

## Department of Clinical Pharmacology & Therapeutics

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### Research Projects:

The aim of our laboratory is to establish the scientific bases of appropriate drug usage and pharmaceutical practice. The efficacy and safety of drugs are closely related to their pharmacokinetics and pharmacodynamics. We have systematically developed the research from drug transport analyses based on the molecular levels to the clinical pharmacokinetics. We are also trying to elucidate the mechanisms underlying adverse effects of anti-cancer reagents, and are studying the mechanisms underlying neurodegenerative disease. To settle the problem found in the pharmacotherapy, we attempt to feedback the achievements of basic research to clinical practice. Topics currently undergoing are outlined below:

**1) Reverse translational research for adverse effects of anti-cancer drugs: elucidation of the mechanisms and development of novel preventive and treatment strategies:** Anti-cancer drugs used in chemotherapy frequently exhibit a variety of adverse effects. Some of them are dose-limiting adverse effects in anti-cancer chemotherapy, but effective clinical preventive and treatment strategies have not been established. We are trying to elucidate the molecular mechanism underlying the uncontrolled adverse effects, in which the findings are originally obtained from the bedside, by in vitro and in vivo experiments (reverse-translational research), and to propose effective preventive and treatment strategies. We are now investigating the mechanism of nephrotoxicity induced by cisplatin, interstitial lung disease induced by EGFR inhibitors (gefitinib and erlotinib), peripheral neuropathy induced various types of anti cancer drugs in cell cultures and animal models.

**2) Clinical and basic studies on Pharmacokinetics and Pharmacodynamics:** Pharmacokinetics consists of four processes, which are regulated by several pharmacokinetic factors, such as drug transporters and drug-metabolizing enzymes. We carry out clinical and basic studies on Pharmacokinetics and Pharmacodynamics (PK/PD). For example, it has been clarified that the efficacy and adverse effects of platinum anticancer drug cisplatin and anti-diabetic drug metformin depended on the characteristics of organic cation transporters. Also, novel riboflavin transporter RFVT has been identified. It has been indicated that RFVT mutation caused

a rare disease. Then, we now try to clarify the mechanism and discover new therapeutic drugs of this rare disease.

**3) Molecular and neural mechanisms underlying pathological pain and dysesthesia:** The physiological (acute) pain is transient and necessary for the alarm system that warns us and helps to protect from tissue damage, while pathological (chronic) pain is usually persistent and unnecessary for survival and protective role. Pathological pain is mediated through plastically altered pain pathways induced by a variety of causes, while it is often resistant to current therapeutic approaches. To elucidate the molecular mechanisms underlying pathological pain/dysesthesia, we are investigating (1) the roles of nociceptors (mainly TRP channels) expressed in sensory neurons in the generation of pathological pain/dysesthesia, and (2) the possible involvement of neuroimmune response mediated by the reciprocal interaction between peripheral/central nervous and immune systems.

**4) Study of the pathogenic mechanism of Parkinson's disease in order to identify a potential novel cure:** Parkinson's disease (PD) is the most common movement disorder caused by dopaminergic neuronal degeneration. It is characterized by the symptoms of resting tremor, rigidity, and akinesia. Many medical treatments have been developed; however, there is no fundamental cure. The goal of our research is to reveal the pathogenic mechanism of PD and to identify a novel cure. We recently reported that zonisamide (antiepileptic drug) and oxicam (non-steroidal anti-inflammatory) prevent cell death in a PD model, and we seek to advance our research to improve the clinical outcome for PD patients.

**5) Application of biomarkers to individualized pharmacotherapy:** Design of a dosing plan for immunosuppressive agents, tacrolimus and cyclosporine, is difficult because of large intra- and interindividual variability in the pharmacokinetics. To overcome these clinical problems, the development of individual immunosuppressive therapies based on the genomic, biochemical and population pharmacokinetic analyses have been attempted. We also focus on biomarkers that predict drug-mediated kidney injury.

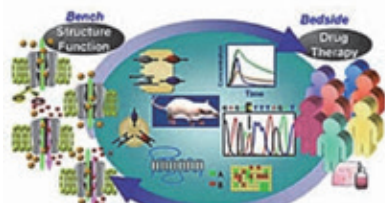


Figure 1. Research on drug transporters -from bench to bedside-

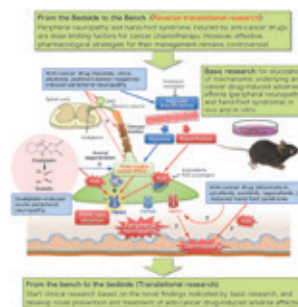


Figure 2. Reverse translational research for adverse effects of anti-cancer drugs

### Recent publications

- Omura T, Sasaoka M, Hashimoto G, Imai S, Yamamoto J, Sato Y, Nakagawa S, Yonezawa A, Nakagawa T, Yano I, Tasaki Y, Matsubara K. Oxidant-derived non-steroidal anti-inflammatory drugs suppress 1-methyl-4-phenyl pyridinium-induced cell death via repression of endoplasmic reticulum stress response and mitochondrial dysfunction in SH-SY5Y cells. *Biochem Biophys Res Commun* **503**: 2963-2969 (2018)
- Nakagawa S, Nakaish M, Hashimoto M, Ito H, Yamamoto W, Nakashima R, Tanaka M, Fujii T, Omura T, Imai S, Nakagawa T, Yonezawa A, Imai H, Mimori T, Matsubara K: Effect of medication adherence on disease activity among Japanese patients with rheumatoid arthritis. *PLOS ONE* **13**: e0206943 (2018)
- Omura T, Matsuda, H, Nomura L, Imai S, Denda M, Nakagawa S, Yonezawa A, Nakagawa T, Yano I, Matsubara K. Ubiquitin ligase HMG-CoA reductase degradation 1 (HRD1) prevents cell death in a cellular model of Parkinson's disease. *Biochem Biophys Res Commun* **506**: 516-521 (2018)
- Imai S, Koyanagi M, Azimi Z, Nakazato Y, Matsumoto M, Ogiwara T, Yonezawa A, Omura T, Nakagawa S, Wakatsuki S, Araki T, Kaneko S, Nakagawa T, Matsubara K: Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. *Sci Rep* **7**: 5947 (2017)