer vaccines: Clinical applications in pancreatic cancer. *World J Gastroenterol*. 2016; **22**: 4446-58.

**Kajihara M, Takakura K, Kanai T, Ito Z, Saito K, Takami S, Shimodaira S<sup>1</sup>** (<sup>1</sup>Shinshu Univ), **Okamoto M<sup>2</sup>** (<sup>2</sup>Kitasato Univ), **Ohkusa T, Koido S.** Dendritic cell-based cancer immunotherapy for colorectal cancer. *World J Gastroenterol*. 2016; **22**: 4275-86.

**Koido S, Okamoto M<sup>1</sup>, Shimodaira S<sup>2</sup>, Sugiyama H<sup>3</sup>** (<sup>1</sup>Kitasato Univ, <sup>2</sup>Shinshu Univ, <sup>3</sup>Osaka Univ). Wilms' tumor 1 (WT1)-targeted cancer vaccines to extend survival for patients with pancreatic cancer. *Immunotherapy*. 2016; **8**: 1309-20.

**Koido S.** Dendritic-Tumor Fusion Cell-Based Cancer Vaccines. *Int J Mol Sci*. 2016; **17**: 828.

**de Carvalho LS<sup>1</sup>, Yoshida H** (<sup>1</sup>State Univ Campinas, Brazil). Monthly PCSK9 inhibitors: The CHOICE for prolonged duration of effect. *Atherosclerosis*. 2016; **254**: 300-2.