

## Division of Clinical Pharmacology and Therapeutics

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### General Summary

The Division of Clinical Pharmacology and Therapeutics was established in July 1995. The aim of the division is to investigate drug treatment, mainly in the area of internal medicine, whereas other departments of clinical pharmacology in Japan focus on registration trials, particularly phase I trials. Because a clinical laboratory where we had performed many human pharmacological studies became unavailable in 2003, we shifted our research from human studies to multicenter clinical trials and pharmacoepidemiological studies.

### Research Activities

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been widely used to treat hyperlipidemia. They have adverse effects on muscle, the liver, kidneys, and other organs. To investigate the incidence of these adverse effects and antihyperlipidemic effects, we performed a study according to a case-cohort design in which detailed data were collected from all cases and from a subcohort representing 5% of all subjects. A full-scale study has been completed with a large sample size of 7,000 patients from 68 institutions. A paper describing this study has been submitted.

The above-mentioned statin study took a long time to complete. We organized a research group comprising academic and industrial organizations (Japanese Society for Pharmacoepidemiology, the Japanese Society of Clinical Pharmacology and Therapeutics, Japan Association for Medical Informatics, Japan Society of Clinical Trials and Research, the Federation of Pharmaceutical Manufacturer's Associations of Japan, Pharmaceutical Research and Manufacturers of America, and European Federation of Pharmaceutical Industries and Associations Japan) to make postmarketing studies more efficient by utilizing the Standardized Structured Medical-record Information eXchange (SS-MIX). The SS-MIX system was started in 2006 as a project supported by the Ministry of Health, Labour and Welfare for promoting the exchange of standardized medical information. The SS-MIX system will increase the efficiency of pharmacoepidemiological studies by identifying "new users" who started the drug after some period of nonuse. The "new user" design is often essential for unbiased results.

An administrative office for registration trials was established in the hospital in February 1999, and the system for registration trials in the hospital has been reformed to meet the demands of the new good clinical practice guidelines. Seven clinical research coordinators (CRCs) — 6 nurses and 1 pharmacist — now facilitate clinical trials. The CRCs have started to help with both registration trials and investigator-initiated trials. CRCs have been introduced into all registration trials since 2004; the quality and speed of these trials were much improved.

The Ministry of Health, Labour and Welfare started a New 5 Yearly Clinical Trial Action Plan to help registration trials to cope with trials performed abroad. This action plan selects 10 core hospitals and 30 major clinical trial institutions. The Jikei University Hospital was named a major clinical trial institution. According to this plan, we reinforced CRCs and introduced a data manager to improve the clinical trial system. We also introduced an information technology system for processing registration trial management.

## Publications

**Yokoyama K, Nakashima A, Urashima M, Suga H, Mimura T, Kimura Y (Shin Kashiwa Clin), Kanazawa Y, Yokota T, Sakamoto M, Ishizawa S, Nishimura R, Kurata H, Tanno Y, Tojo K, Kageyama S, Ohkido I, Utsunomiya K, Hosoya T.** Interactions between serum vitamin D levels and vitamin D receptor gene FokI polymorphisms for renal function in patients with type 2 diabetes. *PLoS One*. 2012; **7**: e51171.

**Kawamori R<sup>1</sup>, Kaku K<sup>2</sup>, Hanafusa T<sup>3</sup>, Kashiwabara D<sup>4</sup>, Kageyama S, Hotta N<sup>6</sup> (Juntendo Univ Grad Sch Med, <sup>2</sup>Kawasaki Med Sch, <sup>3</sup>Osaka Med Coll, <sup>4</sup>Dainippon Sumitomo Pharma, <sup>5</sup>Chubu Rosai Hosp).** Efficacy and safety of repaglinide vs nateglinide for treatment of Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2012; **3**: 302-8.

**Watanabe H<sup>1</sup>, Kageyama S, Kusuoka H<sup>2</sup>, Fujiwara Y<sup>3</sup>, Ono S<sup>4</sup>, Saito K<sup>5</sup>, Nakamura H<sup>6</sup>, Yamamoto H<sup>7</sup>, Kasai H<sup>8</sup>, Kawashima Y<sup>9</sup>, Yonemori K<sup>1</sup>, Yamamoto M<sup>10</sup>, Kurihara C<sup>11</sup>, Nakashima T<sup>12</sup>, Aoki H<sup>12</sup>, Kachi S<sup>1</sup>, Suzuki C<sup>1</sup>, Nakayama T<sup>13</sup>, Kondo E<sup>5</sup>, Hoshi J<sup>5</sup> (Hama-**

**matsu Univ Sch Med, <sup>2</sup>Osaka Nat Hosp, <sup>3</sup>Nat Cancer Hosp, <sup>4</sup>Univ Tokyo, <sup>5</sup>Pharm Med Dev Agcy, <sup>6</sup>Nat Ctr Child Health Dev, <sup>7</sup>Nat Cereb Cardiovasc Ctr, <sup>8</sup>Kyoto Univ Hosp, <sup>9</sup>Shiga Univ Med Sci Hosp, <sup>10</sup>Jpn Med Assoc, <sup>11</sup>Nat Inst Radiol Sci, <sup>12</sup>Jpn Pharm Manu Assoc, <sup>13</sup>Off Med Innovation).** Investigator-initiated clinical trials in Japan: Present and future (in Japanese). *Rinsho Hyoka*. 2012; **40**: 5-18.

**Kurihara C (Nat Inst Radiol Sci), Kageyama S.** "Cooperative IRB" issues in Japan, United States, Europe, and Asia (in Japanese). *Rinsho Hyoka*. 2013; **40**: 419-34.

## Reviews and Books

**Kageyama S.** Fixed combination tablets: History and current situation in Japan, US and EU (in Japanese). *Current Therapy*. 2012; **30**: 1224-7.

**Kageyama S.** How to assure quality of open-label trials (in Japanese). *Circulation*. 2012; **2**(11): 87-90.