

## Department of Pathophysiology and Therapy in Chronic Kidney Disease

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### General Summary

#### *Overview of education and research*

This department aims to advance education and research to prevent the onset and development of chronic kidney disease (CKD) and to slow the increase in the number of patients with renal failure. The number of elderly patients undergoing hemodialysis (HD) for renal failure has increased markedly in Japan and has become a critical social and medical economic problem. One solution for this problem is to prevent the onset and progression of CKD and to reduce the number of patients requiring HD.

Another solution is to improve the quality of life for the rehabilitation of patients who have already undergone HD and to promote home HD (HHD) and continuous ambulatory peritoneal dialysis (CAPD) that can be performed at home. Both HHD and CAPD will greatly benefit patients undergoing HD, particularly patients who have difficulty visiting hospitals because of old age or disability. Furthermore, when the Great East Japan Earthquake occurred, it was shown that CAPD could be performed in disaster areas.

### Research Activities

#### *Prevention of CKD and its progression*

Hyperuricemia has long been suggested to be a risk factor for the onset and progression of CKD, but definitive evidence was lacking, because an antihyperuricemic agent that could reduce uric acid levels effectively and safely in patients with renal dysfunction, such as CKD, was not available. Within the last 3 years, 2 novel antihyperuricemic agents that can be used effectively and safely in patients with renal dysfunction have been developed. The efficacy and safety of one agent, febuxostat, were investigated in patients with CKD IIIb and IV and reported at academic meetings and in a paper. Furthermore, a double-blind multicenter prospective clinical trial (FEATHER study: Febuxostat versus placebo randomized controlled trial regarding reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3), b and the publication is on going, had been conducted in more than 400 patients with CKD IIIa and IIIb by March 2016, and the results will be presented at a conference and published in 2017.

The utility and safety of topiroxostat, another novel antihyperuricemic agent, was investigated in patients with CKD III and hyperuricemia, and its effects on renal function, blood pressure, and albuminuria were examined. The result that albuminuria decreased significantly in patients receiving topiroxostat was reported in a paper. The underlying mechanism of reduced albuminuria is being investigated in basic research, and the effect is

being confirmed separately in a panel of primary diseases for renal failure. Furthermore, a randomized clinical trial to examine the effect of urinary protein loss caused by diabetic nephropathy is in progress. The results, including a comparison with allopurinol and effects according to type of hyperuricemia, were published.

#### *Efforts to promote CAPD*

To promote CAPD, a method of HHD, our department has employed peritoneal dialysis coordinators and had them visit the homes of patients undergoing CAPD to solve the problems presented by the patients and their families. The patients were then asked to answer a questionnaire survey about CAPD; the results were analyzed and presented at academic meetings. Because we believe that HHD by CAPD cannot be promoted without the cooperation of nursing care facilities and health and welfare facilities, CAPD study meetings have been held periodically with colleagues in such facilities near Kashiwa Hospital.

Combination therapy with HD once a week has been tried in patients undergoing CAPD with disturbed peritoneal function or insufficient water removal. A retrospective study and a prospective study (EARTH Study: The study of evaluating adequateness replacement therapy) are ongoing as multicenter collaborative studies to elucidate the effectiveness of the combination therapy. The retrospective study has already been completed and is being prepared for publication. fixed cases and the publication is Registration in the prospective study ended in 2016, and the results will be presented at a conference and published in 2017.

#### *Check-up and evaluation*

Research regarding the onset and development of hyperuricemia and CKD is ongoing. The analysis of the FEATHER study ,has been completed in March 2016, and a paper is being made ready for publication.

That topiroxostat reduces albuminuria similarly in a variety of renal diseases has been verified and reported in a paper. Experiments are in progress to elucidate the underlying mechanism in basic studies.

While CAPD has been promoted in patients with renal failure at the Department of Nephrology and Hypertension of our medical school, we hope other institutions will participate in this project and help establish the clinical efficacy of PD and HD combined therapy. To this end, we would like to make proposals for fulfillment of the systems for patients undergoing CAPD, such as medical insurance and nursing care insurance.

