Department of Clinical Pharmacy and Education

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Research Projects:

1) Clinical pharmacological research for a personalized treatment with therapeutic antibody drugs.
2) Involvement of renal organic cation transporters involved in the side effects of drugs
3) Identification of novel riboflavin transporter RFVT and pathophysiology of rare diseases BVVLS

Many medical drugs have been developed so far, and they have greatly contributed to the development of drug treatment. On the other hand, Japan's medical care has various problems such as aging, rising cost of medical care, complication of diseases and medicines, increase of intractable diseases and rare diseases. In recent years, "Precision Medicine" which conducts the treatment and prevention of diseases based on genetic information, individual differences in living environments and lifestyles, has attracted attention. In the department of clinical pharmacy education, we are promoting reverse translational research, which forms a scientific basis for solving problems found in clinical drug treatment, and translational research, which develop new drug treatments based on basic research results, and are aiming to develop personalized treatments that achieve optimal care for each patient (Figure 1). The following is an overview of research themes developed in this field.

1) Clinical pharmacological research for a personalized treatment with therapeutic antibody drugs.

The importance of antibody drugs in drug treatment has increased in recent years. On the other hand, despite the fact that only about 50 antibody drugs have been approved and marketed, the medical economic point is a social issue, such as accounting for half of the TOP10 drug sales in 2014. In other words, it is urgent to develop biomarkers to predict clinical effects and to realize personalized medicine.

We have established a method for structural analysis of antibody drugs using TOF-MS, and also used pharmacokinetic evaluation techniques for immune cell activation markers using Flow Cytometry and CyTOF, the next-generation Flow Cytometry. We are developing personalized therapies by (PK) and pharmacodynamics (PD) analysis (Figure 2). In addition to cell and animal experiments, we are also promoting clinical research through joint research with the clinical department at Kyoto University Hospital. Furthermore, we are focusing on drug repositioning to search for drugs that enhance the effects of antibody drugs. The research results will lead to the appropriate use of antibody drugs, and will also contribute to the reduction of medical expenses and the development of antibody drugs such as biosimilars.

2) Pharmacokinetics and pharmacological research for transporters

2-1) Involvement of renal organic cation transporters involved in the side effects of drugs

The side effects of drugs are not only caused by pharmacodynamics but also by pharmacokinetics. We have focused on the organic cation transporters OCT2 (uptake type) and MATE (efflux type) in the kidney. We succeeded in identifying the human kidney-specific transporter MATE2-K that belongs to the MATE family. In addition, we have clarified that OCT expression distribution, substrate recognition characteristics, and functional change of MATE are important factors for renal specific toxicity of cisplatin and induction of lactate acidosis by metformin. The elucidation of the mechanism of side effects caused by these transporters is considered to be useful information for drug selection in patients with various pathological conditions, and also leads to the design of a side effect avoidance method in drug discovery.

2-2) dentification of novel riboflavin transporter RFVT and pathophysiology of rare diseases BVVLS

We have successfully identified the first riboflavin transporters RFVT1 (formerly known as RFT1) and RFVT2 (formerly named RFT3) in mammals. Collaborating with foreign laboratories, we also found that this gene defect causes the rare disease Brown-Vialetto-Van Laere syndrome (BVVLS). BVVLS is a disease that causes hypotonia and respiratory failure, but the details of its mechanism were unknown. By performing animal experiments, it was revealed that blood plasma riboflavin concentration is unchanged in RFVT2 deficiency and riboflavin concentration is lowered in RFVT3 deficiency, and BVVLS pathologies with different degrees of severity are exhibited. Based on this research result, each genetic disease was registered in the human genetic disease database OMIM as BVVLS2 (OMIM # 614707) and BVVLS1 (OMIM # 211530). We are currently working on knock-out mice to elucidate the pathophysiology of BVVLS and to develop treatments.

図1. 医薬品の体内動態と薬効・毒性に関する基礎と臨床

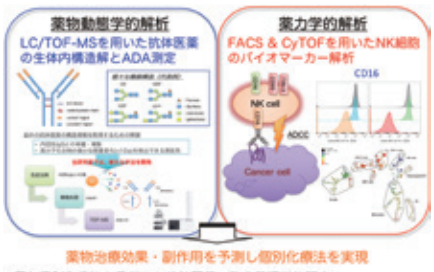

図2. 個別化療法を目指した抗体医薬の臨床薬理学的研究

Recent publications

- Yonezawa A, Otani Y, Kitano T, Mori M, Masui S, Isomoto Y, Tsuda M, Imai S, Ikemi Y, Denda M, Sato Y, Nakagawa S, Omura T, Nakagawa T, Yano I, Hayakari M, Takaori-Kondo A, Matsubara K. Concentration and Glycoform of Rituximab in Plasma of Patients with B Cell Non-Hodgkin's Lymphoma. *Pharm Res.* 36(6):82, 2019
- Otani Y, Yonezawa A, Tsuda M, Imai S, Ikemi Y, Nakagawa S, Omura T, Nakagawa T, Yano I, Matsubara K. Time-Dependent Structural Alteration of Rituximab Analyzed by LC/TOF-MS after a Systemic Administration to Rats. *PLoS One.* 12: e0169588, 2017
- Yoshimatsu H, Yonezawa A, Yamanishi K, Yao Y, Sugano K, Nakagawa S, Imai S, Omura T, Nakagawa T, Yano I, Masuda S, Inui K, Matsubara K. Disruption of Slc52a3 gene causes neonatal lethality with riboflavin deficiency in mice. *Sci Rep* 6:27557, 2016