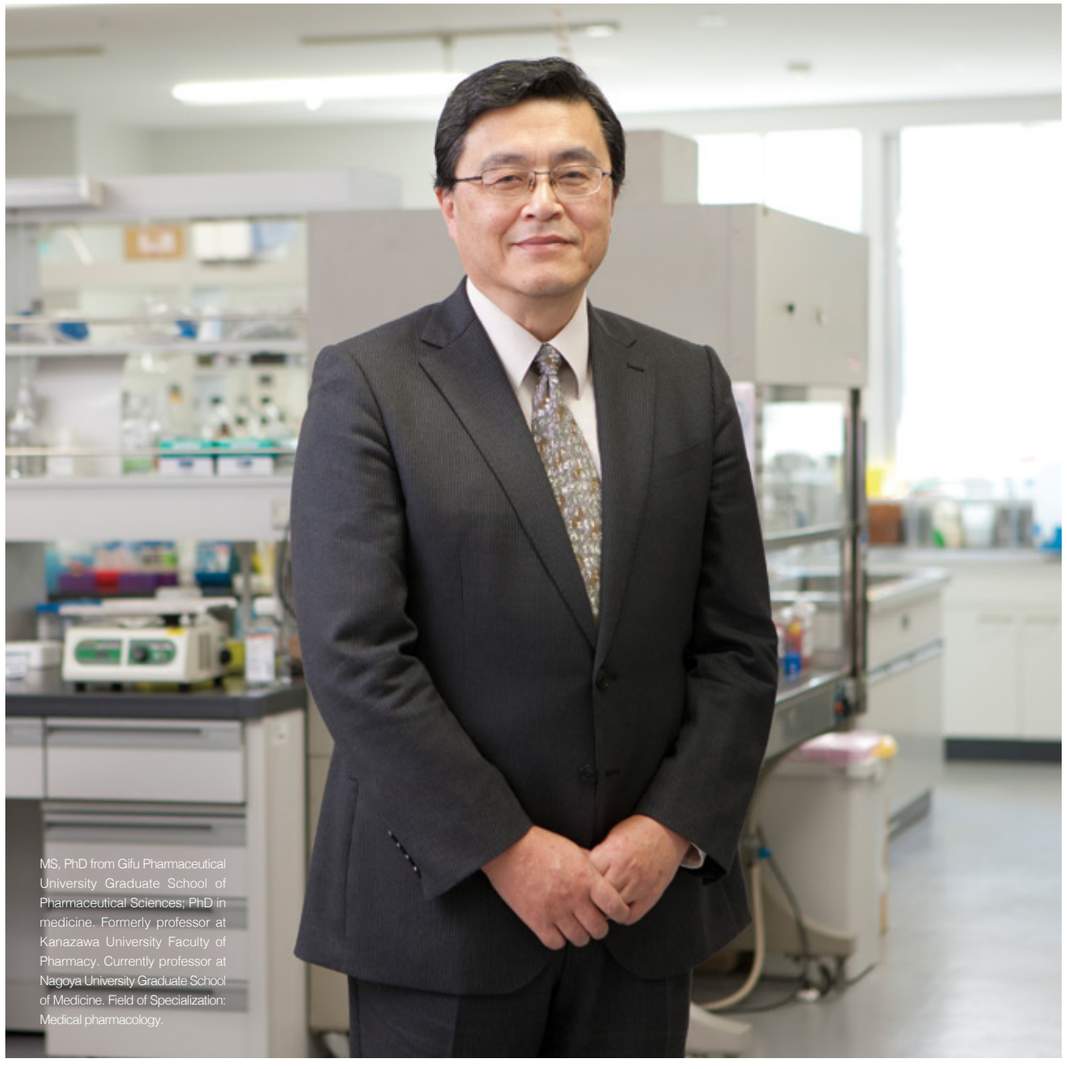

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YOKOI, Tsuyoshi

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Elucidating Adverse Drug Reaction Mechanisms for Safer Pharmacotherapy

Drug Discovery Research to Enhance Clinical Drug Safety

The Division of Clinical Pharmacology was established in the Division of Basic Medicine and the Division of Clinical Medicine during organizational reform at Nagoya University Graduate School of Medicine in FY2013. Nagoya University has no Faculty of Pharmacy and so the Division of Clinical Pharmacology plays an important role in drug discovery and nurturing researchers in this field. Specialists in chemotherapy, medical pharmacists, and biostatisticians adopt an almost clinical approach to both education and research. Researchers from a broad range of disciplines from basic sciences to clinical medicine work in cooperation with pharmaceutical companies to hold collaborative lectures between academia and industry as our department focuses on solving those medical issues that greatly impact society.

Our Toxicogenomics laboratory in the Division of Clinical Pharmacology, is one of the few laboratories in Japan which specialize in drug safety sciences. Drugs are a double-edged sword with both beneficial and toxic effects. They must be proven safe before they are approved for use, but despite such precautions, patients continue to suffer many adverse effects. Although detailed clinical studies must be conducted before the authorities will approve a drug for marketing, these studies only involve about 3,000 patients at most. However, there are large interindividual differences in drug reactions, and a rare reaction that only occurs in 1 out of 10,000 people cannot possibly be predicted. Despite preclinical studies in experimental animal and cell-based models, some adverse reactions will only occur idiopathically in humans, and they may often become apparent during clinical trials. To avoid drug toxicities despite such individual and species-based differences, our Toxicogenomics laboratory is attempting to elucidate the mysterious mechanisms behind idiosyncratic adverse reactions.

Predicting Liver Injury Before Clinical Studies

The focus of our research is drug-induced liver injury. Over half of all drugs on the market carry label warnings against liver injury, and adverse drug reactions occur in as many as 1/5000-6000 patients. The liver is itself responsible for drug detoxification, but occasionally, it produces reactive metabolites that can cause serious effects not only in the liver, but also other organs such as the kidneys or skin. To prevent such toxicities, we studied the mechanism of onset and identified factors related to immune function and inflammation. This has allowed us to build a test model that can detect drugs with a potential for liver injury during preclinical studies before they are ever administered to humans. Recently, we elucidated a mechanism where these reactive liver metabolites cause rhabdomyolysis, the breakdown of muscle cells. To make further strides in research on the causes of adverse drug reactions, it is vital that we conduct interventional clinical studies with full respect for the integrity of patient rights and ensuring patient safety. Towards these objectives, we plan to conduct first-in-human clinical studies at our new Advanced Medical Care Building (tentative title)*1, and believe that this will lead to major strides in drug discovery. Patients who are prescribed drugs from multiple physicians require proactive care measures and should receive essential information about their treatment to prevent potential drug interactions. Thus, at the Division of Clinical Pharmacology, we intend to strengthen our comprehensive role in tying together basic and clinical sciences that cover both medical and pharmaceutical disciplines. Our ultimate goal is to produce research results that will directly benefit both patients and society.

*1／Advanced Medical Care Building (tentative title)
Cutting-edge technologies and medical devices will be available to provide advanced medical care in treatment facilities dedicated to cancer chemotherapy and radiotherapy. Scheduled to open in 2017.