#### **Publications**

**Hosoya T, Sasaki T<sup>1</sup>, Ohashi T<sup>1</sup> (Fuji Yakuhin Co., Ltd).** Clinical efficacy and safety of topiroxostat in Japanese hyperuricemic patients with or without gout: a randomized, double-blinded, controlled phase 2b study. *Clin Rheumatol.* 2017; **36**: 649-56.

**Hosoya T, Ogawa Y<sup>1</sup>, Hashimoto H<sup>1</sup>, Ohashi T<sup>2</sup>, Sakamoto R<sup>1</sup> (Sanwa Kagaku Kenkyusho**

**Co. Ltd., <sup>2</sup>Fuji Yakuhin Co. Ltd).** Comparison of topiroxostat and allopurinol in Japanese hyperuricemic patients with or without gout: a phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study. *J Clin Pharm Ther.* 2016; **41**: 290-7.

**Hosoya T, Sasaki T<sup>1</sup>, Hashimoto H<sup>2</sup>, Sakamoto R<sup>2</sup>, Ohashi T<sup>1</sup> (Fuji Yakuhin Co. Ltd., <sup>2</sup>Sanwa**

- Kagaku Kenkyusho Co. Ltd).** Clinical efficacy and safety of topiroxostat in Japanese male hyperuricemic patients with or without gout: an exploratory, phase 2a, multicentre, randomized, double-blind, placebo-controlled study. *J Clin Pharm Ther.* 2016; **41**: 298-305.
- Matsuo H<sup>1</sup>, Yamamoto K<sup>2</sup>, Nakaoka H<sup>3</sup>, Nakayama A<sup>1</sup>, Sakiyama M<sup>1</sup>, Chiba T<sup>1</sup>, Takahashi A<sup>1</sup>, Nakamura T<sup>1</sup>, Nakashima H<sup>1</sup>, Takada Y<sup>1</sup>, Danjoh J<sup>5,6</sup>, Shimizu S<sup>1</sup>, Abe J<sup>1</sup>, Kawamura Y<sup>1</sup>, Terashige S<sup>1</sup>, Ogata H<sup>1</sup>, Tatsukawa S<sup>1</sup>, Yin G<sup>7,8</sup>, Okada R<sup>8</sup>, Morita E<sup>9</sup>, Naito M<sup>8</sup>, Tokumasu A<sup>9</sup>, Onoue H<sup>1</sup>, Iwaya K<sup>1</sup>, Ito T<sup>10</sup>, Takada T<sup>11</sup>, Inoue K<sup>12</sup>, Kato Y<sup>13</sup>, Nakamura Y<sup>2</sup>, Sakurai Y<sup>1</sup>, Suzuki H<sup>1</sup>, Kanai Y<sup>14</sup>, Hosoya T, Hamajima N<sup>15</sup>, Inoue J<sup>13</sup>, Kubo M<sup>7</sup>, Ichida K<sup>12</sup>, Ooyama H<sup>8</sup>, Shimizu T<sup>15</sup>, Shinomiya N<sup>1</sup> (Natl Defense Med Coll, <sup>2</sup>Kurume Univ Sch Med, <sup>3</sup>Natl Institute Genet, <sup>4</sup>RIKEN, <sup>5</sup>RIKEN BioResource Center, <sup>6</sup>Tohoku Univ, <sup>7</sup>Seinan Jo Gakuin Univ, <sup>8</sup>Nagoya Univ Graduate Sch Med, <sup>9</sup>Ryugoku East Gate Clinic, <sup>10</sup>Self-Defense Forces Central Hosp, <sup>11</sup>Univ Tokyo Hosp, <sup>12</sup>Tokyo Univ Pharmacy Life Sci, <sup>13</sup>Kanazawa Univ, <sup>14</sup>Osaka Univ, <sup>15</sup>Midorigaoka Hosp).** Genome-wide association study of clinically defined gout identifies multiple risk loci and its association with clinical subtypes. *Ann Rheum Dis.* 2016; **75**: 652-9.
