

## Department of Internal Medicine

### Division of Diabetes, Metabolism and Endocrinology

---

Rimei Nishimura, *Professor*  
Masami Nemoto, *Professor*  
Kei Fujimoto, *Associate Professor*  
Shuichi Kato, *Assistant Professor*  
Kiyotaka Ando, *Assistant Professor*  
Kenji Yamashiro, *Assistant Professor*

Yutaka Mori, *Professor*  
Tamotsu Yokota, *Professor*  
Masaya Sakamoto, *Associate Professor*  
Hironari Sano, *Assistant Professor*  
Yasushi Kanazawa, *Assistant Professor*  
Keiichiro Matoba, *Assistant Professor*

#### General Summary

The number of patients we see in our division is more than 15,000 a month and is increasing every year. The patients we see most often have diabetes (including 10% with type 1 diabetes) but some have endocrinological disorders.

We attempt to provide the best healthcare to our patients on the basis of research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our division to perform basic and clinical research of high quality. With respect to education, we accept international students from other institutions. We encourage our trainees to improve their presentation skills. In addition, we strongly encourage our investigators to write manuscripts and publish their findings.

#### Research Activities

##### *Epidemiology*

1. Clinical trials of the treatment of patients with diabetes using continuous glucose monitoring
2. A nationwide epidemiologic study of mortality in approximately 3,500 patients with type 1 diabetes was started in 1986 and has continued to provide important information about the prognosis of Japanese children with type 1 diabetes
3. A population-based study of childhood obesity, insulin resistance and diabetes in the elderly, and genetic factors has also continued in Niigata Prefecture
4. Epidemiological study using data from more than 6,000 patients with diabetes from the 4 hospitals affiliated with The Jikei University

##### *Diabetic vascular complications*

1. Molecular mechanisms governing intracellular signal transduction focusing on cell types relevant to diabetic vascular complications
2. Roles of small guanosine triphosphate-binding protein Rho and Rho-kinase in renal, retinal, neuronal, and endothelial biology
3. Isoform-specific roles of Rho and Rho-kinase protein in the pathogenesis of microvascular and macrovascular complications were studied. Approaches to this study range from *in vitro* to *in vivo* using gene-targeting approaches in mice

*Molecular biology for pancreatic islets*

Type 2 diabetes is known as a “bi-hormonal disorder” because of the dysregulated insulin and glucagon secretion. Reduced  $\beta$  cell mass is a major cause of dysregulated insulin secretion. Although a combination of elevated levels of glucose and free fatty acids (glucolipotoxicity) strongly induces  $\beta$  cell dysfunction and cell death, the underlying cause remains unclear. In addition, the precise molecular mechanism of glucagon secretion from  $\alpha$  cells need to be elucidated. We found that serine/threonine kinase protein kinase c (Pkc)  $\delta$  is involved in  $\beta$  cell death and glucagon secretion from  $\alpha$  cells. Ongoing projects are as follows.

1. Elucidation of the molecular mechanism(s) of Pkc $\delta$ -dependent  $\beta$  cell mass reduction induced by glucolipotoxicity model using  $\beta$  cell specific Pkc $\delta$  knockout mice
2. Elucidation of the molecular mechanism(s) of Pkc $\delta$ -dependent glucagon secretion in glucagon-secreting cell line
3. Construction glucagon-secreting cell line

*Endocrinology*

1. Basic research
  - 1) The role of 12-lipoxygenase in diabetic cardiomyopathy
  - 2) The role of baroreflex sensibility on diabetic macroangiopathy, especially the effects of glycemic variability and blood pressure variability
  - 3) Effect of a sodium-dependent glucose transporter (SGLT) 2 inhibitor in a rat model of diabetes
  - 4) Effect of aldosterone in macula lutea degeneration
2. Clinical research
  - 1) Effect of a SGLT2 inhibitor in patients with diabetes
  - 2) The role of baroreflex sensibility in patients with diabetes
  - 3) The durability of basal insulin affects day-to-day glycemic variability assessed with continuous glucose monitoring in patients with type 2 diabetes
  - 4) Investigation of HbA1c, blood pressure, and body weight variability in patients with type 2 diabetes
  - 5) Achievement of the goals of HbA1c, blood pressure, and low-density lipoprotein cholesterol in patients with type 2 diabetes (the Japan Diabetes Clinical Data Management Study Group)