- Fujita K<sup>1</sup>, Ichida K<sup>1</sup> (Tokyo Univ Pharmacy and Life Sci).** A Novel Compound Heterozygous Mutation in the SLC22A12 (URAT1) Gene in a Japanese Patient Associated with Renal Hypouricemia. *Clin Chim Acta.* 2016; **463**: 119-21.
- Mancikova A<sup>1</sup>, Krylov V<sup>1</sup>, Hurlba O<sup>1</sup>, Sebesta I<sup>1</sup>, Nakamura M<sup>2</sup>, Ichida K, Stiburkova B<sup>1</sup> (Charles Univ, <sup>2</sup>Tokyo Univ Pharmacy and Life Sci).** Functional Analysis of Novel Allelic Variants in URAT1 and GLUT9 Causing Renal Hypouricemia Type 1 and 2. *Clin Exp Nephrol.* 2016; **20**: 578-84.
- Matsuo H<sup>1</sup>, Tsunoda T<sup>2</sup>, Ooyama K<sup>3</sup>, Sakiyama M<sup>1</sup>, Sogo T<sup>2</sup>, Takada T<sup>1</sup>, Nakashima A, Nakayama A<sup>1</sup>, Kawaguchi M<sup>1</sup>, Higashino T<sup>1</sup>, Wakai K, Ooyama H<sup>3</sup>, Hokari R, Suzuki H<sup>4</sup>, Ichida K, Inui A<sup>2</sup>, Fujimori S<sup>6</sup>, Shinomiya N<sup>1</sup> (Natl Defense Med Coll, <sup>2</sup>Saiseikai Yokohamashi Tobu Hosp, <sup>3</sup>Ryugoku East Gate Clinic, <sup>4</sup>Univ Tokyo Hosp, <sup>5</sup>Nagoya Univ Graduate Sch Med, <sup>6</sup>Teikyo Univ).** Hyperuricemia in Acute Gastroenteritis Is Caused by Decreased Urate Excretion Via ABCG2. *Sci Rep.* 2016; **6**: 31003.
- Miyata H<sup>1</sup>, Takada T<sup>1</sup>, Toyoda Y<sup>1</sup>, Matsuo H<sup>2</sup>, Ichida K, Suzuki H<sup>1</sup> (Univ Tokyo Hosp, <sup>2</sup>Natl Defense Med Coll).** Identification of Febuxostat as a New Strong ABCG2 Inhibitor: Potential Applications and Risks in Clinical Situations. *Front Pharmacol.* 2016; **7**: 518.
- Nakayama A<sup>1</sup>, Nakaoka H<sup>2</sup>, Yamamoto K<sup>3</sup>, Sakiyama M<sup>1</sup>, Shaukat A<sup>4</sup>, Toyoda Y<sup>5</sup>, Okada Y<sup>6,7,8</sup>, Kamatani Y<sup>9</sup>, Nakamura T<sup>1</sup>, Takada T<sup>5</sup>, Inoue K, Yasujima T<sup>9</sup>, Yuasa H<sup>9</sup>, Shirahama Y<sup>2</sup>, Nakashima H<sup>1</sup>, Shimizu S<sup>1</sup>, Higashino T<sup>1</sup>, Kawamura Y<sup>1</sup>, Ogata H<sup>1</sup>, Kawaguchi M<sup>1</sup>, Ohkawa Y<sup>10</sup>, Danjoh J<sup>11</sup>, Tokumasu A<sup>12</sup>, Ooyama K<sup>12</sup>, Ito T<sup>13</sup>, Kondo T<sup>14</sup>, Wakai K<sup>14</sup>, Stiburkova B<sup>15</sup>, Pavelka K<sup>15</sup>, Stamp KL<sup>16</sup>, Dalbeth N<sup>17</sup>, Consortium E<sup>18</sup>, Sakurai Y<sup>1</sup>, Suzuki H<sup>2</sup>, Hosoyamada M<sup>19</sup>, Fujimori S<sup>20</sup>, Yokoo T, Hosoya T, Inoue J<sup>2</sup>, Takahashi A<sup>7</sup>, Kubo M<sup>7</sup>, Ooyama H<sup>12</sup>, Shimizu T<sup>21,22</sup>, Ichida K, Shinomiya N<sup>1</sup>, Merri-man TR<sup>5</sup>, Matsuo H<sup>1</sup> (Natl Defense Med Coll); Eurogout Consortium.** GWAS of Clinically Defined Gout and Subtypes Identifies Multiple Susceptibility Loci That Include Urate Transporter Genes. *Ann Rheum Dis.* 2016; **76**: 869-77.
- Okabayashi Y, Yamamoto Y, Komatsuzaki Y, Niikura T, Yamakawa T, Katsumata H, Kawabe M, Katsuma A, Nakada Y, Kobayashi A, Koike Y, Miki J, Yamada H, Tanno Y, Ohkido I, Tsuboi N, Ichida K, Yamamoto H<sup>1</sup>, Yokoo Y (Atsugi City Hosp, <sup>2</sup>Natl Institute Genet, <sup>3</sup>Kurume Univ Sch Med, <sup>4</sup>Univ Otago, <sup>5</sup>Univ Tokyo Hosp, <sup>6</sup>Tokyo Med Dental Univ, <sup>7</sup>RIKEN, <sup>8</sup>Osaka Univ Graduate Sch Med, <sup>9</sup>Nagoya City Univ, <sup>10</sup>Kyushu Univ, <sup>11</sup>Tohoku Univ, <sup>12</sup>Ryugoku East Gate Clinic, <sup>13</sup>Self-Defense Forces Central Hosp, <sup>14</sup>Nagoya Univ Graduate Sch Med, <sup>15</sup>Charles Univ, <sup>16</sup>Univ Otago, <sup>17</sup>Univ Auckland, <sup>18</sup>Tokyo Univ Pharmacy Life Sci, <sup>19</sup>Teikyo Univ, <sup>20</sup>Teikyo Univ Sch Med, <sup>21</sup>Midorigaoka Hosp, <sup>22</sup>Kyoto Industrial Health Assoc).** Rare Case of Nephrocalcinosis in the Distal Tubules Caused by Hereditary Renal Hypouricemia 3 Months after Kidney Transplantation. *Nephrology (Carlton).* 2016; **21**: 67-71.
- Sakiyama M<sup>1</sup>, Matsuo H<sup>1</sup>, Nagamori S<sup>2</sup>, Ling W<sup>2</sup>, Kawamura Y<sup>1</sup>, Nakayama A<sup>1</sup>, Higashino T<sup>1</sup>, Chiba T<sup>1</sup>, Ichida K, Kanai Y<sup>2</sup>, Shinomiya N<sup>1</sup> (Natl Defense Med Coll, <sup>2</sup>Osaka Univ).** Expression of a Human NPT1/SLC17A1 Missense Variant Which Increases Urate Export. *Nucleosides Nucleotides Nucleic Acids.* 2016; **35**: 536-42.
- Iguchi A<sup>1</sup>, Sato T<sup>1</sup>, Yamazaki M<sup>1</sup>, Tasaki K<sup>1</sup>, Suzuki Y<sup>2</sup>, Iino N<sup>3</sup>, Hayakawa H<sup>2</sup>, Ichida K, Narita J<sup>2</sup> (Saiseikai Niigata Daini Hosp, <sup>2</sup>Tokyo Univ Pharmacy Life Sci, <sup>3</sup>Niigata Univ).** A Case of Xanthinuria Type 1 with a Novel Mutation in Xanthine Dehydrogenase. *CEN Case Rep.* 2016; **5**: 158-62.
- Kuriyama S, Nishio S, Kidoguchi S, Honda K, Takahashi Y, Sugano N, Hosoya T, Nakano T, Tanabe T, Stim E, Yokoo T.** A Greater Association of Hyperuricemia than of Metabolic Syndrome with the New Incidence of Chronic Kidney Disease. *Open J Nephrol.* 2016; **6**: 17-27.
- Morisawa N, Sugano N, Yamakawa T, Kuriyama S, Yokoo T.** Successful long-term effect of direct renin inhibitor aliskiren in a patient with atherosclerotic renovascular hypertension. *CEN Case Rep.* 2017; **6**: 66-73. Epub 2017 Jan 16.
- Morisawa N, Koshima Y, Satoh JI<sup>1</sup>, Maruyama Y, Kuriyama S, Yokoo T, Amemiya M<sup>1</sup> (Saitama Red Cross Hospital).** Usefulness of combination therapy with Daclatasvir plus Asunaprevir in chronic hepatitis C patients with chronic kidney disease. *Clin Exp Nephrol.* Epub 2016 Oct 22.