**Publications**

**Pieber TR, Bardtrum L, Isendahl J, Wagner L, Nishimura R.** Commentary to “Differential Effect of Hypoalbuminemia on Hypoglycemia on Type 2 Diabetes Patients Treated with Insulin Glargine 300 U/ml and Insulin Degludec” by Kawaguchi et al. *Diabetes Therapy* 2019. *Diabetes Ther.* 2020 Feb; **11**(2): 561-567.doi: 10.1007/s13300-019-00755-3. Epub 2020 Jan 10. PubMed PMID: 31925723; PubMed Central PMCID: PMC6995791.

**Aranishi T, Nagai Y, Takita Y, Zhang S, Nishimura R.** Usability of Nasal Glucagon Device: Partially Randomized Caregiver and Third-Party User Experience Trial with Simulated Administration at a Japanese Site. *Diabetes Ther.* 2020 Jan; **11**(1): 197-211. doi: 10.1007/s13300-019-00711-1. Epub 2019 Nov 4. PubMed PMID: 31686354; PubMed Central PMCID: PMC6965568.

**Nishimura R, Osonoi T, Koike Y, Miyata K, Shimasaki Y.** A Randomized Pilot Study of the Effect of Trelagliptin and Alogliptin on Glycemic Variability in Patients with Type 2 Diabetes. *Adv Ther.* 2019 Nov; **36**(11):

3096-3109. doi: 10.1007/s12325-019-01097-z. Epub 2019 Sep 27. PubMed PMID: 31562608; PubMed Central PMCID: PMC6822803.

**Nishimura R, Tanaka Y, Koizumi K, Ishida K, Salsali A, Kaspers S, Kohler S, Lund SS.** Effect of Empagliflozin on Free Fatty Acids and Ketone Bodies in Japanese Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Trial. *Adv Ther.* 2019 Oct; **36**(10): 2769-2782. doi: 10.1007/s12325-019-01045-x. PMID: 31444706.

**Shikata K, Kadera R, Utsunomiya K, Koya D, Nishimura R, Miyamoto S, Tajima N; JDCP study group.** Prevalence of albuminuria and renal dysfunction, and related clinical factors in Japanese patients with diabetes: The Japan Diabetes Complication and its Prevention prospective study 5. *J Diabetes Investig.* 2020 Mar; **11**(2): 325-332. doi: 10.1111/jdi.13116. Epub 2019 Sep 25. PubMed PMID: 31317670; PubMed Central PMCID: PMC7078093.

**Kawasaki R, Kitano S, Sato Y, Yamashita H, Nishimura R, Tajima N; Japan Diabetes Complication and its Prevention prospective (JDCP) study Diabetic Retinopathy working group.** Factors associated with non-proliferative diabetic retinopathy in patients with type 1 and type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study (JDCP study 4). *Diabetol Int.* 2018 Apr 26; **10**(1): 3-11. doi: 10.1007/s13340-018-0357-z. eCollection 2019 Jan. PubMed PMID: 30800559; PubMed Central PMCID: PMC6357241.

**Nishimura R, Kato H, Kisanuki K, Oh A, Onishi Y, Guelfucci F, Shimasaki Y.** Comparison of persistence and adherence between fixed-dose combinations and two-pill combinations in Japanese patients with type 2 diabetes. *Curr Med Res Opin.* 2019 May; **35**(5): 869-878. doi:10.1080/03007995.2018.1551192. Epub 2018 Dec 21. PubMed PMID: 30460858.

**Kanda K, Mori Y, Yamasaki K, Kitano H, Kanda A, Hirao T.** Long-term effects of low-intensity training with slow movement on motor function of elderly patients: a prospective observational study. *Environ Health Prev Med.* 2019 Jun 13; **24**(1): 44. doi: 10.1186/s12199-019-0798-4. PubMed PMID: 31189461; PubMed Central PMCID: PMC6563359.

**Sakamoto M, Matsutani D, Minato S, Tsujimoto Y, Kayama Y, Takeda N, Ichikawa S, Horiuchi R, Utsunomiya K, Nishikawa M.** Seasonal Variations in the Achievement of Guideline Targets for HbA1c, Blood Pressure, and Cholesterol Among Patients With Type 2 Diabetes: A Nationwide Population-Based Study (ABC Study: JDDM49). *Diabetes Care.* 2019 May; **42**(5): 816-823. doi: 10.2337/dc18-1953. Epub 2019 Feb 10. PubMed PMID: 30739885.

**Okamura K, Nakagawa Y, Takeda N, Soma K, Sato T, Isagawa T, Kido Y, Sakamoto M, Manabe I, Hirata Y, Komuro I, Ono M.** Therapeutic targeting of mitochondrial ROS ameliorates murine model of volume overload cardiomyopathy. *J Pharmacol Sci.* 2019 Sep; **141**(1): 56-63. doi: 10.1016/j.jphs.2019.09.005. Epub 2019 Sep 28. PubMed PMID: 31611176.

**Takahashi H, Nishimura R, Tsujino D, Utsunomiya K.** Which is better, high-dose metformin monotherapy or low-dose metformin/linagliptin combination therapy, in improving glycemic variability in type 2 diabetes patients with insufficient glycemic control despite low-dose metformin monotherapy? A randomized, cross-over, continuous glucose monitoring-based pilot study. *J Diabetes Investig.* 2019 May; **10**(3): 714-722. doi: 10.1111/jdi.12922. Epub 2018 Oct 9. PubMed PMID: 30171747; PubMed Central PMCID: PMC6497608.

**Akamine T, Takaku S, Suzuki M, Niimi N, Yako H, Matoba K, Kawanami D, Utsunomiya K, Nishimura R, Sango K.** Glyceraldehyde induces sensory neuron death through activation of the c-Jun N-terminal kinase and p-38 MAP kinase pathways. *Histochem Cell Biol.* 2020 Feb; **153**(2): 111-119. doi: 10.1007/s00418-019-01830-3. Epub 2019 Nov 16. PubMed PMID: 31734714.

**Nagai Y, Matoba K, Kawanami D, Takeda Y, Akamine T, Ishizawa S, Kanazawa Y, Yokota T, Utsunomiya K, Nishimura R.** ROCK2 regulates TGF- $\beta$ -induced expression of CTGF and profibrotic genes via NF- $\kappa$ B and cytoskeleton dynamics in mesangial cells. *Am J Physiol Renal Physiol.* 2019 Oct 1; **317**(4): F839-F851. doi: 10.1152/ajprenal.00596.2018. Epub 2019 Jul 31. PMID: 31364374.

**Honzawa N, Fujimoto K, Kitamura T.** Cell Autonomous Dysfunction and Insulin Resistance in Pancreatic  $\alpha$  Cells. *Int J Mol Sci.* 2019 Jul 28; **20**(15). pii: E3699. doi: 10.3390/ijms20153699. Review. PubMed PMID: 31357734; PubMed Central PMCID: PMC6695724.

## Reviews and Books

**Matoba K, Takeda Y, Nagai Y, Kawanami D, Utsunomiya K, Nishimura R.** Unraveling the Role of Inflammation in the Pathogenesis of Diabetic Kidney Disease. *Int J Mol Sci.* 2019 Jul 10; **20**(14). pii: E3393. doi: 10.3390/ijms20143393. Review. PubMed PMID: 31295940; PubMed Central PMCID: PMC6678414.

**Matoba K, Takeda Y, Nagai Y, Yokota T, Utsunomiya K, Nishimura R.** Targeting Redox Imbalance as an Approach for Diabetic Kidney Disease. *Biomedicines.* 2020 Feb 22; **8**(2). pii: E40. doi: 10.3390/biomedicines8020040. Review. PubMed PMID: 32098346; PubMed Central PMCID: PMC7167917.